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# Annual Review of Cosmetic Ingredient Safety Assessments—2002/2003[1]

The Cosmetic Ingredient Review (CIR) program Expert Panel has assessed the safety of almost 1200 cosmetic ingredients since its inception in 1976. The very first safety assessments were published in earlier incarnations of this journal—the *Journal of Environmental Pathology and Toxicology* in 1980, and the *Journal of the American College of Toxicology* from 1982 to 1996.

Because information relevant to the safety of ingredients may have become available since these early safety assessments were published, the CIR Expert Panel has initiated a re-review process. If new information is thought to be available or if a long period of time has passed, the CIR Expert Panel may initiate a search for relevant new data.

In some cases, newly available data are largely redundant with the data available in the original safety assessment. In other cases, there are new safety data. If after considering the newly available information, the CIR Expert Panel decides not to reopen a safety assessment, this finding, along with any background material, is summarized and announced publicly. To assure that the scientific community is aware of any new information and the decision not to reopen, this *Annual Review of Cosmetic Ingredient Safety Assessments* is prepared. This annual review covers all ingredients re-reviewed from February, 2002, to June, 2003.

For each original safety assessment the re-review addresses the import of new studies that were considered by the Panel, if any were available. A reference list is provided that updates the references provided in the original safety assessment. The re-review also captures information on the industry's current practices of ingredient use, updating the data available in the earlier report. Although this material provides the opinion of the CIR Expert Panel regarding the new data described, it does not constitute a full safety review.

The ingredients the CIR Expert Panel reconsidered in 2002/2003, and decided not to reopen are:

Acetylated Lanolin
Acetylated Lanolin Alcohol
Almond Meal
Ammonium Laureth Sulfate
Ammonium Lauryl Sulfate
Beeswax
Benzophenone-1, -2, -3, -4, -5, -6, -8, -9, and -11
n-Butane
Butoxyethanol
Butyl Stearate
Ceresin
Cetearyl Ethylhexanoate (formerly Cetearyl Octanoate)
Cetyl Palmitate
Cetyl Stearate
Choleth-24
Copernica Cerifera (Carnauba) Wax
Dibutyl Phthalate
Diethyl Phthalate
Diisopropyl Adipate
Dimethicone PEG-6 Acetate
Dimethicone PEG-8 Adipate
Dimethicone PEG-8 Benzoate
Dimethicone PEG-7 Phosphate
Dimethicone PEG-10 Phosphate
Dimethicone PEG/PPG-7/4 Phosphate
Dimethicone PEG/PPG-12/4 Phosphate
Dimethicone PEG/PPG-20/23 Benzoate
Dimethicone Copolyol
Dimethyl Phthalate
Diethylhexyl Adipate (formerly Dioctyl Adipate)
Emulsifying Wax N.F.
Ethylhexyl Palmitate (formerly Octyl Palmitate)
Ethylhexyl Stearate (formerly Octyl Stearate)
Euphorbia Cerifera (Candelilla) Wax
Hydrogenated Lanolin
Hydroxylated Lanolin
Isobutane
Isobutyl Stearate
Isocetyl Stearate
Isopentane
Isopropyl Myristate
Isopropyl Palmitate
Isopropyl Stearate
Isostearic Acid
Laneth-5, -16, and -25
Laneth-9 and -10 Acetate
Lanolin
Lanolin Oil

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[1]Reviewed by the Cosmetic Ingredient Review Expert Panel.

Lanolin Acid
Lanolin Alcohol
Lanolin Wax
Laureth-4 and -23
Microcrystalline Wax
Montan Wax
Myrtistyl Myristate
Myristyl Stearate
Octyl Palmitate
Octyl Stearate
Ozokerite
Paraffin
PEG-3, -7, -8, -9, -10, -12, -14, and -17 Dimethicone
PEG-2, -6, -8, -12, -20, -32, -40, -50, -100, and -150 Stearate
PEG/PPG-3/10, -4/12, -6/11, -8/14, -14/4, -15/15, -16/2, -17/18, -18/18, -19/19, -20/6, -20/15, -20/23, -20/29, -22/23, -22/24, -23/6, -25/25, and -27/27 Dimethicone
Polyamino Sugar Condensate
Polybutene
Polyquaternium-11
Potassium Cocyl Hydrolyzed Collagen (formerly Potassium-Coco-Hydrolyzed Animal Protein)
Propane
Propylene Glycol Stearate and Propylene Glycol Stearate SE
Prunus Amygdalus Dulcis Oil (formerly Sweet Almond Oil)
Prunus Amygdalus Dulcis Seed Meal (formerly Almond Meal)
Rhus Succedanea Fruit Wax
Sodium Laureth Sulfate
Sodium Lauryl Sulfate
Sweet Almond Oil
Synthetic Beeswax
Synthetic Wax
TEA-Cocoyl Hydrolyzed Collagen (formerly TEA-Coco-Hydrolyzed Animal Protein)
VA/Crotonates Copolymer (formerly VA/CA Copolymer)

## ACETYLATED LANOLIN, ACETYLATED LANOLIN ALCOHOL, HYDROGENATED LANOLIN, HYDROXYLATED LANOLIN, LANOLIN (ANHYDROUS), LANOLIN ACID, LANOLIN ALCOHOL, LANOLIN OIL, AND LANOLIN WAX

A safety assessment of Acetylated Lanolin, Acetylated Lanolin Alcohol, Hydrogenated Lanolin, Hydroxylated Lanolin, Lanolin (anhydrous), Lanolin Acid, Lanolin Alcohol, Lanolin Oil, and Lanolin Wax was published in 1980 in which the CIR Expert Panel concluded that these ingredients are safe for topical application to humans in the then present practice of use and concentration (Elder 1980). The Panel reviewed new studies (listed at the end of this section), along with updated information regarding types and concentrations of use. The Panel determined to not reopen this safety assessment.

CIR Expert Panel acknowledged that there are current uses of lanolin compounds that may include aerosols. The effects of inhaled aerosols depend on the specific chemical species, the concentration, the duration of exposure, and site of deposition within the respiratory system. Particle size is the most important factor affecting the location of deposition (Jensen and O'Brien 1993). The mean aerodynamic diameter of pump hair spray particles is $\geq 80\ \mu$ and the diameter of anhydrous spray particles is 60 to 80 $\mu$. Typically, less than 1% are below 10 $\mu$, which is the upper limit for respirable particles (Bower 1999). Based on the particle size, lanolin and related compounds would not be respirable in formulation.

The panel also noted that animal derived products may contain residues present in the plant material ingested by the animal. Manufacturers are reminded that cosmetic products containing plant or animal derived ingredients should be formulated to limit the presence of pesticide/heavy metal residues as follows: lead $\leq 10$ ppm, arsenic $\leq 3$ ppm, mercury $\leq 1$ ppm, total PCB/pesticide contamination $\leq 40$ ppm with $\leq 10$ ppm for any specific residue (Andersen 1998). In addition, the CIR Expert Panel has recently stressed that animal-derived ingredients must be free of detectible pathogens and/or infectious agents (e.g., prions). Suppliers and users of these ingredients should assure that these ingredients are risk-free. Tests to assure the absence of a pathogenic agent in the ingredients, or controls to assure deviation from pathogen-free sources are two approaches that should be considered.

Data from the 1980 report on frequency of use and concentration of use (circa 1976) is provided in Table 1 along with current frequency and concentration of use and total products in each category as provided by the Food and Drug Administration (FDA) and Cosmetic, Toiletry, and Fragrance Association (CTFA) (FDA 2002; CTFA 2003). Although the total number of products containing lanolin and related compounds has decreased since 1980 (5196 in 1980 versus 2438 in 2002), there has been an increase in the variety of product categories containing these chemicals. In the 1980 report, the highest concentrations of these ingredients were in makeup and eye makeup preparations, skin care, suntan and sunscreen preparations, manicuring products, noncoloring hair preparations, and hair-coloring preparations. In 2003, lipsticks and rouges have the highest use concentrations.

**Acetylated Lanolin.** Acetylated lanolin is the acetylated ester of lanolin (q.v.) and is used as hair conditioning agent and skin conditioning agent, both emollient and occlusive. It was used in 127 cosmetic products in 1976, with the highest concentration range of >0.1% to 50% in eye and other make-up preparations. Currently Acetylated lanolin is used in 151 products at a maximum use concentration of 7% in makeup foundations. Table 1 provides the available use information.

**Acetylated Lanolin Alcohol** is the acetyl ester of Lanolin Alcohol (q.v.) and is primarily used as a hair conditioning agent and skin-conditioning agent—emollient and occlusive. It was used in 376 cosmetic products in 1976, with the highest concentration

**TABLE 1**

Historical and current cosmetic product uses and concentrations for Acetylated Lanolin, Acetylated Lanolin Alcohol, Hydrogenated Lanolin, Hydroxylated Lanolin, Lanolin (anhydrous), Lanolin Acid, Lanolin Alcohol, Lanolin Oil, and Lanolin Wax

| Product category | 1976 uses (Elder 1980) | 2002 uses (FDA 2002) | 1976 concentrations (Elder 1980) (%) | 2003 concentrations (CTFA 2003) (%) |
|---|---|---|---|---|
| | | *Acetylated Lanolin* | | |
| Baby lotions, oils, powders, and creams | 2 | 1 | >0.1–1 | 3 |
| Bath oils, tablets, and salts | 2 | — | >1–5 | — |
| Eye lotion | — | 1 | — | 0.6 |
| Eye makeup (other) | 5 | 5 | >0.1–50 | 0.1 |
| Bath soaps and detergents | — | — | — | 1 |
| Colognes and toilet waters | 4 | — | >0.1–1 | — |
| Hair conditioners | 3 | 1 | >0.1–5 | — |
| Face powders | — | 2 | — | 0.2–0.3 |
| Foundations | — | 3 | — | 3–7 |
| Lipsticks | — | 33 | — | 5 |
| Makeup (other) | 57 | 3 | >0.1–50 | 0.5–3 |
| Shaving cream | | — | | — |
| Shaving soap | 6* | — | ≤0.1–1* | — |
| Skin-cleansing creams, lotions, liquids, and pads | — | 14 | — | 0.1 |
| Face and neck skin care preparations | —* | 6 | —* | 1 |
| Body and hand skin care preparations | | 20 | | 0.5–2 |
| Moisturizers | — | 35 | — | 1 |
| Night skin care preparations | — | 23 | — | 4 |
| Paste masks (mud packs) | — | 4 | — | 1 |
| Skin care preparations (other) | 50 | 8 | >0.1–25 | 3 |
| Suntan gels, creams, and liquids | — | 4 | — | — |
| **Total uses/ranges for Acetylated Lanolin** | 127 | 151 | ≤0.1–50 | 0.2–7 |
| | | *Acetylated Lanolin Alcohol* | | |
| Baby lotions, oils, powders, and creams | — | 2 | — | 0.01–16 |
| Bath oils, tablets, and salts | | — | | — |
| Bubble baths | | — | | — |
| Bath capsules | 74* | — | >1–5* | — |
| Bath preparations (other) | | — | | — |
| Eye shadow | | 17 | | 0.9 |
| Eye lotions | | 1 | | — |
| Mascara | | 4 | | 0.002 |
| Eyebrow pencils | 31* | — | >0.1–10* | 0.1 |
| Eyeliners | | — | | 0.4 |
| Eye makeup (other) | | 11 | | — |
| Colognes and toilet waters | 16 | 5 | >0.1–25 | 0.07 |
| Powders | — | 6 | — | 0.01 |
| Fragrance preparations (other) | — | 3 | — | 0.1–0.4 |
| Hair conditioners | — | 1 | — | — |
| Hair sprays (aerosol fixatives) | — | 4 | — | 0.01 |
| Hair straighteners | — | 3 | — | — |
| Shampoos (noncoloring) | — | 1 | — | 0.02 |
| Hair tonics, dressings, etc. | — | 6 | — | 0.01 |
| Hair preparations (other) | 4 | 3 | >0.1–5 | — |
| Hair-coloring preparations (other) | — | 1 | — | — |

*(Continued on next page)*

**TABLE 1**
Historical and current cosmetic product uses and concentrations for Acetylated Lanolin, Acetylated Lanolin Alcohol, Hydrogenated Lanolin, Hydroxylated Lanolin, Lanolin (anhydrous), Lanolin Acid, Lanolin Alcohol, Lanolin Oil, and Lanolin Wax *(Continued)*

| Product category | 1976 uses (Elder 1980) | 2002 uses (FDA 2002) | 1976 concentrations (Elder 1980) (%) | 2003 concentrations (CTFA 2003) (%) |
|---|---|---|---|---|
| Blushers (all types) | — | 9 | — | 0.3–0.8 |
| Face powders | — | 10 | — | 0.01–2 |
| Foundations | — | 9 | — | 1–2 |
| Lipstick | — | 100 | — | 2–3 |
| Makeup bases | 133 | 8 | >0.1–25 | — |
| Rouges | — | 1 | — | — |
| Makeup (other) | — | 8 | — | 0.1–3 |
| Nail polish and enamel removers | | 2 | | 0.01 |
| Cuticle softeners | 2* | — | ≤0.1–5* | 0.1 |
| Nail polish and enamel removers | | — | | 0.02 |
| Bath soaps and detergents | — | 4 | — | 0.4 |
| Personal cleanliness products (other) | — | 2 | — | 0.1 |
| Aftershave lotion | — | 2 | — | — |
| Shaving cream | — | 3 | — | 0.02 |
| Skin-cleansing creams, lotions, liquids, etc. | | 10 | | <1 |
| Face and neck skin care preparations | | 4 | | 0.2–3 |
| Body and hand skin care preparations | | 53 | | 0.1–6 |
| Moisturizers | 105* | 33 | >0.1–50* | 0.5–5 |
| Night skin care preparations | | 5 | | 0.1 |
| Paste masks (mud packs) | | 3 | | 0.01 |
| Skin fresheners | | 2 | | — |
| Skin care preparations (other) | | 14 | | 0.01–0.4 |
| Suntan gels, creams, and liquids | 11 | 6 | >0.1–50 | — |
| **Total uses/ranges for Acetylated Lanolin Alcohol** | 376 | 251 | ≤0.1–50 | 0.01–16 |
| | *Hydrogenated Lanolin* | | | |
| Eyeliner | | 2 | | 1 |
| Mascara | 1* | 5 | >5–10* | — |
| Eye makeup (other) | | 1 | | 7–10 |
| Colognes and toilet waters | 1 | — | >1–5 | — |
| Fragrance preparations (other) | — | 1 | — | — |
| Hair conditioners | — | 1 | — | 0.5 |
| Hair dyes and colors | — | — | — | 1 |
| Rinses (noncoloring) | — | 1 | — | — |
| Hair tonics, dressings, etc. | — | 1 | — | — |
| Foundations | | 2 | | — |
| Lipstick | | 30 | | 3–9 |
| Makeup bases | 58* | 1 | >1–25* | — |
| Makeup (other) | | 1 | | — |
| Nail creams and lotions | 1 | 1 | >1–5 | — |
| Underarm deodorants | — | 1 | — | — |
| Skin-cleansing creams, lotions, liquids, etc. | — | 4 | — | — |
| Shaving preparations (other) | 15 | — | >0.1–1 | — |
| Face and neck skin care preparations | | 4 | | 10 |
| Body and hand skin care preparations | | 25 | | 2 |
| Moisturizers | | 16 | | — |

*(Continued on next page)*

**TABLE 1**
Historical and current cosmetic product uses and concentrations for Acetylated Lanolin, Acetylated Lanolin Alcohol, Hydrogenated Lanolin, Hydroxylated Lanolin, Lanolin (anhydrous), Lanolin Acid, Lanolin Alcohol, Lanolin Oil, and Lanolin Wax *(Continued)*

| Product category | 1976 uses (Elder 1980) | 2002 uses (FDA 2002) | 1976 concentrations (Elder 1980) (%) | 2003 concentrations (CTFA 2003) (%) |
|---|---|---|---|---|
| Night skin care preparations | 15* | 3 | >0.1–10* | — |
| Paste masks (mud packs) | | 1 | | — |
| Skin fresheners | | 1 | | — |
| Skin care preparations (other) | | 4 | | 2 |
| Suntan gels, creams, and liquids | 4 | 3 | >0.1–5 | 2 |
| Suntan preparations (other) | | 2 | | — |
| **Total uses/ranges for Hydrogenated Lanolin** | 95 | 111 | >0.1–10 | 0.5–10 |
| | *Hydroxylated Lanolin* | | | |
| Baby products (other) | — | — | — | 2 |
| Eyebrow pencils | — | 3 | — | — |
| Eyeliner | — | 73 | — | 5–10 |
| Eye shadow | — | 7 | — | 3–10 |
| Mascara | — | 10 | — | 1 |
| Eye makeup (other) | — | 3 | — | 2–11 |
| Blushers (all types) | | 2 | | 3 |
| Face powders | | 3 | | 2 |
| Foundations | | 2 | | 2 |
| Lipstick | | 18 | | 0.5–28 |
| Makeup bases | 7* | 2 | >5–25* | — |
| Makeup fixatives | | 1 | | — |
| Leg and body paints | | — | | 10 |
| Makeup (other) | | 1 | | 4 |
| Skin-cleansing creams, lotions, liquids, etc. | | 2 | | — |
| Body and hand skin care preparations | 5* | 2 | >0.1–5* | — |
| Moisturizers | | 6 | | — |
| Night skin care preparations | | 3 | | — |
| Suntan gels, creams, and liquids | — | 1 | — | — |
| **Total uses/ranges for Hydroxylated Lanolin** | 12 | 141 | >0.1–25 | 0.5–28 |
| | *Lanolin* | | | |
| Baby lotions, oils, powders, and creams | 9 | 3 | >0.1–10 | 0.2–4 |
| Bath oils, tablets, and salts | | 1 | | — |
| Bath products (other) | 4* | 1 | >0.1–5* | — |
| Eyebrow pencils | | 16 | | 6–7 |
| Eyeliner | | 6 | | 10–32 |
| Eye shadow | | 11 | | 5–9 |
| Mascara | 243* | 3 | ≤0.1–>50* | 0.1–12 |
| Eye makeup preparations (other) | | 8 | | 5 |
| Colognes and toilet waters | 37 | — | >0.1–10 | — |
| Powders | — | 1 | — | — |
| Sachets | — | 9 | — | — |
| Fragrance preparations (other) | — | 3 | — | — |
| Hair conditioners | | 33 | | 0.2–10 |
| Hair sprays (aerosol fixatives) | | 1 | | 0.001 |
| Hair straighteners | | 7 | | 0.3 |
| Permanent waves | 137* | 2 | ≤0.1–50* | — |

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**TABLE 1**
Historical and current cosmetic product uses and concentrations for Acetylated Lanolin, Acetylated Lanolin Alcohol, Hydrogenated Lanolin, Hydroxylated Lanolin, Lanolin (anhydrous), Lanolin Acid, Lanolin Alcohol, Lanolin Oil, and Lanolin Wax *(Continued)*

| Product category | 1976 uses (Elder 1980) | 2002 uses (FDA 2002) | 1976 concentrations (Elder 1980) (%) | 2003 concentrations (CTFA 2003) (%) |
|---|---|---|---|---|
| Shampoos (noncoloring) | | 9 | | 0.5 |
| Hair tonics, dressings, etc. | | 69 | | 0.5–19 |
| Wave sets | | 2 | | 4 |
| Hair preparations (other noncoloring) | | 1 | | 5 |
| Hair-coloring preparations (other) | 7 | 8 | >1–50 | 0.4 |
| Blusher (all types) | | 31 | | 2–9 |
| Face powders | | 9 | | 1–5 |
| Foundations | | 17 | | 2–9 |
| Lipsticks | 1314* | 133 | ≤0.1–>50* | 1–33 |
| Makeup bases | | 5 | | 0.4–5 |
| Rouges | | 4 | | 5 |
| Makeup (other) | | 12 | | 10–17 |
| Cuticle softeners | | 6 | | 20 |
| Nail creams and lotions | 18* | 1 | >1–50* | 0.3–3 |
| Nail polish and enamel | | — | | 15 |
| Bath soaps and detergents | | 11 | | 0.01–4 |
| Underarm deodorants | 23* | 4 | >0.1–5* | 0.2 |
| Personal cleanliness products (other) | | 7 | | — |
| Aftershave lotion | — | 2 | — | 0.5 |
| Shaving cream | 31 | 11 | ≤0.1–5* | 0.5–2 |
| Skin-cleansing creams, lotions, liquids, etc. | | 48 | | 0.1–3 |
| Depilatories | | 3 | | — |
| Face and neck skin care preparations | | 26 | | 2–4 |
| Body and hand skin care preparations | | 88 | | 2–37 |
| Moisturizers | 531* | 56 | ≤0.1–>50* | 0.2–11 |
| Night skin care preparations | | 32 | | 0.5–10 |
| Paste masks (mud packs) | | 12 | | 16 |
| Skin care preparations (other) | | 51 | | 22 |
| Suntan gels, creams, and liquids | | 11 | | — |
| Indoor tanning preparations | 31* | 7 | >0.1–50* | 2 |
| Suntan preparations (other) | | 1 | | — |
| **Total uses/ranges for Lanolin** | 2384 | 774 | ≤0.1–>50 | 0.001–37 |
| | | *Lanolin Acid* | | |
| Eyeliner | | 3 | | — |
| Eye shadow | | 4 | | — |
| Mascara | 23* | 13 | >0.1–10* | 3 |
| Eye makeup (other) | | 1 | | — |
| Hair conditioners | | 4 | | — |
| Hair straighteners | 2* | 3 | >1–5* | — |
| Hair-coloring preparations (other) | — | 1 | — | — |
| Foundations | | 2 | | — |
| Lipsticks | 13* | 2 | >0.1–10* | - |
| Makeup (other) | | 1 | | — |
| Nail care preparations | 2 | — | >1–5 | — |
| Shaving cream | 1 | 3 | >0.1–1 | — |

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Historical and current cosmetic product uses and concentrations for Acetylated Lanolin, Acetylated Lanolin Alcohol, Hydrogenated Lanolin, Hydroxylated Lanolin, Lanolin (anhydrous), Lanolin Acid, Lanolin Alcohol, Lanolin Oil, and Lanolin Wax *(Continued)*

| Product category | 1976 uses (Elder 1980) | 2002 uses (FDA 2002) | 1976 concentrations (Elder 1980) (%) | 2003 concentrations (CTFA 2003) (%) |
|---|---|---|---|---|
| Moisturizers | | 4 | | — |
| Night skin care preparations | 10* | 1 | >0.1–10* | — |
| Skin care preparations (other) | | 1 | | 1 |
| Suntan gels, creams, and liquids | — | 1 | — | — |
| **Total uses/ranges for Lanolin Acid** | 51 | 44 | >0.1–10 | 1–3 |
| | | *Lanolin Alcohol* | | |
| Baby lotions, oils, powders, and creams | 2 | 2 | >0.1–5 | — |
| Bath oils, tablets, and salts | 28 | 7 | >0.1–10 | — |
| Eyebrow pencils | | 1 | | — |
| Eyeliner | | 1 | | — |
| Eye shadow | | 27 | | — |
| Eye makeup remover | 120* | 3 | >0.1–25* | — |
| Mascara | | 1 | | — |
| Eye makeup (other) | | 7 | | — |
| Colognes and toilet waters | 13 | — | >0.1–25 | — |
| Fragrance preparations (other) | — | 5 | — | — |
| Hair conditioners | | 8 | | — |
| Hair sprays (aerosol fixatives) | 15* | 1 | ≤0.1–25* | — |
| Hair tonics, dressings, etc. | | 2 | | — |
| Hair preparations (other) | | 3 | | — |
| Hair-coloring preparations (other) | 4 | 1 | >0.1–1 | 4 |
| Blushers (all types) | | 16 | | — |
| Face powders | | 7 | | — |
| Foundations | | 28 | | — |
| Lipsticks | 422* | 18 | ≤0.1–25* | — |
| Makeup bases | | 22 | | — |
| Makeup fixatives | | 4 | | — |
| Makeup (other) | | 7 | | — |
| Cuticle softeners | — | 1 | — | — |
| Bath soaps and detergents | | 3 | | — |
| Feminine deodorants | 6* | 2 | ≤0.1–5* | — |
| Other personal cleanliness products | | 1 | | — |
| Aftershave lotions | | 3 | | — |
| Shaving cream | 7* | 6 | >0.1–5* | — |
| Shaving preparation products (other) | | 6 | | — |
| Skin-cleansing creams, lotions, liquids, etc. | | 10 | | — |
| Depilatories | | 1 | | — |
| Face and neck skin care preparations | | 9 | | — |
| Body and hand skin care preparations | | 52 | | 0.6 |
| Moisturizers | 115* | 40 | >0.1–>50* | — |
| Night skin care preparations | | 19 | | — |
| Paste masks (mud packs) | | 7 | | — |
| Skin care preparations (other) | | 10 | | — |
| Suntan gels, creams, and liquids | | 12 | | — |
| Indoor tanning preparations | 6* | 2 | >0.1–5* | — |

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**TABLE 1**
Historical and current cosmetic product uses and concentrations for Acetylated Lanolin, Acetylated Lanolin Alcohol, Hydrogenated Lanolin, Hydroxylated Lanolin, Lanolin (anhydrous), Lanolin Acid, Lanolin Alcohol, Lanolin Oil, and Lanolin Wax *(Continued)*

| Product category | 1976 uses (Elder 1980) | 2002 uses (FDA 2002) | 1976 concentrations (Elder 1980) (%) | 2003 concentrations (CTFA 2003) (%) |
|---|---|---|---|---|
| Suntan preparations (other) | | 3 | | — |
| **Total uses/ranges for Lanolin Alcohols** | 738 | 337 | ≤0.1–>50 | 0.6–4 |
| | | *Lanolin Oil* | | |
| Baby lotions, oils, powders, and creams | 6 | 1 | >0.1–5 | 1 |
| Bath oils, tablets, and salts | | 9 | | 0.1 |
| Bubble baths | 44* | 1 | ≤0.1–25* | — |
| Bath preparations (other) | | 1 | | 3 |
| Eyebrow pencils | | 2 | | 1 |
| Eyeliner | | 8 | | 2–10 |
| Eye shadow | | 55 | | 3–6 |
| Eye makeup remover | 135* | 1 | ≤0.1–50* | — |
| Mascara | | 1 | | 1–3 |
| Eye makeup (other) | | 5 | | 6 |
| Powders (273) | — | 1 | — | — |
| Colognes and toilet waters | 9 | | >0.1–5 | |
| Fragrance preparations | — | 4 | — | — |
| Hair conditioners | | 5 | | 0.4–2 |
| Permanent waves | 17* | 1 | ≤0.1–5* | 1 |
| Shampoo (noncoloring) | | 4 | | 0.3 |
| Tonics, dressings, and other hair-grooming aids | | — | | 0.5–2 |
| Hair bleaches | 9* | 11 | ≤0.1–5* | — |
| Hair color sprays (aerosol) | | 1 | | 0.8 |
| Blushers (all types) | | 11 | | 2–12 |
| Face powders | | 12 | | 2 |
| Foundations | | 10 | | 0.7–2 |
| Lipsticks | 887* | 226 | >0.1–>50* | 3–65 |
| Makeup bases | | 10 | | 0.4 |
| Makeup fixatives | | 1 | | — |
| Makeup (other) | | 8 | | 20–45 |
| Nail basecoats and undercoats | | 2 | | — |
| Cuticle softeners | | 2 | | 2 |
| Nail creams and lotions | 10* | 1 | >0.1–50* | 5 |
| Nail care preparations (other) | | 1 | | 3–25 |
| Bath soaps and detergents | 3* | 9 | >1–5* | — |
| Underarm deodorants | | 1 | | — |
| Shaving cream | 2 | 4 | >0.1–5 | 2 |
| Skin-cleansing creams, lotions, liquids, etc. | | 12 | | 3 |
| Face and neck skin care preparations | | 4 | | 3 |
| Body and hand skin care preparations | | 27 | | |
| Moisturizers | 218* | 37 | ≤0.1–50* | 2 |
| Night skin care preparations | | 6 | | 1 |
| Paste mask (mud packs) | | 1 | | 18 |
| Skin care preparations (other) | | 14 | | 10 |
| Suntan gels, creams, and liquids | | 6 | | 8 |
| Indoor tanning preparations | 16* | 1 | >0.1–10* | — |

*(Continued on next page)*

**TABLE 1**
Historical and current cosmetic product uses and concentrations for Acetylated Lanolin, Acetylated Lanolin Alcohol, Hydrogenated Lanolin, Hydroxylated Lanolin, Lanolin (anhydrous), Lanolin Acid, Lanolin Alcohol, Lanolin Oil, and Lanolin Wax *(Continued)*

| Product category | 1976 uses (Elder 1980) | 2002 uses (FDA 2002) | 1976 concentrations (Elder 1980) (%) | 2003 concentrations (CTFA 2003) (%) |
|---|---|---|---|---|
| Other suntan preparations | | 4 | | 1 |
| **Total uses/ranges for Lanolin Oil** | 1256 | 532 | ≤0.1–50 | 0.1–65 |
| | | *Lanolin Wax* | | |
| Eyeliner | | 4 | | 4 |
| Eye shadow | 41* | 1 | >0.1–25* | 4 |
| Mascara | | 6 | | 2 |
| Colognes and toilet waters | 11 | | >1–25 | |
| Hair tonics, dressings, etc. | 3 | 4 | >0.1–1 | — |
| Blushers (all types) | | 2 | | 4 |
| Face powders | | 1 | | — |
| Foundations | 69* | 2 | ≤0.1–50* | 4 |
| Lipsticks | | 56 | | 20–23 |
| Makeup preparations (other) | | 1 | | 0.5 |
| Manicuring preparations | 1 | — | >1–5 | — |
| Shaving preparations | 1 | — | >1–5 | — |
| Skin-cleansing creams, lotions, liquids, etc. | | 2 | | — |
| Body and hand skin care preparations | | 3 | | 0.5 |
| Moisturizers | | 6 | | — |
| Night skin care preparations | 9* | 2 | >0.1–5* | — |
| Paste masks (mud packs) | | 1 | | — |
| Skin care preparations (other) | | 4 | | — |
| Suntan gels, creams, and liquids | 2* | 1 | >10–25* | — |
| Suntan preparations (other) | | 1 | | — |
| **Total uses/ranges for Lanolin Wax** | 157 | 97 | ≤0.1–50* | 0.5–25 |

*In the original safety assessment, information on frequency of use and concentration of use was provided only as a function of broad product categories, e.g., baby products, skin care preparations, etc.

range of >0.1% to 50% in skin care and suntan and sunscreen preparations. Currently Acetylated Lanolin Alcohol is used in 251 products at a maximum use concentration of 16% in baby lotions, oils, etc. Table 1 provides the available use information.

**Hydrogenated Lanolin** is the end product of controlled hydrogenation of Lanolin (q.v.) which is used as a fragrance ingredient, hair conditioning agent, and skin-conditioning agent—occlusive. It was used in 95 cosmetic products in 1976, with the highest concentration range of >1% to 25% in makeup preparations. Currently Hydrogenated Lanolin is used in 111 products at a maximum use concentration of 10% in face and neck skin care preparations. Table 1 provides the available use information.

**Hydroxylated Lanolin** is the product obtained by controlled hydroxylation of Lanolin (q.v.) and is used as a binder and skin-conditioning agent—miscellaneous. It was used in 12 cosmetic products in 1976, with the highest concentration range of >5% to 25% in makeup preparations. Currently Hydroxylated lanolin is used in 141 products at a maximum use concentration of 28% in lipsticks. Table 1 provides the available use information.

**Lanolin** is the refined derivative of the fat-like sebaceous secretion of sheep. It consists of a highly complex mixture of esters of high-molecular-weight aliphatic, steroids or triterpenoid alcohols, and fatty acids. Lanolin functions as an emulsion-stabilizer agent, hair-conditioning agent, skin-conditioning agent, and skin-protectant agent. Lanolin is an active ingredient is over-the-counter (OTC) drug products as well. In 1976 there were 2384 uses (as Lanolin-anhydrous) at a maximum concentration of >50% in several product categories. Currently, Lanolin (as Lanolin and Lanolin-anhydrous) is used in 774 products at a maximum use concentration of 37% in body and hand skin care preparations. Table 1 provides the available use information.

**Lanolin Acid** is a mixture of organic acids obtained from the hydrolysis of Lanolin (q.v.) and functions as a surfactant-cleansing agent. It was used in 51 cosmetic products in 1976, with the highest concentration range of >1% to 10% in eye

makeup, makeup and skin care preparations. Currently Lanolin Acid is used in 44 products at a maximum use concentration of 3% in mascara. Table 1 provides the available use information.

**Lanolin Alcohols** are a mixture of organic alcohols obtained from the hydrolysis of Lanolin (q.v.). These are used as emulsion stabilizer agent, hair conditioning agent, binder, and nonaqueous viscosity increasing agents. These were used in 738 cosmetic products in 1976, with the highest concentration range of >0.1% to 50% in skin care preparations. Currently Lanolin Alcohols are used in 337 products at a maximum use concentration of 4% in hair coloring preparations (other). Table 1 provides the available use information.

**Lanolin Oil** is the liquid fraction obtained by physical means from whole Lanolin which is used as skin-conditioning agent-emollient and hair conditioning agent. It was used in 1256 cosmetic products in 1976, with the highest concentration range of >0.1% to >50% in makeup preparations. Currently Lanolin oil is used in 532 products at a maximum use concentration of 65% in lipsticks. Table 1 provides the available use information.

**Lanolin Wax** is the semisolid fraction obtained by physical means from whole Lanolin (Pepe et al. 2002). It is used as hair conditioning agent, skin-conditioning agents—emollient, nonaqueous viscosity-increasing agents, and binder. It was used in 157 cosmetic products in 1976, with the highest concentration range of ≤0.1% to 50% in makeup preparations. Currently Lanolin Wax is used in 97 products at a maximum use concentration of 23% in lipsticks. Table 1 provides the available use information.

## REFERENCES


Andersen, F. A. ed. 1998. Final report on the safety assessment of Mink oil. *Int. J. Toxicol.* 17:71–82.

Bower, D. 1999. Unpublished information on hair spray particle sizes provided at the September 9, 1999 CIR Expert Panel meeting.[2]

Clark, E. W. 1980. A brief history of lanolin. *Pharm. Hist. (Lond)*. 10:5–6.

Cooper, T. P. 2002. Use of EMLA cream with vasectomy. *Urology* 60:135–137.

CTFA. 2003. Concentration of use data for lanolin and related compounds. Unpublished data submitted by CTFA, February 6, 2003. 7 pages.[2]

Culviner, W. T., D. W. Leonard, C. L. Wilhelmsen, and W. E. Bolger. 2000. Experimental myospherulosis of the paranasal sinuses: A histologic rabbit study. *Am. J. Rhinol.* 14:131–137.

DeLeo, V. A., S. C. Taylor, D. V . Belsito, J. F. Fowler, Jr., A. F. Fransway, H. I. Maibach, J. G. Marks, Jr., C. G. Mathias, J. R. Nethercott, M. D. Pratt, R. R. Reitschel, E. F. Sherertz, F. J. Storrs, and J. S. Taylor. 2002. The effect of race and ethnicity on patch test results. *J. Am. Acad Dermatol*. 46:S107–S112.

Elder, R. L., ed. 1980. Final report on safety assessment of Acetylated Lanolin, Acetylated Lanolin Alcohol, Hydrogenated Lanolin, Hydroxylated Lanolin, Lanolin (anhydrous), Lanolin Acid, Lanolin Alcohol, Lanolin Oil, and Lanolin Wax. *J. Environ. Pathol. Toxicol.* 4:63–92.

Giordano-Labadie, F., F. Rance, F. Pellegrin, J. Bazex, G. Dutau, and H. P. Schwarze. 1999. Frequency of contact allergy in children with atopic dermatitis: Results of a prospective study of 137 cases. *Contact Dermatitis* 40:192–195.

Heikes, D. L., and J. C. Craun. 1992. Rapid multiresidue procedure for the determination of pesticides in anhydrous lanolin and lanolin-containing pharmaceutical preparations utilizing gel permeation chromatography cleanup with gas chromatographic and mass spectrometric techniques. *J. Agric. Food Chem*. 40:1588–1590.

Hoppe, U., ed. 1999. *The Lanolin book.* Hamburg: Beiersdorf.

Jensen P. A., and D. O'Brien. 1993. Industrial Hygiene. In *Aerosol measurement. Principles techniques and applications*, ed. K. Willeke, P. A. Baron, 538–540. New York: John Wiley and Sons.

Jover, E., and J. M. Bayona. 2002. Trace level determination of organochlorine, organophosphorus and pyrethroid pesticides in lanolin using gel permeation chromatography followed by dual gas chromatography and gas chromatography-negative chemical ionization mass spectrometric confirmation. *J. Chromatogr. A* 950:213–220.

Jover, E., Z. Moldovan, and J. M. Bayona. 2002. Complete characterisation of lanolin steryl esters by sub-ambient pressure gas chromatography–mass spectrometry in the electron impact and chemical ionisation modes. *J. Chromatogr. A* 970:249–258.

Kligman, A. M. 1998. The myth of lanolin allergy. *Contact Dermatitis* 39:103–107.

Lopez-Mesas, M., M. Crespi, J. Brach, and J. P. Mullender. 2000. Clean-up of a pesticide-lanolin mixture by gel permeation chromatography. *J . Chromatogr. Sci.* 38:551–555.

Marks, J. M., D. V. Belsito, V. A. DeLeo, J. F. Fowler, A. F. Fransway, H. I. Maibach, C. G. Toby Mathias, M. D. Pratt, R. L. Reitschel, E. F. Sherertz, F. J. Storrs, and J. S. Taylor. 2000. North American contact dermatitis group patch-test results, 1996–1998. *Arch Dermatol*. 136:272–273.

Marks, J. M., D. V. Belsito, V. A. DeLeo, et al. 2003. North American Contact Dermatitis group patch-test results, 1998–2000. *Am. J. Contact Dermat*. 14:59–62.

Polese, L., M. Sannomiya, A. P. de Olivera Sader, and M. Lucia Ribeiro. 2000. Extraction and clean-up procedure for analysis of organochlorine pesticide residues in ethoxylated lanolin. *Farmacologie* 55:637–640.

Stone, L. 2000. Medilan: A hypoallergenic lanolin for emollient therapy. *Br. J. Nurs.* 9:54–57.

Suleyman, F. 2000. Role of lanolin in managing eczema and dry skin conditions. *Community Nurse* 6:30–31.

Takano, S., M. Yamanaka, K. Okamoto, and F. Saito. 1983. Allergens of lanolin. Part 1. Isolation and identification of the allergens of hydrogenated lanolin. Part 2. Allergenicity of synthetic alkane-alpha-beta-diols and alkane-alpha,omega-diols. *J. Soc. Cosmet. Chem.* 34:99–125.

Trummer, M., W. Aberer, and B. Kranke. 2002. Clinical relevance of + patch test reactions to lanolin alcohol. *Contact Dermatitis* 46:118.

Uter, W., J. Geier, M. Land, A. Pfahlberg, O. Gefeller, and A. Schnuch. 2001. Another look at seasonal variation in patch test results. A multifactorial analysis of surveillance data of the IVDK. Information Network of Departments of Dermatology. *Contact Dermatitis* 44:146–152.

Uter, W., J. Geier, A. Pfahlberg, and I. Effendy. 2002. The spectrum of contact allergy in elderly patients with and without lower leg dermatitis. *Dermatology* 204:266–272.

Wakelin, S. H., H. Smith, I. R. White, R. J. Rycroft, and J. P. McFadden. 2001. A retrospective analysis of contact allergy to lanolin. *Br. J. Dermatol*. 145:28–31.

Zhai, H., P. Willard, and H. I. Maibach.1998. Evaluating skin-protective materials against contact irritants and allergens. An in vivo screening human model. *Contact Dermatitis* 38:155–158.


[2]Avilable for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036-4702, USA.

## BENZOPHENONE AND BENZOPHENONE-1, -2, -3, -4, -5, -6, -7, -8, -9, -10, -11, AND -12

A safety assessment of Benzophenone-1, -3, -4, -5, -9, and -11 was published in 1983 with the conclusion "safe for topical application to humans in the present practices of use and

concentration in cosmetics" (Elder 1983a). An addendum to this safety assessment, addressing the mutagenicity/genotoxicity of Benzophenone-2, -6, and -8, was also published in 1983 with a conclusion stating that they are not mutagenic or genotoxic, but are safe for topical application to humans in the present practices of use and concentration in cosmetics (Elder 1983b). Studies available since the safety assessment and addendum were completed (listed at the end of this section), along with the updated information regarding uses and use concentrations, were considered. The Panel determined to not reopen this safety assessment.

The CIR Expert Panel's discussion focused on National Toxicology Program (NTP) carcinogenicity studies on Benzophenone and Benzophenone-3. An NTP 2-year carcinogenicity study on Benzophenone was initiated in 1999, and the pathology quality assessment for this study is ongoing. Benzophenone-3 is listed among the chemicals that NTP has assigned to a laboratory for toxicology/carcinogenesis testing. The Panel determined to not reopen its safety assessment until results from the NTP carcinogenicity studies are available.

In 1976, Benzophenones were used in 1044 cosmetic products, typically at concentrations ≤0.1%. Currently, there are uses reported in 1008 products, typically at concentrations <1%. Table 2 presents the available use information.

**TABLE 2**
Historical and current cosmetic product uses and concentrations for Benzophenones

| Product category | 1976 use (Elder 1983) | 2002 use (FDA 2002) | 1976 concentrations (Elder 1983) (%) | 2002 concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| | | *Benzophenone-1* | | |
| Bath oils, tablets, and salts | 1 | — | ≤0.1 | — |
| Bubble baths | 2 | — | ≤0.1 | — |
| Colognes and toilet waters | 3 | 1 | ≤0.1 | 0.2–1 |
| Perfumes | — | 1 | — | 0.1–1 |
| Fragrance preparations (other) | 5 | — | ≤0.1 | 1 |
| Shampoos (noncoloring) | 7 | — | ≤0.1 | 0.05 |
| Hair tonics, dressings, etc. | 2 | 1 | ≤0.1–1 | — |
| Wave sets | 4 | — | ≤0.1 | — |
| Hair preparations (other) | 1 | 3 | ≤0.1 | — |
| Blushers (all types) | 1 | — | >0.1–1 | — |
| Lipstick | 7 | 1 | >0.1–1 | 0.2 |
| Nail basecoats and undercoats | 5 | 23 | ≤0.1–1 | 0.4–0.8 |
| Nail creams and lotions | — | 2 | — | — |
| Nail polish and enamel | 87 | 75 | ≤0.1–1 | 0.1–2 |
| Nail polish and enamel removers | — | 8 | — | — |
| Nail care preparations (other) | 4 | 11 | ≤0.1–1 | 0.1 |
| Aftershave lotions | 6 | — | ≤0.1 | 0.2–0.5 |
| Beard softeners (category omitted in 2002) | 2 | — | ≤0.1 | — |
| **Total uses/ranges for Benzophenone-1** | **113** | **127** | **≤0.1–1** | **0.05–2** |
| | | *Benzophenone-2* | | |
| Bath oils, tablets, and salts | 3 | — | ≤0.1 | 0.1–0.2 |
| Bubble baths | 5 | 5 | ≤0.1–1 | 0.05–0.2 |
| Bath preparations (other) | 6 | 4 | ≤0.1 | 0.07–0.2 |
| Eye makeup remover | — | 1 | — | — |
| Colognes and toilet waters | 120 | 193 | ≤0.1–5 | 0.1–0.4 |
| Perfumes | 22 | 53 | ≤0.1–1 | 0.005–0.3 |
| Powders | — | 1 | — | — |
| Sachets | 4 | 1 | ≤0.1 | 0.2 |
| Other fragrance preparations | 15 | 18 | ≤0.1–1 | — |
| Hair conditioners | 2 | 3 | ≤0.1 | 0.1 |
| Hair sprays (aerosol fixatives) | — | 1 | — | 0.05 |

*(Continued on next page)*

**TABLE 2**
Historical and current cosmetic product uses and concentrations for Benzophenones *(Continued)*

| Product category | 1976 use (Elder 1983) | 2002 use (FDA 2002) | 1976 concentrations (Elder 1983) (%) | 2002 concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| Rinses (noncoloring) | 4 | — | ≤0.1 | 0.05 |
| Shampoos (noncoloring) | 14 | 4 | ≤0.1–1 | 0.1 |
| Hair tonics, dressings, etc. | 2 | — | ≤0.1 | 0.1 |
| Wave sets | 3 | — | >0.1–1 | — |
| Hair preparations (other) | — | 2 | — | 0.1 |
| Blushers (all types) | 3 | — | ≤0.1 | — |
| Lipsticks | — | 3 | — | — |
| Rouges | 1 | 1 | ≤0.1 | — |
| Makeup fixatives | 1 | — | ≤0.1 | — |
| Makeup preparations (other) | 4 | 1 | ≤0.1 | — |
| Nail polish and enamel removers | — | 1 | — | — |
| Bath soaps and detergents | — | 1 | — | 0.05–0.2 |
| Underarm deodorants | — | 1 | — | 0.1 |
| Douches | — | — | — | 0.1 |
| Feminine deodorants | 1 | — | ≤0.1 | — |
| Personal cleanliness products (other) | — | — | — | 0.1 |
| Aftershave lotions | 30 | 45 | ≤0.1–1 | 0.2 |
| Preshave lotions | 1 | 1 | ≤0.1 | 0.03–0.1 |
| Shaving preparation products (other) | — | 6 | — | 0.1 |
| Skin cleansing creams, lotions, liquids, and pads | 6 | 6 | ≤0.1–1 | 0.05–0.1 |
| Face and neck skin care preparations | | — | | — |
| Body and hand skin care preparations | 7* | 3 | ≤0.1* | 0.07–0.2 |
| Moisturizers | 9 | 2 | ≤0.1 | 0.1 |
| Night skin care preparations | — | — | — | 0.05 |
| Paste masks (mud packs) | 1 | 3 | ≤0.1 | 0.05 |
| Skin lighteners | 1 | N/A** | ≤0.1 | N/A** |
| Skin fresheners | 27 | 9 | ≤0.1 | 0.2% |
| Skin care preparations (other) | 5 | 11 | ≤0.1–1 | 0.1–0.2 |
| Suntan gels, creams, and liquids | — | — | — | 6 |
| **Total uses/ranges for Benzophenone-2** | **321** | **380** | **≤0.1–5** | **0.005–6** |
| | *Benzophenone-3* | | | |
| Baby shampoos | — | — | — | 0.01 |
| Baby lotions, oils, powders, and creams | — | — | — | 3 |
| Bath oils, tablets, and salts | 1 | 11 | ≤0.1 | 0.2–0.4 |
| Bubble baths | — | 1 | — | 0.1 |
| Bath preparations (other) | — | 18 | — | 0.2 |
| Eyeliner | — | 1 | — | — |
| Eye shadow | — | — | — | 0.5 |
| Eye makeup (other) | — | 1 | — | 0.2–0.4 |
| Colognes and toilet waters | 1 | 9 | >0.1–1 | 0.1–2 |
| Perfumes | 1 | 12 | ≤0.1 | 0.2–2 |
| Fragrance preparations (other) | — | 4 | — | 0.2–2 |
| Hair conditioners | — | 21 | — | 0.05–0.5 |
| Hair sprays | — | 13 | — | 0.01 |
| Shampoos | 1 | 13 | ≤0.1 | 0.01–0.3 |
| Hair tonics, dressings, etc. | — | 18 | — | 0.3–0.5 |
| Hair preparations (other) | — | 5 | — | 0.3 |

*(Continued on next page)*

**TABLE 2**
Historical and current cosmetic product uses and concentrations for Benzophenones *(Continued)*

| Product category | 1976 use (Elder 1983) | 2002 use (FDA 2002) | 1976 concentrations (Elder 1983) (%) | 2002 concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| Blushers | — | 1 | — | 1–6 |
| Face powders | — | 2 | — | 1–4 |
| Foundations | — | 28 | — | 0.1–3 |
| Lipsticks | — | 85 | — | 1–4 |
| Makeup bases | — | 3 | — | 1–2 |
| Makeup (other) | 1 | 4 | >0.1–1 | 0.1–3 |
| Nail basecoats and undercoats | — | 2 | — | 0.4–3 |
| Nail creams and lotions | — | 1 | — | — |
| Nail polish and enamel | 36 | 10 | >0.1–1 | 0.2–1 |
| Nail polish and enamel removers | — | 2 | — | 0.2–0.4 |
| Nail care preparations (other) | — | 1 | — | 0.2 |
| Bath soaps and detergents | — | 2 | — | 0.05–0.06 |
| Personal cleanliness products (other) | — | 1 | — | — |
| Aftershave lotions | 3 | 9 | >0.1–1 | 2–3 |
| Shaving cream | — | — | — | 0.2 |
| Shaving products (other) | — | — | — | 3 |
| Skin-cleansing creams, lotions, liquids, and pads | 2 | 1 | ≤0.1 | 0.05–0.2 |
| Face and neck skin care preparations | | 17 | | 0.3–5 |
| Body and hand skin care preparations | —* | 20 | —* | 2–5 |
| Moisturizers | — | 59 | — | 0.5–7 |
| Night skin care preparations | — | 1 | — | 1–2 |
| Skin fresheners | 1 | — | ≤0.1 | 0.005 |
| Skin care preparations (other) | — | 12 | — | 1–6 |
| Suntan gels, creams, and liquids | — | 47 | — | 1–6 |
| Indoor tanning preparations | — | 9 | — | 1–5 |
| Suntan preparations (other) | — | 8 | — | 3–6 |
| **Total uses/ranges for Benzophenone-3** | **62** | **451** | **≤0.1–1** | **0.005–7** |
| | *Benzophenone-4* | | | |
| Baby shampoos | 2 | 1 | ≤0.1 | 0.01 |
| Baby lotions, oils, powders, and creams | — | 1 | — | 0.2 |
| Bath oils, tablets, and salts | 11 | | ≤0.1 | 0.1 |
| Bubble baths | 2 | 4 | ≤0.1 | 0.1–0.2 |
| Bath capsules | — | 1 | — | — |
| Bath preparations (other) | 4 | 19 | ≤0.1 | 0.1–0.2 |
| Eye shadow | 1 | — | >0.1–1 | — |
| Eye lotion | — | 1 | — | — |
| Eye makeup remover | — | — | — | 0.05 |
| Eye makeup (other) | — | 1 | — | 0.01 |
| Colognes and toilet waters | 8 | — | ≤0.1 | 0.3 |
| Perfumes | — | 3 | — | 0.1 |
| Powders | — | 1 | — | — |
| Fragrance preparations (other) | 11 | 4 | ≤0.1 | 0.1–0.2 |
| Hair conditioners | 29 | 37 | ≤0.1–5 | 0.01–0.5 |
| Hair sprays (aerosol fixatives) | 1 | 18 | ≤0.1 | 0.1 |
| Hair straighteners | — | — | — | 0.01 |
| Permanent waves | 2 | 1 | ≤0.1 | — |

*(Continued on next page)*

**TABLE 2**
Historical and current cosmetic product uses and concentrations for Benzophenones *(Continued)*

| Product category | 1976 use (Elder 1983) | 2002 use (FDA 2002) | 1976 concentrations (Elder 1983) (%) | 2002 concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| Rinses (noncoloring) | 7 | 4 | ≤0.1 | — |
| Shampoos (noncoloring) | 45 | 48 | ≤0.1–5 | 0.01–0.5 |
| Hair tonics, dressings, etc. | 7 | 51 | ≤0.1–1 | 0.01–0.9 |
| Wave sets | 27 | 6 | ≤0.1–1 | 0.4 |
| Hair preparations (other) | 13 | 38 | ≤0.1 | 0.05–0.1 |
| Shampoos (coloring) | 1 | — | >0.1–1 | — |
| Hair-coloring preparations (other) | — | 2 | — | 0.04 |
| Blushers (all types) | 6 | — | ≤0.1–1 | 1 |
| Foundations | 1 | — | ≤0.1 | — |
| Leg and body paints | 1 | — | ≤0.1 | — |
| Makeup bases | 1 | — | >0.1–1 | — |
| Makeup (other) | 2 | 1 | >0.1–1 | 0.05–0.1 |
| Cuticle softeners | 2 | 1 | ≤0.1 | — |
| Nail polish and enamel removers | — | 2 | — | — |
| Nail care products (other) | — | 1 | — | — |
| Bath soaps and detergents | 2 | 18 | >0.1–1 | 0.05–0.5 |
| Underarm deodorants | — | 2 | — | 0.1–0.7 |
| Personal cleanliness products (other) | — | 6 | — | 0.05–0.3 |
| Aftershave lotion | 2 | 5 | ≤0.1 | 0.05–1 |
| Shaving products (other) | — | 2 | — | 0.1 |
| Skin-cleansing creams, lotions, liquids, and pads | 6 | 33 | ≤0.1–1 | 0.01–0.3 |
| Face and neck skin care preparations | 9* | 4 | ≤0.1* | 0.05–2.5 |
| Body and hand skin care preparations | | 20 | | 0.05–0.2 |
| Foot powders and sprays | — | 2 | — | 0.05 |
| Moisturizers | 21 | 33 | ≤0.1 | 0.1–1 |
| Night skin care | — | 1 | — | — |
| Paste masks (mud packs) | — | 1 | — | 0.1–0.2 |
| Skin fresheners | 5 | 16 | ≤0.1 | 0.05–2 |
| Skin care preparations (other) | 9 | 10 | ≤0.1–1 | 0.05–0.5 |
| Suntan gels, creams, and liquids | 2 | 1 | ≤0.1–10 | 2 |
| Suntan preparations (other) | — | — | — | 0.005 |
| **Total uses/ranges for Benzophenone-4** | **251** | **402** | **≤0.1–10** | **0.005–2.5** |
| | *Benzophenone-5* | | | |
| Eye shadow | — | 1 | — | — |
| Colognes and toilet waters | — | — | — | 0.2 |
| Shaving products (other) | — | 1 | — | — |
| Hair tonics, dressings, etc. | — | — | — | 0.2 |
| Skin-cleansing creams, lotions, liquids, and pads | — | 2 | — | — |
| Face and neck skin care preparations | 7* | — | ≤0.1* | — |
| Body and hand skin care preparations | | 6 | | 0.05 |
| Moisturizers | — | 3 | — | — |
| Night skin care preparations | 3 | 1 | ≤0.1 | 0.3 |
| Paste masks (mud packs) | — | 1 | — | — |
| Skin fresheners | — | 4 | — | — |
| **Total uses/ranges for Benzophenone-5** | **11** | **20** | **≤0.1** | **0.05–0.3** |

*(Continued on next page)*

**TABLE 2**
Historical and current cosmetic product uses and concentrations for Benzophenones *(Continued)*

| Product category | 1976 use (Elder 1983) | 2002 use (FDA 2002) | 1976 concentrations (Elder 1983) (%) | 2002 concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| | *Benzophenone-6* | | | |
| Bath oils, tablets, and salts | 2 | 1 | ≤0.1 | — |
| Eye makeup remover | — | 1 | — | — |
| Colognes and toilet waters | 1 | 1 | ≤0.1 | 0.2 |
| Perfumes | 2 | 3 | ≤0.1–1 | 0.2 |
| Shampoos (noncoloring) | 1 | — | ≤0.1 | — |
| Hair tonics, dressings, etc. | 1 | 2 | ≤0.1 | — |
| Wave sets | 2 | — | ≤0.1 | — |
| Cuticle softeners | 1 | — | ≤0.1 | — |
| Nail polish and enamel | 77 | | >0.1–1 | 0.3 |
| Aftershave lotion | — | 1 | — | 0.1 |
| Skin-cleansing creams, lotions, liquids, and pads | 1 | — | ≤0.1 | — |
| Face and neck skin care preparations | | — | | 0.07 |
| Body and hand skin care preparations | —* | 1 | —* | — |
| Moisturizers | 2 | — | ≤0.1–1 | — |
| Skin care preparations (other) | — | 1 | — | — |
| **Total uses/ranges for Benzophenone-6** | **106** | **11** | **≤0.1–1** | **0.07–0.3** |
| | *Benzophenone-8* | | | |
| Bath oils, tablets, and salts | 1 | — | >0.1–1 | — |
| Bubble baths | — | 2 | — | — |
| Bath preparations (other) | — | 1 | — | — |
| Colognes and toilet waters | — | 2 | — | — |
| Hair conditioners | 2 | — | >0.1–1 | — |
| Personal cleanliness products (other) | — | 2 | — | — |
| Moisturizers | 1 | — | ≤0.1 | — |
| Skin care preparations (other) | — | — | — | 0.2 |
| **Total uses/ranges for Benzopheone-8** | **3** | **7** | **≤0.1–1** | **0.2** |
| | *Benzophenone-9* | | | |
| Baby products (other) | — | — | — | 0.2 |
| Bath oils, tablets, and salts | — | — | — | 0.1 |
| Bubble baths | 20 | 6 | ≤0.1 | 0.1–0.2 |
| Bath capsules | 1 | — | ≤0.1 | — |
| Bath preparations (other) | 34 | 14 | ≤0.1 | 0.1–0.2 |
| Colognes and toilet waters | 2 | 4 | ≤0.1–1 | 0.1–0.2 |
| Perfumes | 1 | — | >0.1–1 | — |
| Sachets | — | — | — | 0.1 |
| Fragrance preparations (other) | 1 | 1 | ≤0.1 | 0.2 |
| Hair conditioners | 9 | 1 | ≤0.1–1 | 0.1–0.2 |
| Rinses (noncoloring) | 3 | — | ≤0.1 | 0.05 |
| Shampoos (noncoloring) | 8 | 3 | ≤0.1–1 | 0.1 |
| Hair tonics, dressings, etc. | 1 | 1 | ≤0.1 | 0.03 |
| Wave sets | 2 | — | ≤0.1 | 0.2 |
| Hair preparations (other noncoloring) | 1 | — | ≤0.1 | — |
| Hair-coloring preparations (other) | — | — | — | 0.4 |
| Blushers | 1 | — | ≤0.1 | — |
| Makeup bases | 1 | 1 | >0.1–1 | — |

*(Continued on next page)*

**TABLE 2**
Historical and current cosmetic product uses and concentrations for Benzophenones *(Continued)*

| Product category | 1976 use (Elder 1983) | 2002 use (FDA 2002) | 1976 concentrations (Elder 1983) (%) | 2002 concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| Rouges | 1 | — | ≤0.1 | — |
| Makeup (other) | — | — | — | 0.05 |
| Nail basecoats and undercoats | 1 | — | ≤0.1 | — |
| Cuticle softeners | 1 | — | ≤0.1 | — |
| Nail creams and lotions | 1 | — | ≤0.1 | — |
| Bath soaps and detergents | — | 8 | — | 0.05–0.2 |
| Underarm deodorants | — | — | — | 0.1 |
| Personal cleanliness products (other) | — | — | — | 0.1 |
| Aftershave lotion | 3 | 2 | ≤0.1–1 | 0.1–0.2 |
| Shaving preparations (other) | — | — | — | 0.09 |
| Skin-cleansing creams, lotions, liquids, and pads | 4 | 1 | ≤0.1–1 | — |
| Face and neck skin care preparations | 14* | — | | 0.3 |
| Body and hand skin care preparations | | 2 | ≤0.1–1* | 0.1–0.3 |
| Moisturizers | 2 | 4 | ≤0.1 | 0.05 |
| Night skin care preparations | — | — | — | 0.05 |
| Skin fresheners | 9 | 2 | ≤0.1–1 | 0.1 |
| Skin care preparations (other) | 1 | 1 | ≤0.1 | 0.1 |
| Suntan gels, creams, and liquids | 1 | — | ≤0.1–1 | — |
| Suntan preparations (other) | — | 2 | — | — |
| **Total uses/ranges for Benzophenone-9** | **85** | **53** | **≤0.1–1** | **0.05–0.4** |
| | *Benzophenone-11* | | | |
| Bath oils, tablets, and salts | 4 | 2 | ≤0.1–1 | — |
| Bubble baths | 4 | — | ≤0.1 | — |
| Bath preparations (other) | 1 | — | ≤0.1 | — |
| Colognes and toilet waters | 59 | 3 | ≤0.1–1 | 0.2 |
| Perfumes | 14 | 2 | ≤0.1 | 0.1 |
| Sachets | 7 | — | ≤0.1 | — |
| Fragrance preparations (other) | 8 | — | ≤0.1 | — |
| Hair sprays (aerosol fixatives) | 4 | — | ≤0.1–5 | — |
| Shampoos | 13 | — | ≤0.1 | — |
| Hair tonics, dressings, etc. | 2 | — | >0.1–1 | 0.2 |
| Wave sets | 2 | — | ≤0.1 | — |
| Blushers | 1 | — | ≤0.1 | — |
| Nail polish and enamel | 3 | — | ≤0.1 | — |
| Bath soaps and detergents | 3 | — | ≤0.1 | — |
| Underarm deodorants | — | — | — | 0.1 |
| Aftershave lotion | 16 | 1 | ≤0.1 | 0.2 |
| Preshave lotions (all types) | 1 | — | ≤0.1 | 0.1 |
| Face and neck skin care preparations | 2* | — | ≤0.1* | — |
| Body and hand skin care preparations | | — | | — |
| Moisturizers | 12 | — | ≤0.1 | — |
| Skin fresheners | 11 | — | ≤0.1 | — |
| Skin care preparations (other) | 1 | — | ≤0.1 | — |
| **Total uses/ranges for Benzophenone-11** | **103** | **8** | **≤0.1–5** | **0.1–0.2** |

*These categories were combined when the original safety assessment was performed and are now separate categories.
**No longer considered a cosmetic product category.

## REFERENCES


Abdel-Nabi, I. M., A. M. Kadry, R. A. Davis, and M. S. Abdel-Rahman. 1992. Development and validation of a high-performance liquid chromatographic method for the determination of benzophenone-3 in rats. *J. Appl. Toxicol.* 12:255–259.

Alanko, K., R. Jolanki, T. Estlander, and L. Kanerva. 2001. Occupational allergic contact dermatitis from benzophenone-4 in hair-care products. *Contact Dermatitis* 44:188.

Berne, B., and A. M. Ros. 1998. 7 years of photopatch testing with sunscreen allergens in Sweden. *Contact Dermatitis* 38:61–64.

BIBRA Toxicology International. 1995. BIBRA Working Group. Toxicity profile. Benzophenone. 5 pages.[3]

Bilsland, D., and J. Ferguson. 1993. Contact allergy to sunscreen chemicals in photosensitivity dermatitis/actinic reticuloid syndrome (PD/AR) and polymorphic light eruption (PLE). *Contact Dermatitis* 29:70–73.

Boehncke, W. H., M. Schmitt, T. M. Zollner, and O. Hensel. 1997. Nail varnish allergy. An important differential diagnosis in contact dermatitis. *Dtsch. Med. Wochenschr.* 122:849–852.

Bosca, F., and M. A. Miranda. 1998. Photosensitizing drugs containing the benzophenone chromophore. *J. Photochem. Photobiol.* 43:1–26.

Bronaugh, R. L., R. C. Wester, D. Bucks, H. I. Maibach, and R. Sarason. 1990. In vivo percutaneous absorption of fragrance ingredients in rhesus monkey and humans. *Food Chem. Toxicol.* 28:369–373.

Burdock, G. A., D. H. Pence, and R. A. Ford. 1991. Safety evaluation of benzophenone. *Food Chem. Toxicol.* 29:741–750.

Chew, S., V. A. DeLeo, and L. C. Harber. 1987. An animal model for evaluation of topical photoprotection against ultraviolet A (320–380 nm) radiation. *J. Invest. Dermatol.* 89:410–414.

Collins, P., and J. Ferguson. 1994. Photoallergic contact dermatitis to oxybenzone. *B. J. Dermatol.* 131:124–129.

Cook, N., and S. Freeman. 2001. Report of 19 cases of photoallergic contact dermatitis to sunscreens seen at the Skin and Cancer Foundation. *Australas J. Dermatol.* 42:257–259.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2002. Use concentration data on benzophenones from industry survey. Unpublished data submitted by CTFA, June 26, 2002. 7 pages.[3]

Couteau, C., N. Perez Cullel, A. E. Connan, and L. J. Coiffard. 2001. Stripping method to quantify absorption of two sunscreens in human. *Int. J. Pharm.* 322:153–157.

Darvay, A., I. R. White, R. J. Rycroft, A. B. Jones, J. L. Hawk, and J. P. McFadden. 2001. Photoallergic contact dermatitis is uncommon. *Br. J. Dermatol.* 145:597–601.

DeLeo, V. A., S. M. Suarez, and M. J. Maso. 1992. Photoallergic contact dermatitis. *Arch. Dermatol.* 128:1513–1518.

Douki, T., and J. Cadet. 1999. Modification of DNA bases by photo sensitized one-electron oxidation. *Int. J. Radiat. Biol.* 75:571–581.

Duguid, C., D. O'Sullivan, and G. M. Murphy. 1993. Determination of threshold UV-A elicitation dose in photopatch testing. *Contact Dermatitis* 29:192–194.

Dutta, K., M. Das, and T. Rahman. 1993. Toxicological impacts of benzophenone on the liver of guinea pig (Cavia porcellus). *Bull. Environ. Contam. Toxicol.* 50:282–285.

Elder, R. L. ed. 1983a. Final report on the safety assessment of Benzophenones-1, -3, -4, -5, -9, and -11. *J. Am. Col. Toxicol.* 2:35–77.

Elder, R. L. ed. 1983b. Addendum to the final report on the safety assessment of Benzophenones-1, -3, -4, -5, -9, and -11 to include Benzophenones-2, -6, and -8. *J. Am. Col. Toxicol.* 2:79–84.

Elmets, C. A., A. Vargas, and C. Oresajo. 1992. Photoprotective effects of sunscreens in cosmetics on sunburn and Langerhans cell photodamage. *Photodermatol. Photoimmunol. Photomed.* 9:113–120.

English, J. S., I. R. White, and E. Cronin. 1987. Sensitivity to sunscreens. *Contact Dermatitis* 17:159–162.

Environmental Protection Agency (EPA). (1976) Initial submission: Letter from Upjohn Co to USEPA Re: Production, processing, safety & handling, and toxicity of benzophenone with attachments. Acute oral toxicity (rats), and ocular irritation and dermal irritation studies (rabbits). EPA/OTS Report No. FYI-OTS-0794-0987.

EPA. 1978. Initial submission: Letter from Upjohn Co to USEPA Re: Production, processing, safety & handling, and toxicity of benzophenone with attachments. Bacterial mutagenicity testing. EPA/OTS Report No. FYI-OTS-0794-0987.

EPA. 1990. Preliminary assessment for an epidemiologic study on employees at the North Haven Fine Chemicals Plant (Final Report) with cover letter dated 060790. EPA/OTS Report No. 89-0000042.

EPA. 1980a. Initial submission: Salmonella/Mammalian Microsome plate incorporation assay with cover letter dated 081492. EPA/OTS Report No. 88-920007764.

EPA. 1980b. Initial submission: Test for chemical induction of mutation in mammalian cells in culture. The 2,2′-dihydroxy-4 methoxy benzophenone mouse lymphoma assay with cover letter dated 081492. EPA/OTS Report No. OTS 88-920006804.

EPA. 2001. Initial submission: TK 10050 (Chimassorb 81). Contact hypersensitivity in albino guinea pigs. Maximization-test, with cover letter dated 6/4/2001. EPA/OTS Report Number 88-010000159.

European Economic Community. 1999. EEC Cosmetics Directive 76/768/EEC, as amended through the 26th Adapting Commission Directive 2002/34/EC, Annexes I-VII. Brussels: EEC.

Felix, T., B. J. Hall, and J. S. Brodbelt. 1998. Determination of benzophenone-3 metabolites in water and human urine by solid-phase microextraction and quadruple ion trap GC-MS. *Anal. Chim. Acta* 371:195–203.

Fernandez, C., G. Marti-Mestres, J. P. Mestres, and H. Maillols. 2000. LC analysis of benzophenone-3 in pigskin and in saline solution: Application to determination of in vitro skin penetration. *J. Pharm. Biomed. Anal.* 22:393–402.

Fernandez, C., F. Nielloud, R. Fortune, L. Vian, and G. Marti-Mestres. 2002. Benzophenone-3: Rapid prediction and evaluation using non-invasive method of in vivo human penetration. *J. Pharm. Biomed. Anal.* 28:57–63.

Food and Drug Administration (FDA). 2002. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

FDA. 2002. Sunscreens, tanning products, and sun safety. http://vm.cfsan.fda.gov/~dms/cos-220.html.

Goncalo, M., E. Ruas, A. Figueiredo, and S. Goncalo. 1995. Contact and photocontact sensitivity to sunscreens. *Contact Dermatitis* 33:278–280.

Goswami, S. K., and J. E. Kinsella. 1985. Inhibitory effects of tannic acid and benzophenone on soybean lipoxygenase and ram seminal vesicle cyclooxygenase. *Prostaglandins Leukot. Med.* 17:223–228.

Guin, J. D. 2000. Eyelid dermatitis from benzophenone used in nail enhancement. *Contact Dermatitis* 43:308–309.

Gurish, M. F., L. K. Roberts, C. G. Krueger, and R. A. Daynes. 1981. The effect of various sunscreen agents on skin damage and the induction of tumor susceptibility in mice subjected to ultraviolet irradiation. *J. Invest. Dermatol.* 76:246–251.

Horn, H. M., F. Humphreys, and R. D. Aldridge. 1998. Contact dermatitis and prolonged photosensitivity induced by ketoprofen and associated with sensitivity to benzophenone-3. *Contact Dermatitis* 38:353–354.

Jacobs, M. C. 1998. Contact allergy to benzophenone-2 in toilet water. *Contact Dermatitis* 39:42.

Jiang, R., H. A. Benson, S. E. Cross, and M. S. Roberts. 1998. In vitro human epidermal and polyethylene membrane penetration and retention of the sunscreen benzophenone-3 from a range of solvents. *Pharm. Res.* 15:1863–1868.

Jiang, R., M. S. Roberts, D. M. Collins, and H. A. Benson. 1999. Absorption of sunscreens across human skin: An evaluation of commercial products for children and adults. *Br. J. Clin. Pharmacol.* 48:635–637.

Joint FAO/WHO Expert Committee on Food Additives (JECFA) 2001. Fifty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives.


[3]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036-4702, USA.

Summary and conclusions. Flavoring agents evaluated using the Procedure for the Safety Evaluation of Flavoring Agents. Geneva: World Health Organization.

Kadry, A. M., C. S. Okereke, M. S. Abdel-Rahman, M. A. Friedman, and R. A. Davis. 1995. Pharmacokinetics of benzophenone-3 after oral exposure in male rats. *J. Appl. Toxicol.* 15:97–102.

Knobler, E., L. Almeida, A. M. Ruzkowski, J. Held, L. Harber, and V. DeLeo. 1989. Photoallergy to benzophenone. *Arch. Dermatol.* 125:801–804.

Krainev, A. K., R. I. Viner, and D. J. Bigelow. 1997. Benzophen one-sensitized photooxidation of sarcoplasmic reticulum membranes: Site-specific modification of the Ca(2+)-ATPase. *Free Radic. Biol. Med.* 23:1009–1020.

Le Coz, C. J., A. Bottlaender, J. N. Scrivener, F. Santinelli, B. J. Cribier, E. Heid, and E. M. Grosshans. 1998. Photocontact dermatitis from ketoprofen and tiaprofenic acid: Cross-reactivity study in 12 consecutive patients. *Contact Dermatitis* 38:245–252.

Leroy, D., A. Dompmartin, C. Sczurko, M. Michel, and S. Louvet. 1997. Photodermatitis from ketoprofen with cross-reactivity to fenofibrate and benzophenones. *Photodermatol Photoimmunol Photomed* 13:93–97.

Lhiaubet, V., N. Paillous, and N. Chouini-Lalanne. 2001. Comparison of DNA damage photoinduced by ketoprofen, fenofibric acid and benzophenone via electron and energy transfer. *Photochem. Photobiol.* 74:670–678.

Maquad, M., A. B. Fleischer, Jr., E. F. Sherertz, and S. R. Feldman. 1999. Significance prevalence index number: A reinterpretation and enhancement of data from the North American Contact Dermatitis Group. *J. Am. Acad. Dermatol.* 41:573–576.

Marks, J. G. Jr., D. V. Belsito, V. A. DeLeo, J. F. Fowler, Jr., A. F. Fransway, H. I. Maibach, C. G. Toby Mathias, M. D. Pratt, R. L. Rietschel, E. F. Sherertz, F. J. Storrs, and J. S. Taylor. 2000. North American Contact Dermatitis Group patch-test results, 1996–1998. *Arch. Dermatol.* 136:272–273.

Marks, J. G. Jr., P. Elsner, and V. A. Deleo. eds. 2002. *Contact and occupational dermatology*, 3rd ed., 239, 240, 260. St. Louis: Mosby.

Ministry of Health, Labor and Welfare (MHLW). (June 29, 2001a). MHW Ordinance No. 331, Attached Table 4 [UV Filters]. Ministry of Health, Labor and Welfare, Pharmaceutical and Medical Safety Bureau, Inspection and Guidance Division, 2-2, 1-chome, Kasumigaseki, Chiyoda-ku, Tokyo 100-8045, Japan.

Ministry of Health, Labor and Welfare (MHLW). (June 29, 2001b). MHW Ordinance No. 332. Ingredients of quasi-drugs. Products to be used directly on the body. Ministry of Health, Labor and Welfare, Pharmaceutical and Medical Safety Bureau, Inspection and Guidance Division, 2-2, 1-chome, Kasumigaseki, Chiyoda-ku, Tokyo 100-8045, Japan.

Morin, B., and J. Cadet. 1995. Type I benzophenone-mediated nucleophilic reaction of 5′-Amino-2′,5′-dideoxyguanosine. A model system for the investigation of photosensitized formation of DNA-protein cross-links. *Chem. Res. Toxicol.* 8:792–799.

Mortelmans, K., S. Haworth, T. Lawlor, W. Speck, B. Tainer, and E. Zeiger. 1986. Salmonella mutagenicity tests. 2. Results from the testing of 270 chemicals. *Environ. Mutagen.* 8:1–119.

Nakagawa, Y., T. Suzuki, and S. Tayama. 2000. Metabolism and toxicity of benzophenone in isolated rat hepatocytes and estrogenic activity of its metabolites in MCF-7 cells. *Toxicology* 156:27–36.

Nakagawa, Y., and K. Tayama. 2001. Estrogenic potency of benzophenone and its metabolites in juvenile female rats. *Arch. Toxicol.* 75:74–79.

National Toxicology Program (NTP). 1990. Final report on the reproductive toxicity of 2-hydroxy-4-methoxybenzophenone (CAS No. 131-57-7). NTIS Report No. PB91-158477.

NTP. 1992. NTP technical report on toxicity studies of 2-hydroxy-4-methoxybenzophenone (CAS Number: 131-57-7). NTIS Report No. PB93-126498.

NTP. 2000. Report on the toxicity studies of benzophenone administered in feed to F344/N rats and B6C3F1 mice. NTIS Report No. PB2000-106659.

NTP. July 9, 2002a. Personal communication with NTP's Central Data Management. Year of initiation of 2-year carcinogenicity study on benzophenone (CAS No. 119-61-9). Research Triangle Park: NTP.

NTP. 2002b. NTP management status report. http://ntp-server.niehs.nih.gov/htdocs/Results_Status/Msr/Ref10.html

NTP. (2002c) NTP management status report. http://ntpserver.niehs.nih.gov/ htdocs/Results_Status/Msr/Ref04.html

Okereke, C. S., M. S. Abdel-Rhaman, and M. A. Friedman. 1994. Disposition of benzophenone-3 after dermal administration in male rats. *Toxicol. Lett.* 73:113–122.

Okereke, C. S., S. A. Barat, and M. S. Abdel-Rahman. 1995. Safety evaluation of benzophenone-3 after dermal administration in rats. *Toxicol. Lett.* 80:61–67.

Okereke, C. S., A. M. Kadry, M. S. Abdel-Rahman, R. A. Davis, and M. A. Friedman. 1993. Metabolism of benzophenone-3 in rats. *Drug Metab. Dispos.* 21:788–791.

Pepe, R. C., J. A. Wenninger, and G. N. McEwen, Jr., eds. 2002. *International cosmetic ingredient dictionary and handbook*. 9th ed., 171–174. Washington, DC: CTFA.

Potard, G., C. Laugel, A. Baillet, H. Schaefer, and J. P. Marty. 1999. Quantitative HPLC analysis of sunscreens and caffeine during in vitro percutaneous penetration studies. *Int. J. Pharm.* 189:246–260.

Potard, G., C. Laugel, H. Schafer, and J. P. Marty. 2000. The stripping technique: In vitro absorption and penetration of five UV filters on excised fresh human skin. *Skin Pharmacol. Appl. Skin Physiol.* 13:336–344.

Robison, S. H., M. R. Odio, E. D. Thompson, M. J. Aardema, and A. L. Kraus. 1994. Assessment of the in vivo genotoxicity of 2-hydroxy 4-methoxybenzophenone. *Environ. Mol. Mutagen.* 23:312–317.

Schauder, S., and H. Ippen. 1997. Contact and photocontact sensitivity to sunscreens. Review of a 15-year experience and of the literature. *Contact Dermatitis* 37:221–232.

Schlumpf, M., B. Cotton, M. Conscience, V. Haller, B. Steinmann, and W. Lichtensteiger. 2001. In vitro and in vivo estrogenicity of UV screens. *Environ. Health Perspect.* 109:239–244.

Schmidt, T., J. Ring, and D. Abeck. 1998. Photoallergic contact dermatitis due to combined UVB (4-methylbenzylidene camphor/octyl methoxycinnamate) and UVA (benzoph enone-3/butylmethoxydibenzoylmethane) absorber sensitization. *Dermatology* 196:354–357.

Sheng, P. G., J. Feix, and B. Kalyanaraman. 1990. Characterization of radical adducts formed during photochemical spin trapping in liposomes. *Photochem. Photobiol.* 52:323–331.

Stocklinski, A. W., O. B. Ware, and T. J. Oberst. 1980. Benzophenone metabolism. I. Isolation of *p*-hydroxybenzophenone from rat urine. *Life Sci.* 26:365–369.

Vanquerp, V., C. Rodriguez, C. Coiffard, L. J. Coiffard, and Y. De Roeck-Holtzhauer. 1999. High-performance liquid chromatographic method for the comparison of the photostability of five sunscreen agents. *J. Chromatogr.* 832:273–277.

Yamasaki, K., M. Takeyoshi, Y. Yakabe, M. Sakaki, N. Imatanaka, and M. Takatsuki. 2002. Comparison of reporter gene assay and immature rat uterotrophic assay of twenty-three chemicals. *Toxicology* 170:21–30.

Yesudian, P. D., and C. M. King. 2002. Severe contact urticaria and anaphylaxis from benzophenone-3 (2-hydroxy 4-methoxy benzophenone). *Contact Dermatitis* 46:55–56.

## BUTOXYETHANOL

A safety assessment of Butoxyethanol was published in 1996 with the conclusion "safe in hair and nail products at concentrations up to 10.0%" (Andersen 1996). Studies available since that safety assessment was completed, along with the updated information regarding uses and use concentrations, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

**TABLE 3**
Historical and current cosmetic product uses and concentrations for Butoxyethanol

| Product category | 1984 use (Andersen 1996) | 2001 use (FDA 2001) | 1984 concentrations (Andersen 1996) (%) | 2001 concentrations (CTFA 2001) (%) |
|---|---|---|---|---|
| Eye shadow | — | — | — | 3 |
| Shampoos (noncoloring) | 2 | — | ≤0.1–1 | |
| Hair tonics, dressings, etc. | — | 2 | — | — |
| Wave sets | 1 | — | 1–5 | |
| Hair dyes and colors | 90 | 94 | 1–10 | — |
| Hair tints | — | 3 | — | — |
| Shampoos (coloring) | — | 8 | — | — |
| Hair bleaches | 4 | 2 | 1–10 | — |
| Blushers | — | — | — | 3 |
| Nail polish and enamel | — | 1 | — | 3 |
| Nail polish and enamel removers | 1 | — | 5–10 | 50 |
| **Total uses/ranges for Butoxyethanol** | **121** | **110** | **≤0.1–10** | **3–50** |

The Panel noted that the in vitro hematotoxicity study by Ruchaud et al. (1992), cited in the published Final Report, has been retracted and agreed that the deletion of this reference would have no substantive effect on this safety assessment.

The CIR Expert Panel discussion focused on the questionable evidence of carcinogenicity (in rats and mice) in a 2-year inhalation carcinogenicity study on Butoxyethanol that was published by the NTP in 2000. The conclusions for rats and mice were as follows: no evidence of carcinogenic activity in male rats; equivocal evidence of carcinogenic activity in female rats, based on increased combined incidences of benign or malignant pheochromocytoma (mainly benign) of the adrenal medulla; some evidence of carcinogenic activity in male mice, based on increased incidences of hemangiosarcoma of the liver; marginal increase in incidences of forestomach squamous cell papilloma and increase in incidences of hepatocellular carcinoma may have been exposure related; and some evidence of carcinogenic activity in female mice, based on increased incidences of forestomach squamous cell papilloma or carcinoma (mainly papilloma).

After reviewing the NTP study, the Panel noted that the results are not relevant to man for the following reasons: (1) Pheochromocytomas observed in one rodent species were within the historical control range. (2) Liver cancer observed in a male rat was thought to have been due to hemolysis [it has been shown that rodent red blood cells are very sensitive to hemolysis by Butoxyethanol, and that this effect was due to iron overload]. (3) An increased incidence of forestomach cancers was observed in female mice after inhalation exposure. The forestomach is not a relevant organ for evaluation, and this effect was thought to have been due to irritation, but not genotoxicity.

The Panel also considered current data indicating that Butoxyethanol is used at concentrations up to 50% in nail polish and enamel removers, in light of its previous limitation of 10.0% in hair and nail products. However, it was concluded that the increased use concentration was of little concern because the nail plate is made up of dead tissue, and, thus, the amount of absorption through the nail would be negligible.

Butoxyethanol was used in 121 cosmetic products in 1984, and a maximum use concentration of 10% was reported in 1984. Currently, there are 110 reported uses, with nail polish and enamel removers comprising the product category with the highest ingredient use concentration (50% Butoxyethanol). Table 3 presents the available use information.

## REFERENCES


Aasmoe, L., J. O. Winberg, and J. Aarbakke. 1998. The role of liver alcohol dehydrogenase isoenzymes in the oxidation of glycolethers in male and female rats. *Toxicol. Appl. Pharmacol.* 150:86–90.

Agency for Toxic Substances and Disease Registry (ATSDR). 1998. Toxicological profile for 2-butoxyethanol and 2-butoxyethanol acetate. NTIS Report No. PB99-102527.

Alarie, Y., G. D. Nielsen, and J. Andonian-Haftvan. 1995. Physicochemical properties of nonreactive volatile organic chemicals to estimate RD50: Alternatives to animal studies. *Toxicol. Appl. Pharmacol.* 134:92–99.

American Chemistry Council. 2001. Review of ongoing studies concerning the tumorigenicity of EGBE in rodents—Research Update/Draft. Arlington VI: American Chemistry Council.

Andersen, F. A. ed. 1996. Final report on the safety assessment of butoxyethanol. *J. Am. Col. Toxicol.* 15:462–526.

Battelle Memorial Institute. 1999a. Final Report. Species-, gender-, and age-related differences in the pharmacokinetics of 2-butoxyethanol and 2-butoxycetic acid. II. In vitro renal active transport of 2-butoxyacetic acid. NTIS Report No. OTS06001387.

Battelle Memorial Institute. 1999b. Final Report. Short-term studies to evaluate the dosimetry and modes of action of 2-butoxyethanol in B6C3F1 mice, with cover letter dated 8-6-99. NTIS Report No. OTS0001363.

Boatman, R. J., and J. B. Knaak. 2001. Ethers of Ethylene Glycol and Derivatives. In *Patty's toxicology*, ed. E. Bingham, B. Cohrssen, and C. H. Powell, 73–270. New York: John Wiley & Sons.

Bowden, H. C., O. K. Wilby, C. A. Botham, P. J. Adam, and F. W. Ross. 1995. Assessment of the toxic and potential teratogenic effects of four glycol ethers and two derivatives using the hydra regeneration assay and rat whole embryo culture. *Toxicol. In Vitro* 9:773–781.

Chou, C.-H. S. J., J. Holler, and C. T. De Rosa. 1998. Minimal risk levels (MRLs) for hazardous substances. *J. Clean Tech. Environ. Toxicol. Occup. Med.* 7:1–24.

Corley, R. A. 1996. Assessing the risk of hemolysis in humans exposed to 2-butoxyethanol using a physiologically-based pharmacokinetic model. *Occup. Hyg.* 2:45–55.

Corley, R. A., D. A. Markham, C. Banks, P. Delorme, A. Masterman, and J. M. Houle. 1997. Physiologically based pharmacokinetics and the dermal absorption of 2-butoxyethanol vapor by humans. *Fundam. Appl. Toxicol.* 39:120–130.

Corning Hazleton, Inc. 1995. Draft Report. Clonal transformation assay on RO434.01 DRD:HESE 415, ethylene glycol monobutyl ether, using Syrian golden hamster embryo (SHE) cells w/cover letter dated 8-11–95. NTIS No. OTS0557-846.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2001. Concentration of use—Butoxyethanol. Unpu blished data submitted by CTFA.[4]

Dartsch, P. C., S. Hildenbrand, W. Gfroerer, R. Kimmel, and F. W. Schmahl. 1999. Cytotoxic effects of 2-butoxyethanol in vitro are related to butoxyacetaldehyde, an intermediate oxidation product. *Environ. Toxicol. Pharmacol.* 7:135–142.

Dill, J. A., M. L. Kyeonghee, D. J. Bates, D. J. Anderson, R. E. Johnson, B. J. Chou, L. T. Burka, and J. H. Roycroft. 1998. Toxicokinetics of inhaled 2-butoxyethanol and its major metabolite, 2-butoxyacetic acid, in F344 rats and B6C3F1 mice. *Toxicol. Appl. Pharmacol.* 153:227–242.

Dow Chemical Company. (Published in 1958; made available in 2000a. Results of range finding eye and skin irritation tests on Dowanol EBCrude (ethyleneglycol, butyl ether). NTIS No. OTS0520314.

Eastman Kodak Company. 1994. Ethylene glycol monobutyl ether: Acute oral toxicity study in the guinea pig with cover letter dated 7-21-94. NTIS No. OTS0572612.

Elliott, B. M., and J. Ashby 1997. Review of the genotoxicity of 2-butoxyethanol. *Mutat. Res.* 387:89–96.

European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC). 1994. Butoxyethanol criteria document, including a supplement for 2-butoxyethyl acetate. Special Report No. 7 (71 pages). Brussels: ECETOC.

Food and Drug Administration (FDA). 2001. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

Ghanayem, B. I., P. H. Long, S. M. Ward, B. Chanas, M. Nyska, and A. Nyska. 2001. Hemolytic anemia, thrombosis, and infarction in male and female F344 rats following gavage exposure to 2-butoxethaanol. *Exp. Toxicol. Pathol.* 53:97–105.

Ghanayem, B. I., S. M. Ward, B. Chanas, and A. Nyska. 2000. Comparison of the acute hematotoxicity of 2-butoxyethanol in male and female F344 rats. *Hum. Exp. Toxicol.* 19:185–192.

Gingell, R., R. J. Boatman, and S. Lewis. 1998. Acute toxicity of ethylene glycol mono-n-butyl ether in the guinea pig. *Food Chem. Toxicol.* 36:825–829.

Giraudi, G., and C. Baggiani. 1993. Solvent effect on testosterone-antitestosterone interaction. *Biochim. Biophys. Acta.* 1157:211–216.

Gollapudi, B. B., E. D. Barber, T. E. Lawlor, and S. A. Lewis. 1996. Re-examination of the mutagenicity of ethylene glycol monobutyl ether to *Salmonella* tester strain TA97a. *Mutat. Res.* 370:61–64.

Green, C. E., G. R. Gordon, P. M. Cohen, H. W. Nolen, J. H. Peters, and C. A. Tyson. 1996. In vitro metabolism of glycol ethers by human and rat hepatocytes. *Occup. Hygiene* 2:67–75.

Haufroid, V., F. Thirion, P. Mertens, J. P. Buchet, and D. Lison. 1997. Biological monitoring of workers exposed to low levels of 2-butoxyethanol. *Int. Arch. Occup. Environ. Health.* 70:232–236.

Hoflack, J. C., L. Lambolez, Z. Elias, and P. Vasseur. 1995. Mutagenicity of ethylene glycol ethers and of their metabolites in *Salmonella typhimurium* his$^-$. *Mutat. Res.* 341:281–287.

Hoflack, J. C., P. Vasseur, and G. G. Poirier. 1997. Glycol ethers induce death and necrosis in human leukemia cells. *Biochem. Cell. Biol.* 75:415–425.

[4]Available from Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

International Programme on Chemical Safety (IPCS). 1997. Concise International Assessment Document 10. 2-Butoxyethanol. http://www.inchem.org/documents/cicads/cicads/cicad10.htm.

Judson, I. R., and M. D. Threadgill. 1993. Poly(ADP-ribosyl)ation as target for cancer chemotherapy. *Lancet* 342:632.

Kaphalia, B. S., B. I. Ghanayem, and G. A. Ansari. 1996. Nonoxidative metabolism of 2-butoxyethanol via fatty acid conjugation in Fischer 344 rats. *J. Toxicol. Environ. Health.* 49:463–479.

Kerchaert, G. A., R. Brauninger, R. A. Leboeuf, and R. J. Isfort. 1996. Use of the Syrian hamster embryo cell transformation assay for carcinogenicity prediction of chemicals currently being tested by the National Toxicology Program in rodent bioassays. *Environ. Health Perspect.* 104:1075–1084.

L. A. B. Bio-Res International, Inc. 1996. Dermal bioavailability study of 2-butoxyethanol in fasted volunteers with cover letter dated 12-6-96 . NTIS No. OTS0573540.

Lautier, D., J. Lagueux, J. Thibodeau, L. Ménard, and G. G. Poirier. 1993. Molecular and biochemical features of poly(ADP-ribose) polymerase metabolism. *Biochem. Cell. Biol.* 68:602–608.

Lindahl, T., M. S. Satoh, G. G. Poirier, and A. Klungland. 1995. Post-translational modification of poly(ADP-ribose) polymerase induced by DNA strand breaks. *Trends Biol. Sci.* 20:405–411.

Long, P. H., R. R. Maronpot, B. I. Ghanayem, J. H. Roycroft, and A. Nyska. 2000. Dental pulp infarction in female rats following inhalation exposure to 2-butoxyethanol. *Toxicol. Pathol.* 28:246–252.

Moslen, M. T., L. Kaphalia, H. Balasubramanian, Y. M. Yin, and W. W. Au. 1995. Species differences in testicular and hepatic biotransformation of 2-methoxyethanol. *Toxicology* 96:217–224.

National Toxicology Program (NTP). 2000. Toxicology and carcinogenesis studies of 2-butoxyethanol (CAS No. 111-76-2) in F344/N Rats and B6C3F1 mice (Inhalation Studies). NTIS Report No. PB2000-105865.

Nyska, A., R. R. Maronpot, and B. I. Ghanayem. 1999a. Ocular thrombosis and retinal degeneration induced in female F344 rats by 2-butoxyethanol *Hum. Exp. Toxicol.*18:577–582.

Nyska, A., R. R. Maronpot, P. H. Long, J. H. Roycroft, J. R. Hailey, G. S. Travlos, and B. I. Ghanayem. 1999a. Disseminated thrombosis and bone infarction in female rats following inhalation exposure to 2-butoxyethanol. *Toxicol. Pathol.* 27:287–294.

Raymond L. W., L. S. Williford, and W. A. Burke. 1998. Eruptive cherry angiomas and irritant symptoms after one acute exposure to the glycol ether solvent 2-butoxyethanol. *J. Occup. Environ. Med.* 40:1059–1064.

Sivarao, D. V., and H. M. Mehendale. 1995. 2-Butoxyethanol autoprotection is due to resiliency of newly formed erythrocytes to hemolysis. *Arch. Toxicol.* 69:526–532.

Udden, M. M. 2000. Rat erythrocyte morphological changes after gavage dosing with 2-butoxyethanol: A comparison with the in vitro effects of butoxyacetic acid on rat and human erythrocytes. *J. Appl. Toxicol.* 20:381–387.

Udden M. M., and C. S. Patton. 1994. Hemolysis and deformability of erythrocytes exposed to butoxyacetic acid, a metabolite of 2-butoxyethanol: I. Sensitivity in rats and resistance in normal humans. *J. Appl. Toxicol.* 14:91–96.

Wenninger, J. A., R. C. Canterbery, and G. N. McEwen, Jr., eds. 2000. *International cosmetic ingredient dictionary and handbook*. 8th ed. 162. Washington, DC: CTFA.

Woo, Y.-T., D. Lai, J. Arcos, M. Argus, M. Cimino, S. DeVito, and L. Keifer. 1997. Mechanism-based structure-activity relationship (SAR) analysis of carcinogenic potential of 30 NTP test chemicals. *J. Environ. Sci. Health C Environ. Carcinogen. Ecotoxicol. Rev.* C15:139–160.

Zissu, D. 1995. Experimental study of cutaneous tolerance to glycol ethers. *Contact Dermatitis* 32:74–77.

## BUTYL STEARATE, ISOBUTYL STEARATE, CETYL STEARATE, ISOCETYL STEARATE, ISOPROPYL STEARATE, MYRISTYL STEARATE, AND OCTYL STEARATE

A safety assessment of Butyl Stearate, Isobutyl Stearate, Cetyl Stearate, Isocetyl Stearate, Isopropyl Stearate, Myristyl Stearate, and Octyl Stearate was published in 1985 with the conclusion "safe as cosmetic ingredients in the present practices of use" (Elder 1985). Studies available since that safety assessment was completed, along with the updated information regarding uses and use concentrations, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

Octyl Stearate is now called Ethylhexyl Stearate.

The Panel noted that the reproductive toxicity of 2-ethyl-1-hexanol, a hydrolysis product of Ethylhexyl Stearate, was addressed in a fetotoxicity study on the cosmetic ingredient Diethylhexyl Adipate (Eastman Kodak Company 1992). It was suggested that the fetotoxicity reported for mice in this study was actually due to a zinc deficiency. Furthermore, given the extent of 2-ethyl-1-hexanol absorption and the load that would be expected to enter the hepatic circulation, the potential for 2-ethyl-1-hexanol–induced reproductive toxicity was not thought to be an issue.

**Butyl Stearate** was used in 116 products in 1981, with the single largest use in lipstick in the concentration range of >1% to 25%. In 2002, Butyl Stearate was reportedly used in 78 preparations, with the single largest use in lipstick; use concentration data provided in 2003 indicated use concentrations in this product category ranging from 0.02% to 0.3%. The 2003 use concentration data were provided by CTFA (CTFA 2003). Complete information on Butyl Stearate and the remaining Stearates in this review are shown in Table 4.

No uses of **Isobutyl Stearate** in cosmetics were reported in 1981. In 2002, Isobutyl Stearate was reportedly being used

**TABLE 4**
Historical and current product uses and concentrations for Stearates

| Product category | 1981 use (Elder 1985) | 2002 use (FDA 2002) | 1981 concentrations (Elder 1985) (%) | 2003 concentrations (CTFA 2003) (%) |
|---|---|---|---|---|
| | | *Butyl Stearate* | | |
| Bubble baths | — | — | — | 43 |
| Eyeliner | 4 | 22 | >1–5 | 0.4–9 |
| Eye shadow | 3 | 1 | >0.1–5 | 0.5 |
| Eye makeup remover | — | — | — | 0.2 |
| Mascara | — | — | — | 0.4 |
| Eye makeup (other) | 4 | — | >5–25 | — |
| Perfumes | — | 1 | — | — |
| Hair sprays (aerosol fixatives) | — | — | — | — |
| Hair conditioners | 3 | — | >1–10 | 0.01 |
| Shampoos (noncoloring) | — | — | — | 0.03 |
| Hair tonics, dressings, etc. | — | — | — | 1 |
| Foundations | 1 | 1 | >10–25 | 0.04 |
| Lipsticks | 78 | 34 | >1–25 | 0.02–0.3 |
| Makeup bases | — | 2 | — | — |
| Rouges | — | — | — | 0.002 |
| Makeup (other) | — | — | — | 0.002 |
| Nail polish and enamel removers | 2 | — | >0.1–5 | — |
| Bath soaps and detergents | — | 2 | — | — |
| Underarm deodorants | 1 | 1 | >1–5 | 2 |
| Feminine deodorants | 1 | — | >0.1–1 | — |
| Personal cleanliness products (other) | — | 3 | — | — |
| Aftershave lotion | — | — | — | 0.1 |
| Preshave lotions | 3 | — | >1–10 | — |
| Shaving cream | — | — | — | 1 |
| Cleansing | 1 | — | >1–5 | 1 |
| Depilatories | — | — | — | 1 |

(*Continued on next page*)

**TABLE 4**
Historical and current product uses and concentrations for Stearates *(Continued)*

| Product category | 1981 use (Elder 1985) | 2002 use (FDA 2002) | 1981 concentrations (Elder 1985) (%) | 2003 concentratiions (CTFA 2003) (%) |
|---|---|---|---|---|
| Face and neck skin care preparations | 8* | — | >0.1–5* | 0.8 |
| Body and hand skin care preparations | | 2 | | 0.5 |
| Moisturizers | 3 | 8 | >1–10 | — |
| Night skin care preparations | — | — | — | 0.4 |
| Skin care preparations (other) | 2 | — | >1–25 | 0.05–4 |
| Suntan gels, creams, and liquids | 2 | 1 | >10–25 | — |
| **Total uses/ranges for Butyl Stearate** | **116** | **78** | **>0.1–25** | **0.02–9** |
| | *Isobutyl Stearate* | | | |
| Personal cleanliness products (other) | — | 1 | — | — |
| Moisturizers | — | — | — | 7 |
| Skin care preparations (other) | — | 2 | — | — |
| **Total uses/ranges for Isobutyl Stearate** | **—** | **3** | **—** | **7** |
| | *Isocetyl Stearate* | | | |
| Eye shadow | 1 | — | >5–10 | 30 |
| Eye makeup remover | 1 | 1 | >10–25 | — |
| Eye makeup (other) | — | 1 | — | — |
| Fragrance preparations (other) | — | 4 | — | — |
| Blushers | 2 | 1 | >1–10 | — |
| Face powders | 2 | — | >1–25 | — |
| Foundations | 7 | 24 | >5–25 | — |
| Lipsticks | 1 | 4 | >1–5 | 0.1–24 |
| Makeup bases | 8 | — | >0.1–25 | — |
| Rouges | 1 | — | >10–25 | — |
| Makeup fixatives | — | 1 | — | — |
| Makeup (other) | — | 5 | — | 30 |
| Nail creams and lotions | 1 | 1 | >1–5 | — |
| Bath soaps and detergents | 1 | — | ≤0.1 | — |
| Underarm deodorants | — | — | — | 3 |
| Personal cleanliness products (other) | — | — | — | 30 |
| Aftershave lotion | — | 2 | — | — |
| Shaving products (other) | 1 | — | >1–5 | — |
| Skin-cleansing creams, lotions, liquids, and pads | 5 | 5 | ≤0.1–5 | 0.02–2 |
| Face and neck skin care preparations | 11* | 6 | >0.1–5* | 1 |
| Body and hand skin care preparations | | 8 | | 4–5 |
| Foot powders and sprays | — | — | — | 10 |
| Moisturizers | 10 | 11 | ≤0.1–5 | 0.8–1 |
| Night skin care preparations | 2 | 5 | >0.1–10 | 4–10 |
| Paste masks (mud packs) | — | 1 | — | — |
| Skin care preparations (other) | 2 | 3 | >0.1–10 | 4 |
| Suntan gels, creams, and liquids | 1 | 1 | >10–25 | — |
| Suntan preparations (other) | 1 | — | >0.1–1 | — |
| **Total uses/ranges for Isocetyl Stearate** | **58** | **84** | **≤0.1–25** | **0.02–30** |
| | *Cetyl Stearate* | | | |
| Eye shadow | 3 | — | >5–10 | — |
| Eye makeup remover | — | — | — | 0.6 |
| Hair conditioners | — | — | — | 2 |

(*Continued on next page*)

**TABLE 4**
Historical and current product uses and concentrations for Stearates *(Continued)*

| Product category | 1981 use (Elder 1985) | 2002 use (FDA 2002) | 1981 concentrations (Elder 1985) (%) | 2003 concentrations (CTFA 2003) (%) |
|---|---|---|---|---|
| Shampoos (noncoloring) | — | — | — | 3 |
| Hair tonics, dressings, etc. | — | — | — | 2 |
| Face powders | 1 | — | >1–5 | — |
| Foundations | — | — | — | 10 |
| Lipsticks | — | 2 | — | — |
| Skin-cleansing creams, lotions, liquids, and pads | — | — | — | 3 |
| Face and neck skin care preparations | —* | — | —* | 15 |
| Body and hand skin care preparations | | — | | 2 |
| Night skin care preparations | — | — | — | 0.3 |
| Indoor tanning preparations | — | — | — | 5 |
| **Total uses/ranges for Cetyl Stearate** | **4** | **2** | **>1–10** | **≤15** |
| | *Isopropyl Stearate* | | | |
| Bath oils, tablets, and salts | 1 | — | >5–10 | — |
| Eyeliner | — | — | — | 5 |
| Eye shadow | — | 1 | — | 8 |
| Eye makeup remover | — | — | — | 76 |
| Eye makeup (other) | 1 | 2 | >10–25 | — |
| Fragrance preparations (other) | 1 | — | >25–50 | — |
| Hair conditioners | — | — | — | 6 |
| Hair tonics, dressings, etc. | — | — | — | 8 |
| Foundations | — | — | — | 2 |
| Makeup (other) | — | — | — | 5 |
| Nail polish and enamel removers | — | — | — | 10 |
| Dentifrices | — | — | — | 87 |
| Underarm deodorants | — | — | — | 3 |
| Personal cleanliness products (other) | 3 | 3 | >1–5 | — |
| Skin-cleansing creams, lotions, liquids, and pads | 4 | 1 | >5–25 | 11 |
| Face and neck skin care preparations | —* | 1 | —* | 7 |
| Body and hand skin care preparations | | — | | 3–5 |
| Moisturizers | 4 | 6 | >5–25 | — |
| Night skin care preparations | 1 | 1 | >10–25 | 0.5 |
| Skin lighteners | 1 | N/A** | >10–25 | N/A** |
| Skin care preparations (other) | — | 1 | — | — |
| **Total uses/ranges for Isopropyl Stearate** | **16** | **16** | **>1–50** | **0.5–87** |
| | *Myristyl Stearate* | | | |
| Foundations | 1 | — | >1–5 | — |
| Makeup (other) | — | — | — | 2 |
| Cuticle softeners | — | — | — | 4 |
| Face and neck skin care preparations | —* | — | —* | 4 |
| Body and hand skin care preparations | | — | | 4 |
| Night skin care preparations | — | — | — | 4 |
| **Total uses/ranges for Myristyl Stearate** | **1** | | **>1–5** | **2–4** |
| | *Ethylhexyl Stearate* | | | |
| Bath oils, tablets, and salts | 3 | 2 | >0.1–5 | — |
| Eyeliner | — | 1 | — | 11 |
| Eye shadow | — | 2 | — | 0.8 |

(*Continued on next page*)

**TABLE 4**
Historical and current product uses and concentrations for Stearates *(Continued)*

| Product category | 1981 use (Elder 1985) | 2002 use (FDA 2002) | 1981 concentrations (Elder 1985) (%) | 2003 concentrations (CTFA 2003) (%) |
|---|---|---|---|---|
| Eye makeup remover | — | 1 | — | — |
| Eye makeup (other) | — | 1 | — | 6 |
| Colognes and toilet waters | 4 | — | >0.1–1 | — |
| Powders | — | — | — | 0.5 |
| Fragrance preparations (other) | — | 1 | — | — |
| Blushers | — | 2 | — | — |
| Face powders | — | 2 | — | 0.5 |
| Foundations | 1 | 2 | >0.1–1 | 3 |
| Lipsticks | — | 1 | — | — |
| Makeup (other) | — | — | — | 2–3 |
| Shaving cream | — | 1 | — | — |
| Skin-cleansing creams, lotions, liquids, and pads | — | 1 | — | — |
| Face and neck skin care preparations | 1* | 2 | >0.1–1* | 0.8 |
| Body and hand skin care preparations | | 2 | | 2–6 |
| Moisturizers | — | 3 | — | — |
| Night skin care preparations | 2 | — | >0.1–25 | — |
| Skin care preparations (other) | — | 3 | — | 5 |
| Suntan gels, creams, and liquids | — | 1 | — | 2 |
| Indoor tanning preparations | — | 1 | — | — |
| Suntan preparations (other) | — | 2 | — | — |
| **Total uses/ranges for Ethylhexyl Stearate** | **11** | **31** | **>0.1–25** | **0.5–11** |

*This category was combined when the original safety assessment was performed and is now two separate categories.
**No longer considered a cosmetic product category.

in three cosmetic products. Use concentration data provided in 2003 indicated a use concentration of 7% in moisturizing products.

**Isocetyl Stearate** was used in 58 products in 1981, with the single largest use in face and neck (excluding shaving) preparations in the concentration range of >0.1% to 5%. In 2002, Isocetyl Stearate was reportedly used in 84 preparations, with the single largest use in foundations; use concentration data provided in 2003 did not include a use concentration range for Isocetyl Stearate in this product category. However, the maximum use concentration reported for any product category was 30%.

**Cetyl Stearate** was used in four products in 1981, with the single largest use in eye shadow in the concentration range of >5% to 10%. In 2002, Cetyl Stearate was reportedly used in two lipsticks; use concentration data provided in 2003 did not include a use concentration range for Cetyl Stearate in lipsticks; however, the maximum use concentration reported for any product category was 15%.

**Isopropyl Stearate** was used in 16 products in 1981, with the largest use in both cleansing and moisturizing products (use concentrations of >5% to 25%). In 2002, Isopropyl Stearate was reportedly used in the same number of products, with the single largest use in moisturizing products. Use concentration data provided in 2003 did not include a use concentration range for Isopropyl Stearate in this product category; however, the maximum use concentration reported for any product category was 87%.

**Myristyl Stearate** was used in one product (foundation) in 1981, in the concentration range of >1% to 5%. Frequency of use data provided in 2002 indicated no uses of Myristyl Stearate in cosmetic products. However, use concentration data provided in 2003 in dicated that Myristyl Stearate was used at concentrations up to 4% in cosmetic products.

**Ethylhexyl Stearate** was used in 11 products in 1981, with the largest single use in colognes and toilet waters in the concentration range of >0.1% to 1%. In 2002, Ethylhexyl Stearate was reportedly used in 31 products. Use concentration data provided in 2003 indicated that Ethylhexyl Stearate was used at concentrations up to 11%.

## REFERENCES

Andersen, F. A., ed. 1997. Final report on the safety assessment of cetyl esters. *Int. J. Toxicol.* 16:123–130.

Anonymous. 1994. Henkel KgaA: Submission of IUCLID data set on fatty acids, C16-18, 2-ethylhexylester to the European Chemical Bureau, unpublished documents. D-Düsseldorf and I-Ispra.

Aulmann, W., W. Sterzel, and Henkel KgaA. 1994. Assessment of maternal-, fetotoxic- and teratogenic effects of fatty acids, C 16-18, 2-ethylhexyl ester and its breakdown products 2-ethylhexyl alcohol and 2-ethylhexyl acid. Report-No. 9400096.

Aulman, W., W. Pittermann, F. Bartnik, W. Sterzel, W. Kastner, and M. Potokar. 2000. Developmental toxicity of 2-ethylhexyl stearate. *Food Chem. Toxicol.* 38:57–63.

ChemIDplus. 2003. *ChemIDplus database*. Bethesda: National Library of Medicine.

Chiba, K., and K. Tohyama. 1989. Safety evaluation of oil ingredients for cosmetics using cell culture system. *J. Jpn. Cosmet. Sci. Soc.* 13:194–202.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2003. Use concentration data on Butyl Stearate, Cetyl Stearate, Ethylhexyl Stearate, Isobutyl Stearate, Isocetyl Stearate, Isopropyl Stearate, and Myristyl Stearate from industry survey. Unpublished data submitted by CTFA, April 21, 2003. 3 pages.[5]

Eastman Kodak Co. 1992. Submission summary: Synopsis of teratology study in rats (final report) using di(2-ethylhexyl)adipate with cover letter dated 091391. NTIS Report No. OTS0533689-1.

Elder, R. L. ed. 1985 . Final report on the safety assessment of butyl stearate, cetyl stearate, isobutyl stearate, isocetyl stearate, isopropyl stearate, myristyl stearate, and octyl stearate. *J. Am. Col. Toxicol.* 4:107–146.

Environmental Protection Agency (EPA). No date. Toxic substances control act inventory representation for chemical substances of unknown or variable composition, complex reaction products and biological materials. UVCB substances. http://www.epa.gov/opptintr/newchems/uvcb.txt.

Food and Drug Administration (FDA). 2002. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

Fulton, J. E., Jr., S. R. Pay, and J. E. Fulton, III. 1984. Comedogenicity of current therapeutic products, cosmetics, and ingredients in the rabbit ear. *J. Am. Acad. Dermatol.* 10:96–105.

Hachiya, N. 1987. Evaluation of chemical genotoxicity by a series of short-term tests. *Akita J. Med.* 14:269–292.

Hisashi, T., and R. Hagakaya. 1991. A study on the relation between the result of guinea pig skin irritation test and human patch test with cosmetic ingredients. *Hifu* 33:31–38.

Munro, I. C., and E. Kennepohl. 2001. Comparison of estimated daily capita intakes of flavouring substances with no-observed-effect levels from animal studies. *Food Chem. Toxicol.* 39:331–354.

Pepe, R. C., J. A. Wenninger, and G. N. McEwen, Jr., eds. 2002. *International cosmetic ingredient dictionary and handbook*, 9th ed., 223, 310, 616, 809, 812, 828, 1017. Washington, DC: CTFA.

Vermüe, M., J. Sikkema, A. Verheul, R. Bakker, and J. Tramper. 1993. Toxicity of homologous series of organic solvents for the gram-positive bacteria *Arthrobacter* sp. and *Nocardia* sp. and the gram-negative bacteria *Acinetobacter* sp. and *Pseudomonas* sp. *Biotechnol. Bioeng.* 42:747–758.

World Health Organization (WHO). 1998. Safety evaluation of certain food additives and contaminants. Prepared by The forty-ninth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), 272, 305, 324. WHO Food Additives Series 40. Geneva: WHO.

WHO. 1999. Evaluation of certain food additives and contaminants. Forty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives, 25, 62. WHO Technical Report Series 884. Geneva: WHO.

[5]Available from the Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

## CETEARYL OCTANOATE (aka CETEARYL ETHYLHEXANOATE)

A safety assessment of Cetearyl Octanoate was published in 1982 with the conclusion "safe as a cosmetic ingredient in the present practices of use." Studies available since that safety assessment was completed have been considered by the CIR Expert Panel (see reference list), along with updated information regarding uses and use concentrations. The Panel determined to not reopen this safety assessment.

The terminology for this ingredient in the *International Cosmetic Ingredient Dictionary and Handbook* has changed. Cetearyl Ethylhexanoate is the current terminology.

Significant among the new data were data on 2-ethylhexanoic acid (2-EHA) which has been shown to be a liver and developmental toxicant in animal studies at high dose levels. 2-EHA is a possible metabolite of Cetearyl Ethylhexanoate.

In developmental toxicity studies, it has been postulated that 2-EHA maternal liver toxicity begins a cascade of effects that includes metallothionein (MT) induction, zinc accumulation in the liver due to MT binding, and a resulting zinc deficiency in the developing embryo. In this model, it is the zinc deficiency in the developing embryo that causes developmental toxicity. Support for this mechanism of action comes from several sources. Animal studies have demonstrated that dietary zinc supplementation reduces this toxic effect and that further zinc deficiency makes 2-EHA more toxic. In vitro studies using embryo cultures have demonstrated that either zinc deficient or 2-EHA treated sera produced developmental toxicity. Zinc supplementation of either/both sera eliminated the effect.

To further examine this question, Di-2-ethylhexyl terephthalate (DEHT), a 2-EHA precursor, was chosen as a model that would result in 2-EHA exposures without liver toxicity, MT induction, etc. DEHT is metabolized in the gut and liver to 2-ethylhexanol (2-EH) and terephthalate. Two moles of 2-EH are produced per mole of DEHT. Subsequent hydrolysis of 2-EH produces 2-EHA. It can be hypothesized that this pathway to 2-EHA production from a precursor would not give rise to acute liver toxicity, MT induction, zinc sequestration, and developmental toxicity.

In a reproductive and developmental toxicity study, 0%, 0.3%, 0.6%, and 1% DEHT was provided in the feed of rats. The doses were calculated to be 614 to 823 mg/kg day$^{-1}$ for males and 783 to 1021 mg/kg day$^{-1}$ for females. Neither reproductive toxicity or developmental toxicity were seen at any dose level. These findings suggest that the process of metabolic conversion of DEHT to 2-EH, and subsequent hydrolysis to 2-EHA results in a time course of 2-EHA appearance that allows clearance before sufficient levels can arise to produce acute liver toxicity.

While this study was undertaken to understand 2-EHA developmental toxicity, the Panel considered that it is relevant to the assessment of Cetearyl Ethylhexanoate. Like DEHT, Cetearyl Ethylhexanoate must undergo conversion in order to produce

2-EHA. In addition, Cetearyl Ethylhexanoate, as used in cosmetics, would have to pass through the stratum corneum and the epidermis before entering the blood stream, further moderating the time course of 2-EHA appearing in the liver. The Panel recognized that Cetearyl Ethylhexanoate is used in lipsticks and that ingestion is possible from that use. It was the view of the CIR Expert Panel that these considerations would preclude any possibility that Cetearyl Ethylhexanoate in cosmetics could present a risk of developmental toxicity.

Cetearyl Ethylhexanoate (then called Cetearyl Octanoate) was used in 243 cosmetic products in 1976. The highest concentrations were in eye makeup, makeup, and skin care preparations. Currently there are 229 reported uses of Cetearyl Ethylhexanoate, with the highest concentrations in make-up and skin care preparations. Although current use concentrations have increased compared to those reported in 1976, available skin irritation data show no irritation at concentrations up to 30%.

Table 5 presents the available use information.

**TABLE 5**
Cetearyl ethylhexanoate use

| Product category (no. of formulations in the category) (FDA 2002) | No. of formulations with Cetearyl Ethylhexanoate in 1976 (Elder 1982) | Current no. of formulations with Cetearyl Ethylhexanoate (FDA 2002) | Concentration of use in 1976 (Elder 1982) (%) | Current concentration of use (CTFA 2002a) (%) |
|---|---|---|---|---|
| Baby lotions, oils, powders, and creams (60) | — | 1 | — | — |
| Bath oils, tablets, and salts (143) | 1 | — | Unknown | — |
| Bath capsules (2) | — | — | — | 9 |
| Other bath preparations (196) | 2 | — | 1–10 | — |
| Eyeliners (548) | 1 | — | 0.1–1 | — |
| Eye shadows (576) | 22 | 4 | 0–25 | 26–28 |
| Mascara (195) | 6 | — | 0.1–1 | 0.07 |
| Other eye makeup preparations (152) | 2 | 3 | 0.1–5 | 3–5 |
| Powders (273) | — | 2 | — | — |
| Other fragrance preparation (173) | — | 12 | — | — |
| Hair conditioners (651) | 5 | — | 0–5 | — |
| Hair sprays (aerosol fixatives) (275) | 5 | 5 | 0–5 | — |
| Hair straighteners (63) | 1 | — | 0.1–1 | — |
| Rinses (noncoloring) (42) | 1 | — | 0.1–1 | — |
| Shampoos (noncoloring) (884) | — | — | — | 0.2 |
| Tonics, dressings, and other hair-grooming products (598) | 1 | 32 | 0.1–1 | 0.1 |
| Wave sets (53) | 1 | — | 1–5 | — |
| Other hair preps. (277) | 3 | 2 | 0–5 | — |
| Blushers (all types) (245) | 19 | 3 | 1–25 | 3 |
| Face powders (305) | 10 | 6 | 0.1–1 | 1–4 |
| Foundations (324) | — | 5 | — | 0.1–34 |
| Lipstick (962) | — | 4 | — | 0.1–8 |
| Makeup bases (141) | 25 | — | 0.1–5 | — |
| Rouges (28) | 2 | — | 5–25 | — |
| Makeup fixatives (20) | 1 | — | 5–10 | — |
| Other makeup preparations (201) | 10 | — | 0.1–5 | 35 |
| Nail creams and lotions (15) | 1 | — | 10–25 | — |
| Deodorants (underarm) (247) | — | — | — | 3 |
| Feminine deodorants (4) | 1 | — | 1–5 | — |
| Aftershave lotion (231) | — | 2 | — | — |
| Men's talcum (7) | — | 1 | — | — |
| Preshave lotions (all types) (14) | 1 | — | 1–5 | — |

*(Continued on next page)*

**TABLE 5**
Cetearyl ethylhexanoate use *(Continued)*

| Product category (no. of formulations in the category) (FDA 2002) | No. of formulations with Cetearyl Ethylhexanoate in 1976 (Elder 1982) | Current no. of formulations with Cetearyl Ethylhexanoate (FDA 2002) | Concentration of use in 1976 (Elder 1982) (%) | Current concentration of use (CTFA 2002a) (%) |
|---|---|---|---|---|
| Other shaving preparation products (63) | 1 | — | 1–5 | — |
| Skin-cleansing creams, lotions, liquids and pads (775) | 15 | 7 | 0–10 | 13 |
| Face and neck creams, lotions and powders (310) | 35* | 21 | 0–25* | 3 |
| Body and hand creams, lotions and powders (840) | | 38 | | 3–10 |
| Moisturizing creams, lotions, etc. (905) | 39 | 23 | 0.1–25 | 2–34 |
| Night creams, lotions and powders (200) | 16 | 13 | 0.1–10 | 2–7 |
| Paste masks/mud packs (271) | 3 | 8 | 0.1–5 | — |
| Skin fresheners (184) | 1 | 2 | 0.1–1 | — |
| Other skin care preparations (725) | 4 | 21 | 1–25 | 6 |
| Suntan gels, creams, and liquids (131) | 7 | 9 | 0–5 | 0.5–9 |
| Indoor tanning preparations (71) | — | 2 | — | 3 |
| Other suntan preparations (38) | 1 | 3 | 5–10 | — |
| **Total reported uses (to FDA) and concentration range reported by industry** | **243** | **229** | **0–25** | **0.07–35** |

*This category was combined when the original safety assessment was performed and is now two separate categories.

## REFERENCES


Anonymous. 1993a. Phototoxicity. Unpublished data submitted by the Cosmetic, Toiletry, and Fragrance Association (CTFA). May 8, 2002.[6]

Anonymous. 1993b. Photoallergenicity. Unpublished data submitted by CTFA. May 8 2002.[6]

Anonymous. 1994a. Single Application Patch Test. Unpublished data submitted by CTFA. May 8 2002.[6]

Anonymous. 1994b. Human Repeat Insult Patch Test. Unpublished data submitted by CTFA. May 8 2002.[6]

Anonymous. 1995. Human Repeat Insult Patch Test. Unpublished data submitted by CTFA. May 8 2002.[6]

Bui, L. M., M. W. Taubeneck, J. F. Commiso, J. Y. Uriu -Hare, W. D. Faber, and C. L. Keen. 1998. Altered zinc metabolism contributes to the developmental toxicity of 2-ethylhexanoic acid, 2-ethylhexanol and valproic acid. *Toxicology* 126:9–21.

Chemical Manufacturers Association (CMA). 1987a. Acute toxicity study of 2-ethylhexanoic acid in the rat (Final Report) with attachments and cover letter dated 061 787. NTIS Report No. OTS0525538.

CMA. 1987b. Letter from Chemical Manufacturers Association to USEPA submitting enclosed interim and final reports on the testing of 2-ethylhexanoic acid with attachments. NTIS Report No. OTS0525547.

Consumer Product Testing Co. 1985. Repeated Insult Patch Test Final Report. Unpublished data submitted by CTFA. March 14, 2002. 13 pages.[6]

Consumer Product Testing Co. 1996a. Acute oral toxicity in rats. Unpublished data submitted by CTFA August 5, 2002. 3 pages.[6]

Consumer Product Testing Co. 1996b. Primary ocular irritation in rabbits. Unpublished data submitted by CTFA August 5, 2002. 7 pages.[6]

Consumer Product Testing Co. 1996c. Primary dermal irritation in rabbits. Unpublished data submitted by CTFA August 5, 2002. 6 pages.[6]

Consumer Product Testing Co. 1996d. Comedogenicity assay in rabbits. Unpublished data submitted by CTFA August 5, 2002. 10 pages.[6]

Consumer Product Testing Co. 1998. 48 hour patch test in humans (dermal irritation study). Unpublished data submitted by CTFA. March 22, 2002. 8 pages.[6]

Consumer Product Testing Co. 1999a. Skin irritation by MatTex Epiderm Skin Model. Unpublished data submitted by CTFA. March 22, 2002. 14 pages.[6]

Consumer Product Testing Co. 1999b. Eye irritation by Mat Tek Epiocular Model. Unpublished data submitted by CTFA. March 22, 2002. 14 pages.[6]

Cosmetic, Toiletry, and Fragrance Association. 1990a. Report regarding the primary eye irritation of neopentyl glycol diethylhexano ate; COSMOL 525. Unpublished data provided by CTFA September 14, 1990. 6 pages.[6]

CTFA. 1990b. Report regarding the primary dermal irritation of neopentyl glycol diethylhexanoate; COSMOL 525. Unpublished data provided by CTFA August 24, 1990. 4 pages.[6]


[6]Unpublished data available from the Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Washington, DC 20036, USA.

CTFA. 1990c. Report assay of comedogenicity in the rabbit ear of neopentyl glycol diethylhexanoate; COSMOL 525. Unpublished data provided by CTFA December 16, 1990. 8 pages.[6]

CTFA. 2001a. Report rearding the primary eye irritation of pentaerythrityl tetraethylhexanoate; Salacos 5408. Unpublished data provided by CTFA October 22, 2001. 7 pages.[6]

CTFA. 2001b. Report rearding the primary dermal irritation of pentaerythrityl tetraethylhexanoate; Salacos 5408. Unpublished data provided by CTFA October 30, 2001. 5 pages.[6]

CTFA. 2002a. Concentration of use of ethylhexanoate ingredients. Unpublished data provided by CTFA. Updated October 21, 2002. 6 pages.[6]

CTFA. 2002b. Concentration of 2-E thylhexanoic Acid in Cetearyl Ethylhexanoate. Unpublished data provided by CICD committee of CTFA Sept. 6, 2002.[6]

Eastman Kodak Company. 1992. Initial submission: Dermal corrosivity test of 2-ethylhexanoic acid in rabbits with cover letter dated 09/28/92. NTIS Report No. OTS0555383.

Elder, R. L., ed. 1982. Final report on the safety assessment of Cetearyl Octanoate. *J. Am. Col. Toxicol.*1:81–90.

English, J. C., P. J. Deisinger, and D. Guest. 1998. Metabolism of 2-ethylhexanoic acid administered orally or dermally to the female Fischer 344 rat. *Xenobiotica* 28: 699–714.

European Commission. 1999. EEC Cosmetics Directive 76/768/EEC, as amended through the 26th Adapting Commission Directive 2002/34/EC, Annexes I-VII. Brussels: EEC. http://europa.eu.int/scadplus/leg/en/lvb/l21191.htm

Faber, W. 2003. Presentation made at the February, 2003 meeting of the CIR Expert Panel.[6]

Food and Drug Administration (FDA). 1984. Cosmetic product formulation and frequency of use data. *FDA database*. Washington, DC: FDA.

FDA. 1992. Modification in Voluntary Filing of Cosmetic Product Ingredient and Cosmetic Raw Composition Statements. Final Rule. *Fed. Register* 57:3128–3130.

FDA. 2002. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

Hauck, R. S., C. Wegner, P. Blumtritt, J. H. Fuhrhop, and H. Nau. 1990. Asymmetric synthesis and teratogenic activity of (R)- and (S)-2-ehtylhexanoic acid, a metabolite of the plasticizer di-(2-ethylhexyl) phthalate. *Life Sci.* 46:513–518.

Hendrickx, A. G., P. E. Peterson, R. W. Tyl, L. C. Fisher, L. J. Fosnight, M. F. Kubena, M. A. Vrabanic, and G. V. Katz. 1993. Assessment of the develpmental toxicity of 2-ethylhexanoic acid in rats and rabbits. *Fundam. Appl. Toxicol.* 20:199–209.

Huntingdon Research Centre. 1977a. Acute oral toxicity to rats of Crodamol CAP. Unpublished data submitted by CTFA. March 14, 2002. 3 pages.[6]

Huntingdon Research Centre. 1977b. Irritant effects of Crodamol CAP on rabbit eye mucosa. Unpublished data submitted by CTFA. March 14, 2002. 5 pages.[6]

Huntingdon Research Centre. 1979. Irritant effects of Crodamol CAP on rabbit skin. Unpublished data submitted by CTFA. March 14, 2002. 4 pages.[6]

Huntingdon Research Centre. 1985. Repeated Insult Patch Test. Unpublished data submitted by CTFA. March 14, 2002. 13 pages.[6]

Juberg, D. R., R. M. David, G. V. Katz, L. G. Bernard, D. R. Gordon, M. S. Vlaovic, and D. C. Topping. 1998. 2-ethylhexanoic acid: Subchronic oral toxicity studies in the rat and mouse. *Food Chem. Toxicol.* 36:429–436.

Kröger, S. 1989. Gas chromatographic determination of 2-ethylhexanoic acid in urine as its pentafluorobenzyl ester. *Analyst* 114:1647–1648.

Kröger, S., J. Liesivuori, and A. Manninen. 1990. Evaluation of workers' exposure to 2-ethylhexanoic acid (2-EHA) in Finnish sawmills. *Int. Arch. Occup. Environ. Health* 62:213–216.

Laboratoire de Recherche et d'Experimentation. 1997. Industry data regarding cetearyl ethylhexanoate. Unpublished data submitted by CTFA. March 12, 2002. 7 pages.[6]

Manninen, A., S. Kröger, J. Liesivuori, and H. Savolainen. 1989. 2-Ethylhexanoic acid inhibits urea synthesis and stimulates carnitine acetyltransferase activity in rat liver mitochondria. *Arch. Toxicol*. 63:160–161.

Ministry of Health, Labor, and Welfare (MHLW). 2001a. Unofficial translation of MHW Ordinance No. 331, Attached Table 1 [Negative List]. Ministry of Health, Labor and Welfare, Pharmaceutical and Medical Safety Bureau, Inspection and Guidance Division, 2-2, 1-chome, Kasumigaseki, Chiyoda-ku, Tokyo 100-8045, Japan.[6]

MHLW. 2001b. Unofficial translation of MHW Ordinance No. 331, Attached Table 2 [Restricted List]. Ministry of Health, Labor, and Welfare, Pharmaceutical and Medical Safety Bureau, Inspection and Guidance Division, 2-2, 1-chome, Kasumigaseki, Chiyoda-ku, Tokyo 100-8045, Japan.[6]

Pennanen, S., and A. Manninen. 1991. Distribution of 2-ethylhexanoic acid in mice and rats after an intraperitoneal injection. *Pharmacol. Toxicol.* 68: 57–59.

Pennanen, S., A. Manninen, and H. Savolainen. 1990. Urinary arginine and ornithine in occupational exposure to 2-ethylhexanoic acid. *Arch. Toxicol.* 64:426–427.

Pennanen, S., K. Tuovinen, H. Huuskonen, and H. Komulainen. 1992. The developmental toxicity of 2-ethtylhexanoic acid in Wistar rats. *Fundam. Appl. Toxicol.* 19:505–511.

Pennanen, S., K. Tuovinen, H. Huuskonen, V. M., Kosma, and H. Komulainen. 1993. Effects of 2-ethylhexanoic acid on reproduction and postnatal development in Wistar rats. *Fundam. Appl. Toxicol*. 21:204–212.

Pradhan, M. 2002. Letter with independent toxicologist's evaluation of toxicological data, exposure levels, and assessment to Dr. F. Alan Andersen, dated April 11, 2002.[6]

Ritter, E. J., W. J. Scott, Jr., J. L. Randall, and J. M. Rittter. 1987. Teratogenicity of di(2-ethylhexyl) phthalate, 2-ethylhexanol, 2-ethylhexanoic acid, and valp roic acid, and potentia tion by caffeine. *Teratology* 35:41–46.

Scott, W. J., Jr., M. S. Collins, and H. Nau. 1994. Pharmacokinetic determinants of embryotoxicity in rats associated with organic acids. *Environ. Health Perspect*. 102:97–101.

Shell Oil Company. 1992a. Initial submission: Two-week oral (dietary administration) toxicity study of 2-ethylhexanoic acid in the mouse (Final Report) with cover letter dated 041792. NTIS Report No. OTS0539188.

Shell Oil Company. 1992b. Initial submission: Two-week oral toxicity study of 2-ethylhexanoic acid in the rat (Final Report) with cover letter dated 041792. NTIS Report No. OTS0539183.

Sipi, P., H. Jarventaus, and H. Norppa. 1992. Sister-chromatid exchanges induced by vinyl esters and respective carboxylic acids in cultured human lymphocytes. *Mutat. Res.* 279:75–82.

Union Carbide Corporation. 1992a. Initial Submission: Letter from Union Carbide Corp. to USEPA submitting information on the enclosed 90 day (dietary administration) toxicity study of 2-ethylhexanoic acid in the rat and mouse. NTIS Report No.OTS0543763.

Union Carbide Corporation. 1992b. Initial Submission: Letter from Union Carbide Corp. submitting two developmental toxicity studies with 2-ethylhexanoic acid in rats and rabbits with attachments. NTIS Report No. OTS0539327.

Wil Research Laboratories, Inc. 2001. A dietary two-generation reproductive toxicity study of di-2-ethylhexyl terephthalate in rats. Final Report. Unpublished data submitted by the American Chemistry Council. 3250 pages.[6]

## CETYL PALMITATE, OCTYL PALMITATE AND ISOPROPYL PALMITATE

A safety assessment of these ingredients was published in 1982 with the conclusion "safe as cosmetic ingredients in the present practices of use and concentration" (Elder 1982a). Studies available since that safety assessment was completed, along with the updated information regarding uses and use

concentrations, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

The Panel noted that Octyl Palmitate is now termed Ethylhexyl Palmitate (Wenninger et al. 2000).

In 1976, collectively, Cetyl Palmitate, Ethylhexyl Palmitate, and Isopropyl Palmitate were used in 1335 cosmetic products, with the largest single use in lipsticks in the concentration range of >1% to 10% (Elder 1982a). Currently, these three ingredients are collectively used in 1188 cosmetic products (FDA 2001), with the largest single use reported for eye shadows at concentrations up to 19% (CTFA 2001). Frequency and concentration of use data are displayed in Table 6.

**TABLE 6**
Historical and current cosmetic product uses and concentrations for Cetyl, Ethylhexyl, and Isopropyl Palmitate

| Product category | 1976 use (Elder 1982) | 2001 use (FDA 2001) | 1976 concentrations (Elder 1982) (%) | 2001 concentrations (CTFA 2001) (%) |
|---|---|---|---|---|
| | *Cetyl Palmitate* | | | |
| Eyebrow pencil | — | 9 | — | — |
| Eyeliner | — | 24 | — | 5–8 |
| Eye shadow | 7 | 2 | >1–5 | 11 |
| Eye lotion | — | 2 | — | — |
| Mascara | — | 1 | — | 0.2 |
| Eye makeup (other) | — | 16 | — | — |
| Sachets | 6 | 2 | >1–5 | — |
| Fragrance preparations (other) | — | 1 | — | — |
| Shampoos (noncoloring) | — | 12 | — | 1 |
| Hair tonics, dressings, etc. | 1 | — | >1–5 | — |
| Hair-coloring preparations (other) | — | — | — | 0.2 |
| Blushers | 24 | — | >0.1–5 | — |
| Foundations | 12 | 4 | >1–5 | 3 |
| Lipsticks | 290 | 10 | >1–10 | 10 |
| Makeup bases | 15 | — | >1–5 | — |
| Makeup (other) | 4 | 5 | >1–5 | 3 |
| Underarm deodorants | 1 | — | >1–5 | 0.3 |
| Personal cleanliness products (other) | 2 | — | >1–5 | 0.02 |
| Aftershave lotion | — | 3 | — | 1 |
| Shaving preparations (other) | — | 2 | — | — |
| Skin-cleansing creams, lotions, liquids, and pads | 3 | 10 | >1–5 | <0.1–1 |
| Face and neck skin care preparations | 1* | 18 | >1–5* | 3 |
| Body and hand skin care preparations | | 40 | | 0.01–6 |
| Moisturizers | 5 | 33 | >0.1–5 | 2–3 |
| Night skin care preparations | 1 | 12 | >1–5 | 3 |
| Paste masks (mud packs) | — | 4 | — | — |
| Skin fresheners | — | 1 | — | — |
| Skin care preparations (other) | 1 | 15 | >1–5 | 5 |
| Suntan gels, creams, and liquids | — | 5 | — | 2 |
| Suntan preparations (other) | — | 5 | — | 2 |
| **Total uses/ranges for Cetyl Palmitate** | **373** | **236** | **>0.1–10** | **0.01–11** |
| | *Ethylhexyl Palmitate* | | | |
| Bath oils, tablets, and salts | 7 | — | >1–10 | 10–23 |
| Bath preparations (other) | — | — | — | 6 |
| Eyeliner | — | 2 | — | 2–42 |
| Eye shadow | 24 | 129 | >1–50 | 0.2–19 |
| Eye makeup remover | 1 | 2 | >50 | 3 |
| Eye makeup (other) | 2 | 8 | >25–>50 | 2–24 |
| Colognes and toilet waters | — | 2 | — | — |
| Perfumes | 3 | — | >1–>50 | — |

*(Continued on next page)*

**TABLE 6**
Historical and current cosmetic product uses and concentrations for Cetyl, Ethylhexyl, and Isopropyl Palmitate *(Continued)*

| Product category | 1976 use (Elder 1982) | 2001 use (FDA 2001) | 1976 concentrations (Elder 1982) (%) | 2001 concentrations (CTFA 2001) (%) |
|---|---|---|---|---|
| Powders | 3 | 1 | >0.1–1 | 0.3 |
| Fragrance preparations (other) | 1 | — | >1–5 | 15 |
| Hair conditioners | — | — | — | 4–17 |
| Rinses (noncoloring) | — | — | — | 2 |
| Hair tonics, dressings, etc. | — | — | — | 4–17 |
| Hair preparations (other) | — | — | — | 17 |
| Blushers | 14 | 46 | >1–>50 | 0.1–46 |
| Face powders | 14 | 12 | >1–10 | 5–22 |
| Foundations | 9 | 16 | ≤0.1–5 | 4–42 |
| Lipsticks | 51 | 100 | >1–10 | 4–42 |
| Makeup bases | 8 | 9 | >1–5 | 5 |
| Rouges | — | 1 | — | — |
| Makeup (other) | 1 | 8 | >1–5 | 1–50 |
| Cuticle softeners | — | 1 | — | 30 |
| Nail creams and lotions | — | 2 | — | 28 |
| Nail polish and enamel | — | — | — | 7 |
| Manicuring preparations (other) | — | — | — | 5–10 |
| Underarm deodorants | — | 1 | — | 2 |
| Personal cleanliness products (other) | 3 | — | >0.1–5 | 6 |
| Aftershave lotion | 1 | 1 | >1–5 | 1–4 |
| Preshave lotions | 2 | — | >1–5 | — |
| Shaving cream | — | 3 | — | — |
| Skin-cleansing creams, lotions, liquids, and pads | 1 | 4 | >1–5 | 2–10 |
| Face and neck skin care preparations | 21* | 3 | ≤0.1–25* | 12–21 |
| Body and hand skin care preparations | | 16 | | 3–30 (21% in a spray) |
| Moisturizers | 21 | 26 | ≤0.1–25 | 2–29 |
| Night skin care preparations | 20 | 8 | >0.1–25 | 8–21 |
| Paste masks (mud packs) | — | 1 | — | 3–8 |
| Skin fresheners | 4 | — | >1–5 | 3 |
| Skin care preparations (other) | 7 | 12 | >1–25 | 4–21 |
| Suntan gels, creams, and liquids | 8 | — | >1–10 | 2–6 |
| Indoor tanning preparations | — | 3 | — | 3–21 |
| Suntan preparations (other) | — | — | — | 0.5–16 |
| **Total uses/ranges for Ethylhexyl Palmitate** | **226** | **417** | **≤0.1–>50** | **0.1–46** |
| | *Isopropyl Palmitate* | | | |
| Baby lotions, oils, powders, and creams | 3 | 4 | >0.1–5 | 5 |
| Baby products (other) | — | 1 | — | — |
| Bath oils, tablets, and salts | 42 | 20 | >0.1–>50 | 26–60 |
| Bubble baths | — | — | — | 0.3–1 |
| Bath capsules | 3 | — | >25–50 | 45 |
| Bath preparations (other) | 8 | — | ≤0.1–>50 | 41 |
| Eyebrow pencil | — | 1 | — | 3 |
| Eyeliner | — | — | — | 2 |
| Eye shadow | 16 | 5 | >1–10 | 3–10 |
| Eye lotion | — | 1 | — | — |
| Eye makeup remover | 4 | 5 | ≤0.1–50 | 7 |
| Mascara | — | 1 | — | 0.25 |
| Eye makeup (other) | 6 | 6 | >5–25 | 7 |

*(Continued on next page)*

**TABLE 6**
Historical and current cosmetic product uses and concentrations for Cetyl, Ethylhexyl, and Isopropyl Palmitate *(Continued)*

| Product category | 1976 use (Elder 1982) | 2001 use (FDA 2001) | 1976 concentrations (Elder 1982) (%) | 2001 concentrations (CTFA 2001) (%) |
|---|---|---|---|---|
| Colognes and toilet waters | 2 | 3 | ≤0.1 | 31–46 |
| Perfumes | 58 | 10 | >1–>50 | 39–46 |
| Powders | 10 | 1 | >0.1–10 | — |
| Fragrance preparations (other) | 51 | 9 | ≤0.1–50 | 40–60 |
| Hair conditioners | 1 | 9 | >1–5 | 4 |
| Hair sprays (aerosol fixatives) | 2 | 2 | >0.1–5 | — |
| Shampoos (noncoloring) | 1 | 3 | >0.1–1 | 0.00005 |
| Hair tonics, dressings, etc. | 1 | 3 | >1–5 | 3–12 |
| Wave sets | 2 | — | >1–5 | 2 |
| Hair bleaches | 2 | 16 | >0.1–1 | — |
| Blushers | 17 | 11 | >1–50 | 4–8 |
| Face powders | 31 | 11 | >0.1–5 | 0.00001–14 |
| Foundations | 28 | 19 | >0.1–50 | 7–22 |
| Lipsticks | 220 | 80 | >1–25 | 5–22 |
| Makeup bases | 4 | 28 | >1–25 | 0.7 |
| Rouges | 1 | — | >25–50 | — |
| Makeup fixatives | — | — | — | 37 |
| Makeup (other) | 6 | 6 | >0.1–25 | 6–22 |
| Cuticle softeners | 1 | 2 | >1–5 | 0.06–4 |
| Nail creams and lotions | — | 1 | — | 4–10 |
| Nail polish and enamel | — | — | — | 3 |
| Nail polish and enamel removers | 3 | 1 | >0.1–5 | 5 |
| Nail care preparations (other) | — | 2 | — | 0.5–3 |
| Bath soaps and detergents | — | 3 | — | 0.00005–5 |
| Underarm deodorants | 9 | 1 | >0.1–10 | 0.003–17 |
| Feminine deodorants | 12 | — | >0.1–5 | — |
| Personal cleanliness products (other) | 15 | 8 | >0.1–10 | 0.00001 |
| Aftershave lotion | 2 | 9 | >0.1–5 | 5–8 |
| Beard softeners | — | — | — | 0.001 |
| Preshave lotions | 1 | — | >10–25 | — |
| Shaving cream | 1 | 1 | >0.1–1 | — |
| Shaving preparations (other) | — | 1 | — | — |
| Skin-cleansing creams, lotions, liquids, and pads | 20 | 27 | >1–>50 | 0.000002–11 |
| Face and neck skin care preparations | 61* | 15 | | 2–10 |
| Body and hand skin care preparations | | 80 | >0.1–>50* | 3–15 (11% in a spray) |
| Hormone preparations | 4 | N/A** | >1–25 | N/A** |
| Foot powders and sprays | 3 | 2 | >0.1–1 | 0.2 |
| Moisturizers | 57 | 61 | ≤0.1–50 | 4–15 |
| Night skin care preparations | 17 | 8 | >0.1–25 | 2–10 |
| Paste masks (mud packs) | — | 7 | — | 7 |
| Skin fresheners | 1 | 2 | >5–10 | 2 |
| Skin care preparations (other) | 2 | 32 | >50 | 6–44 |
| Suntan gels, creams, and liquids | 8 | 12 | >0.1–50 | 2–5 |
| Indoor tanning preparations | — | 4 | — | 0.8–5 |
| Suntan preparations (other) | — | 1 | — | 1–2 |
| **Total uses/ranges for Isopropyl Palmitate** | **736** | **535** | **≤0.1–>50** | **0.000002–44** |

*This category was combined when the original safety assessment was performed and is now two separate categories.
**No longer considered a cosmetic product category.

## REFERENCES


Alvarado, R., M. Dickens, M. Klausner, K. Renskers, and M. Stern. 1998. Evaluation of the EpiOcular™ tissue model as an alternative to the Draize eye irritation test. *Toxicol. In Vitro* 12:455–461.

Andersen, F. A., ed. 1997. Final report on the safety assessment of cetylesters. *Int. J. Toxicol.* 16:123–130.

Bagheri, D., B. W. Blake, K. Enslein, V. K. Gombar, J. J. Hostynek, H. I. Maibach, and C. C. Sigman. 1997. A quantitative structure-toxicity relationships model for the dermal sensitization guinea pig maximization assay. *Food Chem. Toxicol.* 35:1091–1098.

Basketter, D. A., M. Chamberlain, H. A. Griffiths, M. Rowson, E. Whittle, and M. York. 1997. The classification of skin irritants by human patch test. *Food Chem. Toxicol.* 35:845–852.

Blevins, R. D., and D. E. Taylor. 1982. Mutagenicity screening of twenty-five cosmetic ingredients with the Salmonella/microsome test. *J. Environ. Sci. Health A* 17:217–239.

Blum, R. P., A. Dingler, S. Gohla, R. H. Muller, and H. Niehus. 1999. Solid lipid nanoparticles (SLN/Lipopearls)-a pharmaceutical and cosmetic carrier for the application of vitamin E in dermal products. *J. Microencapsul.* 16:751–767.

Brabec, V., and V. Sebestik. 1983. Experimental elimination of the splenic function by ethyl and methyl palmitate and significance of these substances from an immunological point of view. *Folia Haematol. Int. Mag. Klin. Morphol. Blutforsch.* 110:917–923.

Conte, A., C. Coviello, F. Rantuccio, A. Scardigno, and D. Sinisi. 1984. Histological changes in rabbits after application of medicaments and cosmetic bases (III). *Contact Dermatitis* 10:212–219.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2001. Concentrations of use of stearates. Unpublished data submitted by CTFA.[7]

Dreher, F., P. Elsner, P. L. Luisi, and P. Walde. 1996. Human skin irritation studies of a lecithin microemulsion gel and of lecithin liposomes. *Skin Pharmacol.* 9:124–129.

Dreher, F., P. Walde, P. Walther, and E. Wehrli. 1997. Interaction of a lecithin microemulsion gel with human stratum corneum and its effect on transdermal transport. *J. Controlled Release* 45:131–140.

Elder, R. L., ed. 1982a. Final report on the safety assessment of octyl palmitate, cetyl palmitate, and isopropyl palmitate. *J. Am. Col. Toxicol.* 1:13–35.

Elder, R. L., ed. 1982b. Final report on the safety assessment of myristyl myristate and isopropyl myristate. *J. Am. Col. Toxicol.* 1:55–80.

Elder, R. L., ed. 1985. Final report on the safety assessment of butyl stearate, cetyl stearate, isobutyl stearate, isocetyl stearate, isopropyl stearate, myristyl stearate, and octyl stearate. *J. Am. Col. Toxicol.* 4:107–146.

Finn, M. D., E. D. Schneiderman, and S. R. Schow. 1992. Osseous regeneration in the presence of four common hemostatic agents. *J. Oral Maxillofac. Surg.* 50:608–612.

Food and Drug Administration (FDA). 2001. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

Fulton, J. E., Jr., J. E. Fulton 3rd, and S. R. Pay. 1984. Comedogenicity of current therapeutic products, cosmetics, and ingredients in the rabbit ear. *J. Am. Acad. Dermatol.* 10:96–105.

Hahn, H., U. Katzfey, O. Liesenfeld, R. H. Muller, N. Scholer, and E. Zimmermann. 2000. Preserved solid lipid nanoparticles (SLN) at low concentrations do cause neither direct nor indirect cytotoxic effects in peritoneal macrophages. *Int. J. Pharm.* 196:235–239.

Hansen, E., P. Liu, J. Nightingale, and J. Sclafani. 1997. Effect of water on a new binary transdermal flux enhancer (Peg3-Me): In vitro evaluation using estradiol. *Drug Dev. Ind. Pharm.* 23:9–14.

Jung, S., S. Kang, J. Kim, and M. Park. 1999. Skin organ culture for cutaneous irritancy screening. *In Vitro Mol. Toxicol.* 12:77–82.

Klykken, P. C., and K. L. White. Jr. 1996. The adjuvancy of silicones: Dependency on compartmentalization. *Curr. Top. Microbiol Immunol.* 210:113–121.

Lazzarini, S. 1982. Contact allergy to benzyl alcohol and isopropyl palmitate, ingredients of topical corticosteroid. *Contact Dermatitis* 8:349–350.

Opdyke, D. L. 1981. Monographs on fragrance raw materials. *Food Cosmet Toxicol.* 19:237–254.

Wenninger, J. A., R. C. Canterbery, and G. N. McEwen. Jr., eds. 2000. *International Cosmetic Ingredient Dictionary and Handbook*, 8th ed., 254, 532, 722. Washington, DC: CTFA.


[7]Available from the Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

## CHOLETH-24

A safety assessment of Choleth-24 was published in 1982 with the conclusion "safe for topical application to humans in the present practices of use and concentration" (Elder 1982).

Studies available since that safety assessment was completed, along with the updated information regarding uses and use concentrations, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

The CIR Expert Panel noted that Choleth-24 may increase the skin penetration of other cosmetic ingredients, and that this should be considered when formulating cosmetic products.

In 1976, Choleth-24 was used in 135 cosmetic products, with the largest single use in hair dyes and colors in the concentration range of >0.1% to 1%. Currently there are uses reported in 191 products, with the largest single use also in hair dyes and colors at a maximum concentration of 0.5% (0.3% after dilution).

Table 7 presents the available use information.

## REFERENCES


Cosmetic, Toiletry, and Fragrance Association (CTFA). 2002. Use concentrati on data on choleth-24 from in dustry survey. Unpublished data submitted by CTFA, April 2001. 2 pages.[8]

Dimitrijevic, D., C. Lamandin, I. F. Uchegbu, A. J. Shaw, and A. T. Florence. 1997. The effect of monomers and of micellar and vesicular forms of nonionic surfactants (Solulan C24 and Solulan 16) on Caco-2 cell monolayers. *J. Pharm. Pharmacol.* 49:611–616.

Dimitrijevic, D., A. J. Shaw, and A. T. Florence. 2000. Effects of some nonionic surfactants on transepithelial permeability in Caco-2 cells. *J. Pharm. Pharmacol.* 52:157–162.

Drewe, J., G. Fricker, J. Vonderscher, and C. Beglinger. 1993. Enteral absorption of octreotide: Absorption enhancement by polyoxyethylene-24-cholesterol ether. *Br. J. Pharmacol.* 108:298–303.

Elder, R. L., ed. 1982. Final report on the safety assessment of choleth-24. *J. Am. Col. Toxicol.* 1:119–126.

Ennis, R. D., L. Borden, and W. A. Lee. 1993. The effects of permeation enhancers on the surface morphology of the rat nasal mucosa: A scanning electron microscopy study. *Pharm. Res.* 7:468–475.

Food and Drug Administration (FDA). 2001. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

Food and Drug Administration (FDA). 2002. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

Franz, J. M., and J. P. Vonderscher. 1981. Enhancement of the intestinal absorption of ergot peptide alkaloids in the rat by micellar solutions of polyoxyethylene-24-cholesteryl ether. *J. Pharm. Pharmacol.* 33:565–568.


[8]Available from the Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

**TABLE 7**
Historical and current cosmetic product uses and concentrations for Choleth-24

| Product category | 1976 use (Elder 1982) | 2002 use (FDA 2002) | 1976 concentrations (Elder 1982) (%) | 2002 concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| Bubble baths | 1 | 2 | >1–5 | — |
| Eyeliner | 14 | — | >1–5 | 0.3 |
| Eye shadow | 2 | 1 | >0.1–1 | — |
| Eye lotion | — | 1 | — | 0.3 |
| Mascara | 6 | — | >0.1–5 | 0.2 |
| Eye makeup preparations (other) | 1 | 2 | >0.1–1 | 0.3 |
| Perfumes | — | 9 | — | 0.3 |
| Sachets | — | — | — | 0.3 |
| Fragrance preparations (other) | — | 8 | — | — |
| Hair conditioners | 10 | 9 | >0.1–5 | 0.3–1 |
| Rinses (noncoloring) | — | — | — | 0.2 |
| Shampoos (noncoloring) | 3 | 1 | >0.1–5 | — |
| Hair tonics, dressings, etc. | 1 | 2 | >1–5 | — |
| Hair preparations (other) | — | 3 | — | — |
| Hair dyes and colors | 71 | 38 | >0.1–1 | 0.5 (0.3 after dilution) |
| Blushers | 1 | — | >0.1–1 | — |
| Face powders | — | — | — | 0.2 |
| Foundations | — | 19 | — | 0.2–0.3 |
| Leg and body paints | 1 | — | >1–5 | — |
| Makeup bases | 1 | — | >0.1–1 | 0.5 |
| Makeup (other) | 1 | 2 | >1–5 | 0.2–0.5 |
| Cuticle softeners | — | — | — | 0.3 |
| Bath soaps and detergents | — | — | — | 0.002–0.7 |
| Aftershave lotion | 1 | 7 | >1–5 | 0.3 |
| Skin-cleansing creams, lotions, liquids, and pads | 4 | — | >0.1–1 | 0.3 |
| Face and neck skin care preparations | 5* | 4 | ≤0.1–1* | 0.4 |
| Body and hand skin care preparations | | 28 | | 0.1–0.7 |
| Foot powders and sprays | — | 1 | — | 0.3 |
| Moisturizers | 2 | 28 | 0.1–1 | 0.008–1.3 |
| Night skin care preparations | 2 | 6 | >0.1–1 | 0.2–0.3 |
| Paste masks (mud packs) | — | 1 | — | 0.3 |
| Skin fresheners | 2 | 2 | >0.1–5 | — |
| Skin care preparations (other) | 8 | 11 | >0.1–1 | 0.1–0.3 |
| Suntan gels, creams, and liquids | — | 3 | — | 0.3 |
| Indoor tanning preparations | — | 2 | — | — |
| Suntan preparations (other) | — | 1 | — | — |
| **Total uses/ranges for Choleth-24** | **135** | **191** | **≤0.1–5** | **0.002–1.3** |

*This category was combined when the original safety assessment was performed and is now two separate categories.

Pepe, R. C., J. A. Wenninger, and G. N. McEwen, Jr., eds. 2002. *International Cosmetic Ingredient Dictionary and Handbook*, 9th ed., 328. Washington, DC: CTFA.

Robinson, C. J., S. G. Shirley, and G. H. Dodd. 1989. The detergent Solulan C-24 reveals properties of the olfactory adenylate cyclase system. *Biochem. J.* 260:683–688.

Tasset, C., F. Goethals, V. Preat, and M. Roland. 1990. Effect of polyoxyethyleneglycol (24) cholesterol on the solubility, toxicity, and activity of amphotericin B. *Int. J. Pharm.* 58:41–48.

Tasset, C., V. Preat, A. Bernard, and M. Roland. 1992. Comparison of nephrotoxicities of different polyoxyethylene formulations of amphotericin B in rats. *Antimicrob Agents Chemother.* 36:1525–1531.

Uchegbu, I. F., J. A. Double, J. A. Turton, and A. T. Florence. 1995. Distribution, metabolism, and tumoricidal activity of doxorubicin administered in sorbitan monostearate (Span 60) niosomes in the mouse. *Pharm. Res.* 12:1019–1024.

Uchegbu, I. F., and R. Duncan. 1997. Niosomes containing (2-hydroxypropyl)methacrylamide copolymer-doxorubicin (PK1): Effect of method of preparation and choice of surfactant on niosome characteristics and a preliminary study of body distribution. *Int. J. Pharm.* 155:7–17.

Viernstein, H., B. Gottwald, and A. Wottawa. 1987. The mutagenic potential of sterol ethers. *Oesterr Forschungszent Seibersdorg* Report No. OEFZS-4388:1–10.

Werner, U., T. Kissel, and M. Reers. 1996. Effects of permeation enhancers on the transport of a peptidomimetic thrombin inhibitor (CRC 220) in a human intestinal cell line (Caco-2). *Pharm. Res.* 13:1219–1227.

## DIBUTYL PHTHALATE, DIETHYL PHTHALATE, AND DIMETHYL PHTHALATE

A safety assessment of Dibutyl Phthalate (DBP), Diethyl Phthalate (DEP), and Dimethyl Phthalate (DMP) was published in 1985 with the conclusion that these ingredients "are safe for topical application in the present practices of use and concentrations in cosmetics" (Elder 1985). Since then many additional studies have appeared in the scientific literature. These studies, along with the updated information in Table 8 regarding uses and use concentrations, were considered by the CIR Expert Panel. Based on its consideration of the data discussed below, the Panel decided not to reopen this safety assessment.

DBP, DEP, and DMP are phthalate diesters that are used in cosmetics as plasticizers, solvents and fragrance ingredients in a wide variety of cosmetic product types. DEP is also used as a denaturant. DBP is found primarily in nail care products (at concentrations up to 15%) and in some hair care formulations (up to 0.1%). DEP is found in certain bath preparations, fragrance products, deodorants, lotions, and other skin care products. The highest reported concentration of use of DEP is 11% in perfumes. DMP is an ingredient in some hair care products, including aerosol fixatives. The reported maximum concentration of use of DMP in cosmetics is 2% in aerosol hair sprays. Table 8 provides the frequency and concentration of use as a function of product type.

Recent studies document that DBP, DEP, and DMP all absorb readily through the skin and through the gastrointestinal (GI) tract. Once absorbed, most short-chain phthalate diesters are hydrolyzed to the corresponding monoester and alcohol. The phthalates and their metabolites distribute to most tissues, and cross the placenta, but they do not accumulate in any specific tissue type. Phthalates are quickly eliminated in the urine, usually as the corresponding monoester or its glucuronide conjugate. However, humans and primates metabolize longer-chain diester phthalates (e.g., DEHP) into the glucuronide-conjugated monoester forms to a much larger extent than do rats. Also, rats excrete three to four times more free unconjugated MBP than do hamsters given similar doses of DBP or MBP, possibly due to greater testicular $\beta$-glucuronidase activity in rats than in hamsters. Phthalates undergo some enterohepatic cycling, and some phthalate is eliminated in the feces.

New data on acute and short-term toxicity were consistent with previously available data.

In a NTP study, DBP, DEP, and DMP were not found to be dermal irritants or sensitizers, confirming previous data using human and animal subjects.

Although previous data had identified that orally administered (in feed or by gavage) DBP and its metabolite MBP have reproductive and developmental effects in rodents, with impaired male development being the most sensitive effect, newly available data provided additional demonstration of such effects.

When pregnant rats and mice were exposed to 1.0% DBP in powdered feed throughout gestation, the pregnancy outcome showed reductions in fertility, number of pups per litter, number of live pups, and body weights of pups. Adult male rats exposed to 1.0% DBP showed signs of liver and kidney toxicity and reduced weights of the prostate, testes, and seminal vesicles. Pregnant rats exposed to 2% DBP in feed throughout pregnancy had a higher incidence of preimplantation loss and resorptions, and no male pups were born alive. Exposure to 1% or 2% DBP in feed only during the latter half of gestation did not show the preimplantation loss and resorption rate seen in rats exposed throughout pregnancy. However, the increased survivability of these fetuses allowed the morphological defects of developing fetuses to be observed. These defects included reduced body weights in both sexes at 2% DBP, reduced anogenital distance and undescended testes in male fetuses at 1% and 2% DBP, and increased incidence of cleft palate and fused sternebrae. Adverse fetal effects were not seen in this study in a 0.5% DBP feed group, or at 331 mg/kg/day, based on average food consumption.

Oral intubation (gavage) of DBP in rats during gestation produced similar effects to those seen in the feeding studies described above. Pregnant rats given oral doses of approximately 0.63 to 0.75 g/kg/day and higher on certain gestation days produced litters with higher incidences of fetal toxicity and malformations. Exposure to DBP on gestation days 7 through 9 or on days 13 through 15 results in increased incidence of skeletal malformations such as cleft palate, fused sternebrae, and vertebral anomalies, as well as dilatation of the renal pelvis and undescended testes. However, exposure to DBP on gestation days 10 through 12 did not produce these effects, suggesting that DBP teratogenicity may be age dependent. Prenatal exposure to MBP appears to produce fetotoxicity and teratogenicity similar to DBP, following the same patterns of age-dependent sensitivity and dose efficacy. This supports the proposal that it is the monoester metabolite that produces the developmental toxicity of DBP and other phthalates.

DEP fed to mice at concentrations up to 2.5% (calculated to be 3.64 g/kg/day) in a continuous breeding protocol produced no effects of DEP on fertility or pregnancy outcome in the $F_0$ generation. $F_1$ male mice of the 2.5% DEP group had enlarged prostates and reduced sperm counts, but sperm motility and morphology were not affected. The $F_2$ generation showed no treatment-related differences between DEP and control groups. Pregnant rats fed up to 5.0% DEP mixed in feed on gestation days 6 through 15 produced no treatment-related alterations in fetal viability or development.

Repeated dermal application of 2 ml/kg up to 50% DEP to pregnant rabbits on gestation days 6 through 18 did not produce maternal or fetal toxicity or affect fetal development.

DMP was not fetotoxic or teratogenic when administered dermally (in rats) or orally (in rats and mice) during gestation.

**TABLE 8**
Historical and current cosmetic product uses and concentrations for Dibutyl, Diethyl, and Dimethyl Phthalate

| Product category | 1981 use (Elder 1985) | 2001 use (FDA 2001) | 1981 concentrations (FDA 1981) (%) | 2001 concentrations (CTFA 2001a, 2001b, 2001c) (%) |
|---|---|---|---|---|
| | | *Dibutyl Phthalate* | | |
| Perfumes | — | — | — | 38–890 ppm** |
| Hair sprays | — | — | — | 55–160 ppm** |
| Shampoos (noncoloring) | — | — | — | 0.007 |
| Hair preparations (other noncoloring) | 3 | — | >0.1–1 | — |
| Hair-coloring preparations (other) | 3 | — | >0.1–1 | 0.1 |
| Aftershave lotions | 3 | — | >0.1–1 | — |
| Hair bleaches | — | — | — | 0.1 |
| Makeup (other) | 1 | — | >0.1–1 | 0.5 |
| Nail basecoats and undercoats | 36 | 32 | >1–10 | 1–6; 15* |
| Nail creams and lotions | — | 2 | — | 5 |
| Nail extenders | — | — | — | 1; 1* |
| Nail polish and enamel | 522 | 88 | ≤25 | 0.5–15; 15* |
| Nail polish and enamel removers | 3 | — | 0.1–25 | 2 |
| Nail care preparations (other) | 14 | 25 | ≤25 | 5–7; 6* |
| Underarm deodorants | — | — | — | 140–200 ppm** |
| Personal cleanliness products (other) | 5 | 3 | >1–5 | — |
| **Total uses/ranges for Dibutyl Phthalate** | **590** | **150** | **0.1–25** | **0.0038–15** |
| | | *Diethyl Phthalate* | | |
| Baby shampoos | — | — | — | 0.03 |
| Baby lotions, oils, powders, and creams | — | — | — | 0.00003 |
| Baby products (other) | — | — | — | 0.05 |
| Bath oils, tablets, and salts | 3 | 1 | ≤5 | — |
| Bubble baths | — | — | — | 0.06 |
| Bath preparations (other) | 2 | 2 | ≤0.1 | 0.008–0.09 |
| Colognes and toilet waters | 19 | 24 | ≤5 | 0.2–2 |
| Perfumes | 23 | 7 | ≤50 | 1–11 |
| Powders | 1 | 5 | >0.1–1 | — |
| Sachets | 3 | 2 | >0.01–5 | — |
| Other fragrance preparations | 2 | 11 | >0.1–50 | 0.01–1<br>67–28,000 ppm** |
| Hair conditioners | — | — | — | 0.1–0.2 |
| Hair sprays (aerosol fixatives) | 5 | — | >0.1–5 | 0.4<br>17–1500 ppm** |
| Shampoos (noncoloring) | — | — | — | 0.0008–0.2 |
| Hair tonics, dressings, etc. | — | 1 | — | 14–220 ppm** |
| Wave sets | 1 | — | >0.1–1 | — |
| Face powders | — | — | — | 0.4 |
| Eye shadow | 1 | — | ≤0.1 | — |
| Eyebrow pencil | — | — | — | 0.007 |
| Mascara | — | — | — | 0.007–0.07 |
| Eye makeup preparations (other) | — | — | — | 0.07 |
| Foundations | — | — | — | 0.3 |
| Makeup (other) | — | — | — | 0.0003 |
| Nail polish and enamel | — | — | — | 0.1 |
| Nail polish and enamel remover | 1 | — | >1–5 | — |

*(Continued on next page)*

**TABLE 8**
Historical and current cosmetic product uses and concentrations for Dibutyl, Diethyl, and Dimethyl Phthalate *(Continued)*

| Product category | 1981 use (Elder 1985) | 2001 use (FDA 2001) | 1981 concentrations (FDA 1981) (%) | 2001 concentrations (CTFA 2001a, 2001b, 2001c) (%) |
|---|---|---|---|---|
| Nail care preparations (other) | — | — | — | 0.2 |
| Bath soaps and detergents | 1 | — | >0.1–1 | 2 |
| Underarm deodorants | — | 4 | — | 0.3–1<br>20–3300 ppm** |
| Feminine hygiene deodorants | — | — | — | 0.4 |
| Other personal cleanliness products | — | — | — | 1 |
| Aftershave lotion | 3 | 4 | >0.1–1 | 0.5–2 |
| Shaving cream (aerosol, brushless, and lather) | — | — | — | 0.001 |
| Other shaving preparation products | — | — | — | 1 |
| Skin-cleansing creams, lotions, liquids and pads | — | — | — | 0.0002 |
| Face and neck skin care preparations | 1*** | — | ≤0.1*** | 0.3 |
| Body and hand skin care preparations | | 2 | | 0.008–0.5<br>26–190 ppm** |
| Foot powders and sprays | — | — | — | 1 |
| Night skin care preparations | — | — | — | 0.0004 |
| Paste masks (mud packs) | — | 1 | — | 0.1 |
| Skin fresheners | — | 4 | — | 0.1–0.9 |
| Skin care preparations (other) | 1 | 5 | >0.1–1 | 0.00003–0.9 |
| **Total uses/ranges for Diethyl Phthalate** | **67** | **73** | **≤ 0.1–50** | **0.00003–2** |
| | *Dimethyl Phthalate* | | | |
| Hair conditioners | 2 | — | >0.1–1 | — |
| Hair sprays (aerosol fixatives) | — | 8 | — | 0.00002–2 |
| Hair rinses | 1 | — | >0.1–1 | — |
| Shampoos (noncoloring) | — | — | — | 0.00002 |
| Hair tonics, dressings, etc. | 2 | — | >0.1–5 | — |
| Wave sets | 2 | — | >0.1–1 | — |
| Hair preparations (other noncoloring) | 4 | 3 | >0.1–1 | — |
| Hair color sprays (aerosol) | — | 1 | — | — |
| Blushers | — | — | — | 0.00008 |
| Face powders | — | — | — | 0.00008 |
| Foundations | — | — | — | 0.005 |
| Bath soaps and detergents | — | — | — | 0.004 |
| Underarm deodorants | — | — | — | 33 ppm**–0.2 |
| Aftershave lotions | — | — | — | 0.2 |
| **Total use/ranges for Dimethyl Phthalate** | **11** | **12** | **>0.1–5** | **.00002–2** |

*Maximum concentrations reported by Nail Manufacturers Council (NMC 2001).
**Concentrations found in off-the-shelf products (Houlihan et al. 2002).
***These categories were combined when the original safety assessment was performed and are now separate categories.

Exposure to some phthalates has been shown to cause impairments of normal male development in rodents. The documented male-specific effects of phthalates include malformations of the epididymis and vas deferens, undescended testes, hypospadias, retention of thoracic nipples, and reduced anogenital distance. DEP and DMP did not cause the dramatic effects on male development seen with longer-chain dialkyl phthalates. Many studies have reviewed the mechanisms of the male-targeted toxicity of phthalates. DBP, DEP, and DMP have weak or no binding affinity for the estrogen receptor and do not affect estrogen-regulated developmental endpoints. An antiandrogenic mechanism has been proposed, but many studies show that these phthalates do not bind with androgen receptors, either. However, phthalate esters inhibit the synthesis of testosterone, which is an important

hormone in normal development in males. DBP has also been shown to inhibit the action of Müllerian Inhibiting Substance produced by Sertoli cells.

DBP, DEP, and DMP previously had been screened for mutagenicity in the Ames bacterial reverse mutation assay with no mutagenic potential found. Additional data were available reporting that DBP caused an increase in the number of TA100 revertants in the absence but not in the presence of S9 rat liver fraction. DEP caused increases in the numbers of TA100 and TA1535 revertants, but this effect was also eliminated by the presence of S9. DMP caused an increase in the number of TA1535 revertants, but S9 prevented the effect. Overall, DBP, DEP, and DMP continue to have little genotoxic potential. One study on males of subfertile couples examined the relationship between environmental exposures to phthalates and DNA damage in human sperm using the neutral comet assay which is said to measure at least two aspects of DNA integrity. Neither the monobutyl form of DBP nor DMP had a significant association with comet assay parameters, and a significant association with the monobutyl form of DEP was seen only with one measure of DNA integrity.

Phthalates are a matter of concern for those responsible for public health and have been (and continue to be) reviewed by many government and international organizations. Phthalates are ubiquitous in the modern environment. The monoester metabolites sof phthalates have been detected in the urine of an adult reference population and in the urine of young children in a small pilot study.

The Centers for Disease Control and Prevention (2003) found that the urinary concentrations of the monoester metabolites of DBP and DEP in 2536 Americans were similar or slightly lower than those reported in a preliminary study of 289 adults (Blount et al. 2000). Environmental exposure to phthalates and other endocrine disruptors have been proposed to be linked to an increased incidence of hypospadias in humans. The developmental effects of phthalates seen in rodents raise questions about the potential for human health risks. However, these effects seen in rodents are at much higher exposure levels than humans are likely to encounter, and they are subject to the species differences in the metabolism of phthalate diesters. The estimated median exposure levels of DEP and DBP are 57 $\mu$g/kg/day and 7 $\mu$g/kg/day, respectively, while the U.S. EPA reference doses (RfD) for DEP and DBP are 800 $\mu$g/kg/day and 100 $\mu$g/kg/day, respectively. Thus, the human exposure is well below the safety limits set by the U.S. EPA. Even the median exposure levels of the highest-exposed group (women aged 20 to 40 years) are well below the RfDs. Exposure levels were not available for DMP.

Scientific committees with the governments of the United States and the European Union have evaluated the human risks of DBP and DEP and expressed minimal to no concern over consumer exposure to these compounds (NTP Center for the Evaluation of Risks to Human Reproduction 2000; Netherlands Organization for Applied Scientific Research and National Institute of Public Health and the Environment 2000; Scientific Committee on Cosmetic Products and Non-Food Products 2002).

As in the original safety assessment of these phthalate diesters in 1984, the primary safety issue regarding phthalate esters in this re-review is antiandrogenic activity and the potential effects on male development. The CIR Expert Panel noted that the free monoester metabolite appears to be the active agent in phthalate diester toxicity. Of the three compounds reviewed in this safety assessment, Dibutyl Phthalate raised the most concern.

The Panel reviewed the numerous studies that describe the developmental toxicity of DBP in rodents. The Panel noted that the no observed adverse effect level (NOAEL) of DBP in a gavage study was 50 mg/kg/day (Mylchreest et al. 2000). However, a feeding study reported a NOAEL of 331 mg/kg/day (Ema et al. 1998). Overall, the Panel felt that feeding studies better represent the type of exposure that humans would receive from cosmetics than do gavage studies, but agreed that a worst-case NOAEL of 50 mg/kg/day should be considered.

The Panel considered a Margin of Safety (MOS) approach to assess the risk of DBP exposure to human users of cosmetics based on calculated exposures and the animal developmental toxicity data. Exposure calculations were based on ingredient concentration of use in cosmetic products (CTFA, 2001a, 2001b, 2001c; Houlihan et al. 2002), extent of cosmetic use survey data (Environ Corporation 1985; CTFA 2002b), and dermal (Mint et al. 1994) and subungual penetration data (Jackson Research Association 2002). A conservative approach to penetration was used; i.e., an estimate of approximately 5% absorption of DEP in human skin was considered to be a conservative estimate of DBP absorption, because data suggest that DEP is more readily absorbed in rat skin than DBP (Scott et al. 1987). The Panel used an estimated consumer body weight of 60 kg.

The expected exposure was calculated as follows:

### Nail Basecoat or Polish

- 280 mg/application to 10 fingernails (Environ Corporation 1985)
- 15% maximum DBP in nail basecoats and polish (CTFA 2001a, 2001b, 2001c; Houlihan et al. 2002)
- 8.5% penetration through nail in 14 days (Jackson Research Association 2002)

280 mg/day $\times$ 15% $\times$ 8.5%/14 days = 0.255 mg/day/60 kg = 4.25 $\mu$g/kg/day and 4.25 $\mu$g/kg/day $\times$ 2 (for fingers and toes) = 8.5 $\mu$g/kg/day.

### Hair Spray

- 5 g/day hair spray use (CTFA, 2002)
- 160 $\mu$g/g DBP in hair spray (Houlihan et al. 2002)
- 20% skin contact, from CTFA maximum worst case
- 5% skin absorption (Mint et al. 1994)

5 g/day $\times$ 160 $\mu$g/g $\times$ 20% $\times$ 5% = 8 $\mu$g/day/60 kg = 0.14 $\mu$g/kg/day.

### Deodorant

- 0.52 g/day deodorant use (Environ Corporation 1984)
- 200 $\mu$g/g DBP in deodorant (Houlihan et al. 2002)
- 5% skin absorption (Mint et al. 1994)

0.52 g/day $\times$ 200 $\mu$g/g $\times$ 5% = 5.2 $\mu$g/day/60 kg = 0.09 $\mu$g/kg/day.

### Perfume

- 0.53 g/day perfume use (CTFA 2002)
- 890 $\mu$g/g DBP in perfume (Houlihan et al. 2002)
- 5% skin absorption (Mint et al. 1994)

0.53 g/day $\times$ 890 $\mu$g/g $\times$ 5% = 24 $\mu$g/day/60 kg = 0.4 $\mu$g/kg/day.

### Total Exposure

- Sum of each of the separate exposures

8.5 $\mu$g/kg/day + 0.14 $\mu$g/kg/day + 0.09 $\mu$g/kg/day + 0.4 $\mu$g/kg/day = 9.13 $\mu$g/kg/day

The calculated estimated exposure level of DBP from the concurrent use of multiple cosmetic products was 9.13 $\mu$g/kg/day. This value is within the reported range of total human exposure to DBP from all sources in women, 32 $\mu$g/kg/day (upper 95th percentile for women of reproductive age) to 6.5 $\mu$g/kg/day (upper 95th percentile for rest of group). Therefore, the Panel accepted 9.13 $\mu$g/kg/day as a not unreasonable approximation of DBP exposure from cosmetic products.

The Panel calculated the MOS of DBP by dividing the NOAEL of 331 mg/kg/day (from a feeding study) by the expected exposure of 9.13 $\mu$g/kg/day, yielding an MOS of 36,254. If the more conservative NOAEL of 50 mg/kg/day (from a gavage study) is used, the MOS is 5476. The Panel also noted that both NOAEL figures were obtained from rat studies, and detoxification metabolism of DBP is faster in humans than in rats.

The Panel acknowledged the use of DBP, DEP, and DMP in hair sprays. The effects of inhaled aerosols depend on the specific chemical species, the concentration, the duration of exposure, and site of deposition (Jensen and O'Brien 1993) within the respiratory system. Particle size is the most important factor affecting the location of deposition. The mean aerodynamic diameter of pump hair spray particles is approximately 80 $\mu$m, and the diameter of anhydrous hair spray particles is 60 to 80 $\mu$m. Typically less than 1% are below 10 $\mu$m which is the upper limit for respirable particles (Bowen 1999). Based on the particle size, DBP, DEP, and DMP would not be respirable in formulation. Therefore, exposure of the lung by inhalation was not considered likely.

Based on the available information included in this report, the CIR Expert Panel concluded that Dibutyl Phthalate, Dimethyl Phthalate, and Diethyl Phthalate are safe for use in cosmetic products in the present practices of use and concentrations.

## REFERENCES


Agarwal, D. K., W. H. Lawrence, L. J. Nunez, and J. Autian. 1985. Mutagenicity evaluation of phthalic acid esters and metabolites in Salmonella Typhimurium cultures. *J. Toxicology Environ. Health* 16:61–69.

Agency for Toxic Substances and Disease Registry. 1995. Toxicological profile for diethyl phthalate. NTIS Report No. PB95264214.

Albro, P. W. 1986. Absorption, metabolism, and excretion of di(2-ethylhexyl)phthalate by rats and mice. *Environ. Health Perspect.* 65:293–298.

Anderson, W. A., L. Castle, M. J. Scotter, R. C. Massey, and C. Springall. 2001. A biomarker approach to measure human dietary exposure to certain phthalate diesters. *Food Addit. Comtam.* 18:1068–1074.

Api, A. M. 1997. *In vitro* assessment of phototoxicity. *In Vitro Toxicol.* 10:339–350.

Api, A. M. 2001. Toxicological profile of diethyl phthalate: A vehicle for fragrance and cosmetic ingredients. *Food Chem. News.* 39:97–108.

Bagley, D. M., J. R. Garner, G. Holland, R. W. Lewis, J.-F. Regnier, D. A. Stringer, and A. P. Walker. 1996. Skin irritation: Reference chemicals data bank. *Toxicol. In Vitro.* 10:1–6.

Barber, E. D., M. Cifone, J. Rundell, R. Pryzgoda, B. D. Astill, E. Moran, A. Mulholland, E. Robinson, and B. Schneider. 2000. Results of the L5178Y mouse lymphoma assay and the Balb/3T3 cell *in vitro* transformation assay for eight phthalate esters. *J. Appl. Toxicol.* 20:69–80.

Baskin, L. S., K. Himes, and T. Colborn. 2001. Hypospadias and endocrine disruption: Is ther e a connection? *Environ. Health Perspect.* 109:1175–1183.

BASF. no date. Di-n-butyl phthalate—subacute inhalation study in Wistar rats. 20 exposures as a liquid aerosol. Unpublished data submitted by Phthalate Esters Panel, American Chemistry Council. 57 pages.[9]

BASF. 1992. Study on the oral toxicity of dibutyl phthalate in Wistar rats. Administration via the diet over 3 months. Unpublished data submitted by Phthalate Esters Panel, American Chemistry Council. 369 pages.[9]

BASF. 1999. Di-n-butyl phthalate—subacute inhalation study in Wistar rats. 20 exposures as a liquid aerosol. Unpublished data submitted by Phthalate Esters Panel, American Chemistry Council. 189 pages.[9]

Blair, R. M., H. Fang, W. S. Branham, B. S. Hass, S. L. Dial, C. L. Moland, W. Tong, L. Shi, R. Perkins, and D. M. Sheehan. 2000. The estrogen receptor relative binding affinities of 188 natural and xenochemicals: Structural diversity of ligands. *Toxicol. Sci.* 45:138–153.

Blount, B. C., M. J. Silva, S. P. Caudill, et al. 2000. Levels of seven urinary phthalate metabolites in a human reference population. *Environ. Health Perspect.* 108:979–982.

Bower, D. 1999. Unpublished information on hair spray particle size provided at the September 9, 1999 CIR Expert Panel meeting.[9]

Brock, J. W., S. P. Caudill, M. J. Silva, L. L. Needham, and E. D. Hilborn. 2002. Phthalate monoesters levels in the urine of young children. *Bull. Environ. Contam. Toxicol.* 68:309–314.

Butala, J., M. Moore, M. Cifone, J. Bankston, and B. Astill. 1996. Oncogenicity study of di(isononyl) phthalate in rats. *Toxicologist.* 30:202.

Butala, J., M. Moore, M. Cifone, J. Bankston, and B. Astill. 1997. Oncogenicity study of di(isononyl) phthalate in mice. *Toxicologist* 36:173.

Castle, L., A. Mercer, J. R. Startin, and J. Gilbert. 1988 . Migration from plasticized films into foods 3. Migration of phthalate, sebacate, citrate and phosphate esters from films used for retail food packaging. *Food Addit. Contami.* 5:9–20.

Centers for Disease Control and Prevention. 2003. Second national report on human exposure to environmental chemicals. Available at http://www.cdc.gov/exposurereport/pdf/SecondNER.pdf

Chu-Tse, W., P. Xue-Tao, C. Jun-Rong, and X. Hui-Hua. 1993. A new pharmacological activity of dibutyl phthalate (dbp) on selective elimination of tumor cells from bone marrow. *Leukemia Res.* 17 7:557–560.


[9]Available from Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

Colón, A., D. Caro, C. J. Bourdony, and O. Rosario. 2000. Identification of phthalate esters in the serum of young Puerto Rican girls with premature breast development. *Environ. Health Perspect.* 108 9:895–900.

Consumer Product testing. 1978a. Oral LD50 (rat) study no. 78-032. Unpublished data submitted by CTFA. 13 pages.[9]

Consumer Product testing. 1978b. Dermal LD50 (rat) study no. 78-033. Unpublished data submitted by CTFA. 13 pages.[9]

Consumer Product testing. 1978c. Guinea pig sensitization study no. 78-034. Unpublished data submitted by CTFA. 13 pages.[9]

Cosmetic, Toiletry, and Fragrance Administration (CTFA). 2001a. Unpublished data regarding current concentrations of cosmetic uses of Dibutyl Phthalate. January 4, 2001. 2 pages.[9]

CTFA. 2001b. Unpublished data regarding current concentrations of cosmetic uses of Dibutyl Phthalate. April 20, 2001. 2 pages.[9]

CTFA. 2001c. Unpublished data regarding current concentrations of cosmetic uses of Dimethyl and Diethyl Phthalate. October 18, 2001. 2 pages.[9]

CTFA. 2001d. Unpublished data available on the CTFA International Cosmetic Legal & Regulatory Database Global Ingredient Search.[9]

CTFA. 2002a. Unpublished data regarding physical properties of dibutyl phthalate. Submitted August 30, 2002. 3 pages.[9]

CTFA. 2002b. Unpublished data regarding average hairspray and perfume use. June 26, 2002. 3 pages.[9]

Cummings, A. M., and L. E. Gray. 1987. Dibutyl Phthalate: Maternal effects versus fetotoxicity. *Toxicol. Lett.* 39:43–50.

David. R., M. Moore, M. Cifone, D. Finney, and D. Guest. 1999. Chronic peroxisome proliferation and hepatomegaly associated with the hepatocellular tumorigenesis of di(2-ethylhexyl)phthalate and the effects of recovery. *Toxicol. Sci.* 50:195–205.

David, R. M. 2000. Exposure to phthalate esters. *Environ. Health Perspect.* 108:A440.

Dirven, H., P. H. H. Vandenbroek, A. M. M. Arends, H. H. Nordkamp, A. Delepper, P. T. Henderson, and F. J. Jongeneelen. 1993. Metabolites of the plasticizer di(2-ethylhexyl)phthalate in urine samples of workers in polyvinylchloride processing industries. *Int. Arch. Occup. Environ. Health* 64:549–554.

Duty, S. M., N. P. Singh, M. J. Silva, D. B. Barr, J. W. Brock, L. Ryan, R. F. Herrick, D. C. Christiani, and R. Hunter. 2002. The relationship between environmental exposures to phthalates and DNA damage in human sperm using the neutral comet assay. *Environ. Health Perspect.* available at http://dx.doi.org/doi:10.1289/ehp.5756.

E. I. du Pont de Nemours and Company. 1946. Possibility of dermatitis from dimethyl phthalate when used as an insect repellant. Unpublished data collected Haskell Laboratory of Industrial Toxicology and submitted by Phthalate Esters Panel, American Chemical Council. 2 pages.[9]

E. I. du Pont de Nemours and Company. 1970. Skin primary irritation and sensitization test on guinea pigs. Unpublished data collected Haskell Laboratory for Toxicology and Industrial Medicine and submitted by Phthalate Esters Panel, American Chemical Council. 2 pages.[9]

E. I. du Pont de Nemours and Company. 1974. Dimethyl phthalate. Unpublished data collected Haskell Laboratory for Toxicology and Industrial Medicine and submitted by Phthalate Esters Panel, American Chemical Council. 2 pages.[9]

Elder, R. L., ed. 1985. Final report on the safety assessment of Dibutyl Phthalate, Dimethyl Phthalate, and Diethyl Phthalate. *J. Am. Col. Toxicol.* 4:267–303.

Elsisi, A. E., D. E. Carter, and I. G. Sipes. 1989. Dermal absorption of phthalate diester in rats. *Fundam. Appl. Toxic.* 12:70–77.

Ema, M., H. Amano, T. Itami, and H. Kawasaki. 1993. Teratogenic evaluation of di-n-butyl phthalate in rats. *Toxicol. Lett.* 69:197–203.

Ema, M., H. Amano, and Y. Ogawa. 1994. Characterization of the developmental toxicity of di-n-butyl phthalate in rats. *Toxicology* 86:163–174.

Ema, M., A. Harazono, E. Miyawaki, and Y. Ogawa. 1997a. Developmental effects of di-n-butyl phthalate after a single administration in rats. *J. Appl. Toxicol.* 17:223–229.

Ema, M., A. Harazono, E. Miyawaki, and Y. Ogawa. 1997b. Embryolethality following maternal exposure to dibutyl phthalate during early pregnancy in rats. *Bull. Environ. Contam. Toxicol.* 58:636–643.

Ema, M., R. Kurosaka, H. Amano, and Y. Ogawa. 1995a. Comparative developmental toxicity of n-butyl benzyl phthalate and di-n-butyl phthalate in rats. *Arch. Environ. Contam. Toxicol.* 28:223–228.

Ema, M., R. Kurosaka, H. Amano, and Y. Ogawa. 1995b. Developmental toxicity evaluation of mono-n-butyl phthalate in rats. *Toxicology Lett.* 78:101–106.

Ema, M., R. Kurosaka, A. Harazono, H. Amano, and Y. Ogawa. 1996. Phase specificity of developmental toxicity after oral administration of mono-n-butyl phthalate in rats. *Arch. Environ. Contam. Toxicol.* 31:170–176.

Ema, M., and E. Miyawaki. 2001a. Adverse effects on development of the reproductive system in male offspring given monobutyl phthalate, a metabolite of dibutyl phthalate, during late pregnancy. *Reprod. Toxicol.* 15:189–194.

Ema, M., and E. Miyawaki. 2001b. Effects of monobutyl phthalate on reproductive function in pregnant and pseudopregnant rats. *Reprod. Toxicol.* 15:261–267.

Ema, M., E. Miyawaki, and K. Kawashima. 1998. Further evaluation of developmental toxicity of di-n-butyl phthalate following administration during late pregnancy in rats. *Toxicol. Lett.* 98:87–93.

Ema, M., E. Miyawaki, and K. Kawashima. 2000a. Critical period for adverse effects on development of reproductive system in male offspring of rats given di-n-butyl phthalate during late pregnancy. *Toxicol. Lett.* 111:271–278.

Ema, M., E. Miyawaki, and K. Kawashima. 2000b. Effects of dibutyl phthalate on reproductive function in pregnant and pseudopregnant rats. *Reprod. Toxicol.* 14:13–19.

Environ Corporation. 1984. Summary of the Results of Surveys of the Amount and Frequency of Use of Cosmetic Products by Women. Unpublished report submitted by CTFA. 7 pages.[9]

Environment Canada. 1994. Canadian environmental protection act priority substances list assessment report: dibutyl phthalate. NTIS Report No. PB94169059.

Epstein, W. L. 1978. Human sensitization study of diethyl phthalate. Unpublished data submitted by CTFA. 4 pages.[9]

Essex Testing Clinic, Inc. 1989. Clinical safety evaluation of diethyl phthalate in repeated insult patch test, with cover letter dated 05/09/94 (sanitized). NTIS Report No. OTS0557309.

Essex Testing Clinic, Inc. 1990. Final report, clinical safety evaluation of test article diethyl phthalate control (neat); repeated insult patch test with cover letter dated 05/09/94 (sanitized). NTIS Report No. OTS0557311.

European Commission. 2002. The rules governing cosmetic products in the European Union. Volume 1. Cosmetics legislation—Cosmetic products. Accessed April 22, 2002. http://dg3.eudra.org/F3/home.html.

Field, E. A., C. J. Price, R. S. Sleet, J. D. George, M. C. Marr, C. B. Myers, B. A. Schwetz, and R. E. Morrissey. 1993. Developmental Toxicity evaluation of diethyl and dimethyl phthalate in rats. *Teratology.* 48:33–44.

Food and Drug Administration (FDA). 2001. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

Foster, P. M., M. W. Cook, L. V. Thomas, D. G. Walters, and S. D. Gangolli. 1983. Differences in urinary metabolic profile from di-n-butyl phthalate-treated rats and hamsters. A possible explanation for species differences in susceptibility to testicular atrophy. *Drug Metab. Dispos.* 11:59–61.

Foster, P. M. D., R. C. Cattley, and E. Mylchreest. 2000. Effects of di-n-butyl phthalate (DBP) on male reproductive development in the rat: Implications for human risk assessment. *Food Chem. Toxicol.* 38:S97–S99.

Fredricsson, B., L. Möller, Å. Pousette, and R. Westerholm. 1993. Human sperm motility is affected by plasticizers and diesel particle extracts. *Pharmacol. Toxicol.* 72:128–133.

Fukuoka, M., T. Kobayashi, Y. Zhou, and T. Hayakawa. 1993. Mechanism of testicular atrophy introduced by di-n-butyl phthalate in rats. Part 4. Changes in the activity of succinate dehydrogenase and the levels of transferrin and ferritin in the Sertoli and germ cells. *J. Appl. Toxicol.* 13:241–246.

Fukuoka, M., S. Nhmi, Y. Zhou, T. Kobayashi, and T. Hayakawa. 1996. Responsiveness of rat nonparenchymal liver cells and spleen cells to the decomposition of erythrocytes exposed to di-n-butyl phthalate and its metabolite. *Biol. Pharm. Bull.* 19:1154–1159.

Fukuoka, M., T. Tanimoto, Y. Zhou, N. Kawasaki, and A. Tanaka. 1989. Mechanism of testicular atrophy by di-n-butyl phthalate in rats. Part 1. *J. Appl. Toxicol.* 9:277–283.

Fukuoka, M., Y. Zhou, A. Tanaka, I. Ikemoto, and T. Machida. 1990. Mechanism of testicular atrophy induced by di-n-butyl phthalate in rats. Part 2. The effects on some testicular enzymes. *J. Appl. Toxicol.* 10:285–293.

Gall, H., A. Köhler, and R. U. Peter. 1999. Anaphylactic shock reaction to dibutyl-phthalate-containing capsules. *Dermatology*. 199:169–170.

Gray, T. J. B., I. R. Rowland, P. M. D. Foster, and S. D. Gangolli. 1982. Species differences in the testicular toxicity of phthalate esters. *Toxicology Lett.* 11:141–147.

Gray, L. E., J. Ostby, J. Furr, M. Price, D. N. Veeramachaneni, and L. Parks. 2000. Perinatal exposure of the phthalates DEHP, BBP, and DINP, but not DEP, DMP, or DOTP, alters sexual differentiation of the male rat. *Toxicol. Sci.* 58:350–365.

Gray, L. E., C. Wolf, C. Lambright, et al. 1999. Administration of potentially antiandrogenic pesticides (procymidone, linuron, iprodione, chlozolinate, *p*,*p*′-DDE, and ketoconazole) and toxic substances (dibutyl- and diethylhexyl phthalate, PCB 169, and ethane dimethane sulphonate) during sexual differentiation produces diverse profiles of reproductive malformations in the male rat. *Toxicol. Ind. Health* 15:94–118.

Hall, M., A. Mathews, L. Webley, and R. Harling. 1999. Effects of diisononyl phthalate (DINP) on peroxisomal markers in the marmoset-DINP is not a peroxisome proliferator. *J. Toxicol. Sci.* 24:237–244.

Hansen, E., and O. Meyer. 1989. No embryotoxic or teratogenic effect of dimethyl phthalate in rats after epicutaneous application. *Pharmacol. Toxicol.* 64:237–238.

Harris, C. A., P. Henttu, M. G. Parker, and J. P. Sumpter. 1997. The estrogenic activity of phthalate esters *in vitro*. *Environ. Health Perspect.* 105:802–811.

Harrison Research Laboratories. 1998. Repeated insult patch test (RIPT) on a nail enamel. Unpublished data submitted by CTFA. 13 pages.[9]

Hill Top Research, Inc. 1968. Primary irritation patch test on 3239K. Unpublished data submitted by CTFA. 13 pages.[9]

Hill Top Research, Inc. 1971. Repeated insult patch test of group number 69, A-40-DIETPH. Unpublished data submitted by CTFA. 11 pages.[9]

Hill Top Research, Inc. 1998. Evaluation of phototoxicity in humans. HTR project no. 101649. Unpublished data submitted by CTFA. 56 pages.[9]

Hill Top Research, Inc. 1999. Evaluation of phototoxicity in humans. HTR project no. 100688. Unpublished data submitted by CTFA. 62 pages.[9]

Hill Top Research, Ltd. 1997a. Evaluation of human photoallergy by repeated insult patch test. Project no. 97-4182-74. Unpublished data submitted by CTFA. 58 pages.[9]

Hill Top Research, Ltd. 1997b. Evaluation of human photoallergy by repeated insult patch test. Project no. 97-4193-74. Unpublished data submitted by CTFA. 84 pages.[9]

Hoppin, J. A., J. W. Brock, B. J. Davis, and D. D. Baird. 2002. Reproducibility of urinary phthalate metabolites in first morning urine samples. *Environ. Health Perspect.* 110:515–518.

Houlihan, J., C. Brody, and B. Schwan. 2002. Not too pretty. Phthalates, beauty products & the FDA. Unplublished report released by Environmental Working Group, Coming Clean, and Health Care Without Harm. Available at http://www.nottoopretty.org

Imajima, T., T. Shono, O. Zakaria, and S. Suita. 1997. Prenatal phthalate causes cryptorchidism postnatally by inducing transabdominal ascent of the testes in fetal rats. *J. Pediatr. Surg.* 32:18–21.

Inveresk Research International. 1990. 2 weeks dermal dose range finding study in rats. Unpublished data submitted by CTFA. 652 pages.[9]

Ivy Research Laboratories. 1973. The primary irritation potential of one fragrance material in six different vehicle formulations. Unpublished data submitted by CTFA. 5 pages.[9]

Ivy Research Laboratories. 1984. The determination of the contact-sensitizing potential of four materials by means of the maximization study. Unpublished data submitted by CTFA. 4 pages.[9]

Jackson Research Associates. 2002. Analysis of the Subungual Penetration of 100% Dibutyl Phthalate (DBP) in Human Fingernails. Unpublished report submitted by the American Beauty Association, 10-25-02.[9]

Japanese Plasticizer Industrial Association. 1997. Evaluation of estrogen activity of phthalate esters by receptor-binding test (Study no. 6L471). Unpublished data submitted by Phthalate Esters Panel, American Chemistry Council. 59 pages.[9]

Japanese Plasticizer Industrial Association. 1998. Evaluation of estrogen activity and mechanism of action of DBP and DEHP by *in vivo* assay using rats (Study no.: 7L432). Unpublished data submitted by Phthalate Esters Panel, American Chemistry Council. 27 pages.[9]

Jensen, P. A., and O'Brien, D. 1993. Industrial Hygiene. In *Aerosol measurement. principles techniques and applications*, ed. K. Willeke and P. A. Baron. New York: John Wiley and Sons.

Jones, H. B., D. A. Garside, R. Liu, and J. C. Roberts. 1993. The influence of phthalate esters on Leydig cell structure and function *in vitro* and *in vivo*. *Exp. Molecul. Pathol.* 58:179–193.

Jury, H. H., T. R. Zacharewski, and G. L. Hammond. 2000. Interaction between human plasma sex hormone-binding globulin and xenobiotic ligands. *J. Steroid Biochem. Mol. Biol.* 75:167–176.

Kageyama, K., Y. Onoyama, T. Nakajima, S. Otani, I. Yano, H. Hotta, I. Matsui-Yuasa, H. Kogawa, and N. Miwa. 1994. DNA synthesis inhibition and transmembrane permeation into tumor cells by various dialkyl phthalates upon hyperthermia. *Anticancer Res.* 14:2769–2772.

Kanerva, L., R. Jolanki, K. Alanko, and T. Estlander. 1999. Patch-test reactions to plastic and glue allergens. *Acta. Derm. Venereol.* 79:296–300.

Kanerva, L., R. Jolanki, and T. Esterlander. 1997. Allergic and irritant patch test reactions to plastic and glue allergens. *Contact Dermatitis.* 37:301–302.

Karmin, M. A., and G. H. Mayor. 1991. Diethyl phthalate: A perspective. *J. Clin. Pharmacol.* 31:484–489.

Kavlock, R., K. Boekelheide, R. Chapin, M. Cunningham, E. Faustman, P. Foster, M. Golub, R. Henderson, I. Hinberg, R. Little, J. Seed, K. Shea, S. Tabacova, R. Tyl, P. Williams, and T. Zacharewski. 2002. NTP Center for the Evaluation of Risks to Human Reproduction: Phthalates expert panel report on the reproductive and developmental toxicity of di-*n*-butyl phthalate. *Reprod. Toxicol.* 16:489–527.

Khaliq, M. A., M. S. Alam, and S. P. Srivastava. 1992. Implications of physicochemical factors on the migration of phthalate esters from tubing commonly used for oral/nasal feeding. *Bull Environ Toxicol.* 48:572–578.

Kim, S. H., S. S. Kim, O. Kwon, K. H. Sohn, et al. 2002. Effects of dibutyl phthalate and monobutyl phthalate on cytotoxicity and differentiation in cultured rat embryonic limb bud cells; protection by antioxidants. *Toxicol. Environ. Health.* 65:461–472.

Kleinsasser, N. H., E. R. Kastenbauer, H. Weissacher, R. K. Muezenrieder, and U. A. Harréus. 2000. Phthalates demonstrate genotoxicity on human mucosa of the upper aerodigestive tract. *Environ. Mol. Mutagen.* 35:9–12.

Kluwe, W. M. 1982. Overview of phthalate ester phamacokinetics in mammalian species. *Environ. Health Perspect.* 45:3–10.

Kohn, M. C., F. Parham, S. A. Masten, C. J. Portier, M. D. Shelby, J. W. Brock, and L. L. Needham. 2000. Human exposure estimates for phthalates. *Environ. Health Perspect.* 108:A440–A442.

Koo, J. W., F. Parham, M. C. Kohn, S. A. Masten, J. W. Brock, L. L. Needham, and C. J. Portier. 2002. The association between biomarker based exposure estimates for phthalates and demographic factors in a human reference population. *Environ. Health Perspect.* 110:405–410.

Kozombo, W. J., R. Kroll, and R. J. Rubin. 1982. Assessment of the mutagenicity of phthalate esters. *Environ. Health Perspect.* 45:103–109.

Kurata, Y., F. Kidachi, M. Yokoyama, N. Toyota, M. Tsuchitani, and M. Katoh. 1998. Subchronic toxicity of di(2-ethylhexyl) phthalate in common marmosets: Lack of peroxisomal proliferation, testicular atrophy, or pancreatic acinar cell hyperplasia. *Toxicol. Sci.* 42:49–56.

Lamb, J. C., R. E. Chapin, J. Teague, A. D. Lawton, and J. R. Reel. 1987. Reproductive effects of four phthalic acid esters in the mouse. *Toxicol. Appl. Pharmacol.* 88:255–269.

Lamb, J. C., J. Reel, and A. D. Lawton. 1997a. Diethylphthalate. *Environ. Health Perspect*. 105:245–246.

Lamb, J. C., J. Reel, and A. D. Lawton. 1997b. Di-n-butylphthalate, mice. *Environ. Health Perspect.* 105:247–248.

Leberco Laboratories. 1963. Rabbit eye irritation study of 12.5% diethyl phthalate. Unpublished data submitted by CTFA. 5 pages.[9]

Lington, A., M. Bird, R. Plutnick, W. Stubblefield, and R. Scala. 1997. Chronic toxicity and carcinogenic evaluation of di-isononylphthalate in rats. *Fundam. Appl. Toxicol.* 36:79–89.

Lisheng, W., W. Chutse, P. Xuetao, et al. 1996a. Dibutyl phthalate purged autologous bone marrow transplant in the treatment of leukemia. *Leukemia Rese.* 20:343–348.

Lisheng, W., W. Chutse, P. Xuetao, X. Li, C. Jurong, and H. Fuchu. 1996b. Purging effect of dibutyl phthalate on leukemic cells associated with apoptosis. *Leukemia Res.* 20:989–992.

Liss, G. M., P. W. Albro, R. W. Hartle, and W. T. Stringer. 1985. Urine phthalate determinations as an index of occupational exposure to phthalic anhydride and di(2-ethylhexyl)phthalate. *Scand. J. Work Environ. Health.* 11:381–387.

Lovekamp, T. N., and B. J. Davis. 2001. Mono-(2-ethylhexyl) phthalate suppresses aromatase transcript levels and estrodiol production in cultured rat granulosa cells. *Toxicol. Appl. Pharmacol.* 172:217–224.

Lygre, H., E. Solheim, and N. R. Gjerdet. 1995. Leaching from denture base materials *in vitro*. *Acta Odontol. Scand.* 53:75–80.

McKee, R. H. 2000. The role of inhibition of gap junction intercellular communication in rodent liver tumor induction by phthalates: Review of data on selected phthalates and their potential relevance to man. *Regula. Toxicol. Pharmacol.* 32:51–55.

Melnick, R. L., and C. M. Schiller. 1985. Effect of phthalate esters on energy coupling and succinate oxidation in rat liver mitochondria. *Toxicology* 34:13–27.

Milligan, S. R., A. V. Balasubramanian, and J. C. Kalita. 1998a. Relative potency of xenobiotic estrogens in an active *in vivo* mammalian assay. *Environ. Health Perspect.* 106:23–26.

Milligan, S. R., O. Khan, and M. Nash. 1998b. Competitive binding of xenobiotic oestrogens to rat alpha-fetoprotein and to sex steroid binding proteins in human and rainbow trout (Oncorhynchus mykiss) plasma. *Gen. Comp. Endocrinol.* 112:89–95.

Ministry of Health, Labor and Welfare. 2001a. Unofficial translation of MHW Ordinance No. 331, Attached Table 1 [Negative List]. Ministry of Health, Labor and Welfare, Pharmaceutical and Medical Safety Bureau, Inspection and Guidance Division, 2-2, 1-chome, Kasumgaseki, Chiyoda-ku, Tokyo 100-8045, Japan.

Ministry of Health, Labor and Welfare. 2001b. Unofficial translation of MHW Ordinance No. 331, Attached Table 2 [Restricted List]. Ministry of Health, Labor and Welfare, Pharmaceutical and Medical Safety Bureau, Inspection and Guidance Division, 2-2, 1- chome, Kasumgaseki, Chiyoda-ku, Tokyo 100-8045, Japan.

Mint, A., S. A. M. Hotchkiss, and J. Caldwell. 1994. Percutaneous absorption of diethyl phthalate through rat and human skin *in vitro*. *Toxicol. In Vitro.* 8:251–256.

Monsanto Europe. No date. Study to evaluate the effect of monobutyl phthalate on uterine growth in immature female rats after oral administration. Unpub lished data submitted by Phthalate Esters Panel, American Chemistry Council. 16 pages.[9]

Moura, C., M. Dias, and T. Vale. 1994. Contact dermatitis in painters, polishers and varnishers. *Contact Dermatitis.* 31:51–52.

Murakami, K., K. Nishiyama, and T. Higuti. 1986a. Mitochondria effect of orally administered dibutyl phthalate in rats. *Jpn. J. Hyg.* 41:769–774.

Murakami, K., K. N ishiyama, and T. Higuti. 1986b. Toxicity of dibutyl phthalate and its metabolites in rats. *Jap. J. Hyg.* 41:775–781.

Murature, D. A., S. Y. Tang, G. Steinhardt, and R. C. Dougherty. 1987. Phthalate esters and semen quality parameters. *Biomed. Environ. Mass Spectrom.* 14:473–477.

Mylchreest, E., R. C. Cattley, and P. M. D. Foster. 1998. Male reproductive tract malformations in rats following gestational and lactational exposure to di(n-butyl) phthalate: An androgenic mechanism? *Toxicol. Sci.* 43:47–60.

Mylchreest, E., M. Sar, R. C. Cattley, and P. M. D. Foster. 1999. Disruption of androgen-regulated male reproductive development by di(n-butyl) phthalate during late gestation in rats is different from flutamide. *Toxicol. Appl. Pharmacol.* 156:81–95.

Mylchreest, E., M. Sar, D. G. Wallace, and P. M. Foster. 2002. Fetal testosterone insufficiency and abnormal proliferation of Leydig cells and gonocytes in rats exposed to di(n-buytl) phthalate. *Reprod. Toxicol.* 16:19–28.

Mylchreest, E., D. G. Wallace, R. C. Cattley, and P. M. D. Foster. 2000. Dose-dependent alterations in androgen-regulated male reproductive development in rats exposed to di(n-butyl) phthalate during late gestation. *Toxicol. Sci.* 55:143–151.

Nail Manufacturers Council (NMC). 2001. Letter from NMC including ingredient use product type and concentration survey. Unpublished data submitted by NMC of May 7, 2001. 4 pages.[9]

National Toxicology Program (NTP). 1991. Final report: On the reproductive toxicity of di-n-butyl phthalate (CAS No. 84-72-2) in Sprague-Dawley rats. NTIS Report No. PB92111996.

NTP. 1995a. NTP technical report on toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F34 4/N rats and B6C3F1 mice. NTIS Report No. PB95232427.

NTP. 1995b. Toxicology and carconigenesis studies of diethylphthalate in F344/n rats and B6C3F1 mice with dermal initiation/promotion study of diethylphth alate and dimethylphthalate in male Swiss (CD-1) mice. Unpublished data submitted by Phthalate Esters Panel, American Chemistry Council. 278 pages.[9]

Netherlands Organization for Applied Scientific Research and National Institute of Public health and the Environment. 2001. Risk assessment, dibutylphthalate. Unpublished data submitted by CTFA. 183 pages.[9]

Ohtani, H., I. Miura, and Y. Ichikawa. 2000. Effects of dibutyl phthalate as an environmental endocrine disruptor on gona dal sex differentiation of genetic males of the frog Rana rugosa. *Environ. Health Perspect.* 108:1189–1193.

Ow, R. K. K. and S. Amrith. 1997. Ocular prosthetics: Use of a tissue conditioner material to modify a stock ocular prosthesis. *J. Prosthet. Dentistry.* 78:218–222.

Paganet, G., F. Campi, K. Varani, A. Piffanelli, G. Giovannini, and P. A. Borea. 2000. Endocrine-distrupting agents on healthy human tissues. *Pharmacol. Toxicol.* 86:24–29.

Page, B. D., and G. M. Lacroix. 1992. Studies into the transfer and migration of phthalate esters from aluminum foil-paper laminates to butter and margerine. *Food Add. Contami.* 9:197–212.

Payan, J. P., J. P. Marty, J. P. Fabry, D. Beydon, I. Boudry, E. Ferrari, F. Canel, M. C. Grandclaude, and C. M. Vincent. 2001. *In vivo* and *in vitro* percutaneous absorption of [14C]di-n-butylphthalate in rat. *Drug Metab. Distrib.* 29:843–854.

Peakall, D. B. 1975. Phthalate esters: occurrence and biological effects. *Residue Rev.* 54:1–41.

Pfordt, J., and E. Bruns-Weller. 1999. Phthalate esters as a group of environmental chemicals with an endocrine disruption potential. Lower Saxony Ministry of Food, Agriculture and Forestry: Hamburg. Unpublished data submitted by the Phthalate Esters Panel, American Chemistry Council. 53 pages.[9]

Phthalate Esters Panel, American Chemistry Council. 1982a. Toxicity tests of dibutyl phthalate, dibutyl isophthalate, and dibutyl terephthalate. Unpublished data submitted by the Phthalate Esters Panel, American Chemistry Council. 5 pages.[9]

Phthalate Esters Panel, American Chemistry Council. 1982b. 28-day subacute percutaneous toxicity SL: VE-1005-20, SR: TGSE 1037, P75-006. Unpublished data submitted by the Phthalate Esters Panel, American Chemistry Council. 10 pages.[9]

Phthalate Esters Panel, American Chemistry Council. 1999. Di-n-butylphthalate (DBP). Unpublished data submitted by the Phthalate Esters Panel, American Chemistry Council. 42 pages.[9]

Plasterer, M. R., W. S. Bradshaw, G. M. Booth, M. W. Carter, R. L. Schuler, and B. D. Hardin. 1985. Developmental toxicity of nine selected compounds following prenatal exposure in the mouse: Napthalene, p-nitrophenol, sodium selenate, dimethyl phthalate, ethylenethiourea, and four glycol ether derivatives. *J. Toxicol. Environ. Health* 15:25–38.

Proctor & Gamble Co. 1984. Teratogenicity study of E-2426.01 (diethyl phthalate) by dermal application to rabbits with cover letter dated 05/02/94. NTIS Report No. OTS0572465.

Pugh, G., J. Isenberg, L. Kamendulis, L. Clare, W. Brown, A. Lington, D. Ackley, J. Smith, and J. Klaunig. 2000. Effects of di-isononyl phthalate, di-2-ethylhexyl phthalate, and clofibrate in cynomolgus monkeys. *Toxicol Sci.* 56:181–188.

Research Triangle Institute. 1995. The toxicokinetics and metabolism of di-n-butyl phthalate. Unpublished data submitted by CTFA. 58 pages.[9]

Research Institute for Fragrance Materials (RIFM). 1984. Acute dermal irritation study. RIFM 1795. Unpublished data submitted by CTFA. 13 pages.[9]

RIFM. 1984. Acute dermal irritation study. RIFM 3099. Unpublished data submitted by CTFA. 13 pages.[9]

Saillenfait, A. M., J. P. Payan, J. P. Fabry, et al. 1998. Assessment of the developmental toxicity, metabolism, and placental transfer of di-n-butyl phthalate administered to pregnant rats. *Toxicol. Sci.* 45:212–224.

Saillenfaint, A. M., I. Langonné, and B. Leheup. 2001. Effects of mono-n-butyl phthalate on the development of rat embryos: *in vivo* and *in vitro* observations. *Pharmacol. Toxicol.* 89:104–112.

Schreck, C. E. 1991. Permethrin and dimethyl phthalate as tent fabric treatments against *Aedes aegypti. J. Am. Mosquito Control Assoc.* 7:533–535.

Sciences International, Inc. 1995. Toxicological profile for diethyl phthalate. Unpublished data submitted by CTFA on August 30, 2002. 3 pages.[9]

Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP). 2002. Opinion of the scientific committee on cosmetic products and non-food products intended for consumers concerning diethyl phthalate. Unpublished data submitted by CTFA. 36 pages.[9]

Scott, R. C., P. H. Dugard, J. D. Ramsey, and C. Rhodes. 1987. *In vitro* absorption of some *o*-phthalate diesters through human and rat skin. *Environ. Health Perspect.* 74:223–227.

Selene, C. H., J. Chou, J. Holler, and C. De Rosa. 1998. Minimal risk levels (MRLs) for hazardous substances. *J. Clean Technol. Environ. Toxicol. Occup. Med.* 7:1–24.

Shultz, V. D., S. Phillips, M. Sar, P. M. D. Foster, and K. W. Gaido. 2001. Altered gene profiles in fetal rats after in utero exposure to di(n-butyl) phthalate. *Toxicol. Sci.* 64:233–242.

Small, L. D., E. O. Dillingham, and J. Autian. 1973. Tissue distribution and excretion of diethyl phthalate following percutaneous administration to female albino rats. Unpublished data submitted by CTFA. 23 pages.[9]

Sonde, V., A. D'souza, R. Tarapore, L. Pereira, M. P. Khare, P. Sinkar, S. Krishnan, and C.V. Rao. 2000. Simultaneous administration of diethylphth alate and ethyl alcohol and its toxicity in male Sprague-Dawley rats. *Toxicology.* 147:23–31.

Srivastava, S., G. B. Singh, S. P. Srivastava, and P. K. Seth. 1990a. Testicular toxicity of di-n-butyl phthalate in adult rats: Effect on marker enzymes of spermatogenesis. *Ind. J. Exp. Biol.* 28:67–70.

Srivastava, S. P., S. Srivastava, D. K. Saxena, S. V. Chandra, and P. K. Seth. 1990b. Testicular effects of di-n-butyl phthalate (DBP): Biochemical and histopathological alterations. *Arch. Toxicol.* 64:148–152.

Tarvainen, K. 1995. Analysis of patients with allergic patch test reactions to a plastics and glues series. *Contact Dermatitis* 32:346–351.

Tavares, I. A., and N. D. Vine. 1985. Phthalic acid esters inhibit arachidonate metabolism by rat peritoneal leucocytes. *J. Pharm. Pharmacol.* 37:67–68.

Tokunaga, H., Y. Ching, T. Uchino, and M. Ando. 2001 . Studies of diethyl phthalate on in vitro percutaneous permeation. *J. Soc. Cosmet. Chem. Jpn.* 35:312–316.

Unilever. 1999. Diethyl phthalate: assessment for oestrogenic potentia l. Unpublished data submitted by CTFA. 126 pages.[9]

US Environmental Protection Agency. 1994a. Final report, clinical safety evaluation of test article diethyl phthalate control (neat); repeated insult patch test, with cover letter dated 05/09/94 (sanitized). NTIS No. OTS0557311.

US Environmental Protection Agency. 1994b. Final report, clinical safety evaluation of test article diethyl phthalate in repeated insult patch test, with cover letter dated 05/09/94 (sanitized). NTIS No. OTS0557309.

Van Beek. L. 1974. Primary skin irritation and eye irritation tests with a perfume concentrate. Unpublished data submitted by CTFA. 9 pages.[9]

Waliszewski, St. M., and G. A. Szymczyński. 1989. Determination of phthalate esters in human semen. *Andrologia* 229:69–73.

Walseth, F. and O. G. Nilsen. 1984. Phthalate esters: II. Effects of inhaled dibutyl phthalate on cytochrome P-450 mediated metabolism in rat liver and lung. *Arch. Toxicol.* 55:132–136.

Walseth, F., and O. G. Nilsen. 1986. Phthalate esters: Effects of orally administered dibutylphthalate on cytoch rome P-450 mediated metabolism in rat liver and lung. *Acta Pharmacol. Toxicol.* 59:263–269.

White, R. D., D. L. Earnest, and D. E. Carter. 1983. The effect of intestinal esterase inhibition on the *in vivo* absorption and toxicity of di-n-butyl phthalate. *Food Chem. Toxicol.* 21:99–101.

Wilkinson, S. M., and M. H. Bech. 1992. Allergic contact dermatitis from dibutyl phthalate, propylgallate and hydrocortisone in Timodine®. *Contact Dermatitis* 27:197.

Williams, D. T., and B. J. Blanchfield. 1975. The retention, distribution, excretion, and metabolism of dibutyl phthalate-7-$^{14}$C in the rat. *J. Agric. Food Chem.* 23:854–858.

Wine, R. N., L. H. Li, L. H. Barnes, D. K. Gulati, and R. E. Chapin. 1997. Reproductive toxicity of di-n-butylphthalate in a continuous breeding protocol in Sprague-Dawley rats. *Environ. Health Perspect*. 105:102–107.

Zacharewski, T. R., M. D. Meek, J. H. Clemons, Z. F. Wu., M. R. Fieldon, and J. B. Mathews. 1998. Examination of the *in vitro* and *in vivo* estrogenic activities of eight commercial phthalate esters. *Toxicol. Sci.* 46:282–293.

Zhou, Y., M. Fukuoka, and A. Tanaka. 1990. Mechanism of testicular atrophy induced by di-n-butyl phthalate in rats. Part 3. Changes in the activity of some enzymes in the Sertoli and germ cells, and in the levels of metal ions. *J. Appl. Toxicol.* 10:447–453.

## DIMETHICONE COPOLYOL

A safety assessment of Dimethicone Copolyol was published in 1982 with the conclusion that this ingredient "is safe as a cosmetic ingredient in the present practices of use and concentration" (Elder 1982). New studies, along with updated information regarding types and concentrations of use, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

Dimethicone Copolyol as an ingredient name has been deleted from the *International Cosmetic Ingredient Dictionary and Handbook* and replaced with several ingredients that adhere to the former definition of Dimethicone Copolyol as "a polymer of dimethylsiloxane with polyoxyethylene and/or polyoxypropylene side chains" (Pepe et al. 2002).

The new ingredients that are described by this definition include: Dimethicone PEG-7 Phosphate, Dimethicone PEG-10 Phosphate, Dimethicone PEG/PPG-7/4 Phosphate, Dimethicone PEG/PPG-12/4 Phosphate, Dimethicone PEG/PPG-20/23 Benzoate, Dimethicone PEG-8 Benzoate, Dimethicone PEG-6 Acetate, Dimethicone PEG-8 Adipate, PEG-3 Dimethicone, PEG-9 Dimethicone, PEG/PPG-20/29 Dimethicone,

PEG/PPG-6/11 Dimethicone, PEG-7 Dimethicone, PEG-8 Dimethicone, PEG-14 Dimethicone, PEG/PPG-14/4 Dimethicone, PEG/PPG-4/12 Dimethicone, PEG/PPG-20/20 Dimethicone, PEG/PPG-8/14 Dimethicone, PEG/PPG-20/6 Dimethicone, PEG/PPG-20/15 Dimethicone, PEG-12 Dimethicone, PEG/PPG-18/18 Dimethicone, PEG/PPG-17/18 Dimethicone, PEG-10 Dimethicone, PEG/PPG-25/25 Dimethicone, PEG/PPG-19/19 Dimethicone, PEG/PPG-27/27 Dimethicone, PEG/PPG-22/23 Dimethicone, PEG/PPG-3/10 Dimethicone, PEG/PPG-16/2 Dimethicone, PEG/PPG-22/24 Dimethicone, PEG/PPG-15/15 Dimethicone, PEG-17 Dimethicone, PEG/PPG-20/23 Dimethicone, and PEG/PPG-23/6 Dimethicone.

Dimethicone Copolyol was used in 164 cosmetic products in 1976, with the largest use occurring in makeup bases at concentrations of ≤10%. In spite of the deletion of the term, Dimethicone Copolyol, in 2002, it was reported to FDA as used in 710 cosmetic products (FDA 2002).

In data provided by industry, specific use concentrations for Dimethicone PEG-7 Phosphate; Dimethicone PEG-8 Benzoate; PEG/PPG-14/4 Dimethicone; PEG/PPG-17/18 Dimethicone; PEG/PPG-18/18 Dimethicone; PEG/PPG-20/15 Dimethicone; PEG/PPG-20/6 Dimethicone; PEG/PPG-22/23 Dimethicone; PEG/PPG-4/12 Dimethicone; PEG-10 Dimethicone; PEG-12 Dimethicone; PEG-7 Dimethicone; and PEG-8 Dimethicone were provided—these identifications are made by footnotes in Table 9. The maximum use concentration reported was 21% for PEG-10 Dimethicone in suntan gels, creams, and liquids (CTFA 2003).

Table 9 presents the available use information for Dimethicone Copolyols.

**TABLE 9**
Historical and current frequencies and concentrations of use for Dimethicone Copolyols

| Product type | 1976 uses (Elder 1982) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1982) (%) | 2002 use concentrations (CTFA 2003) (%) |
|---|---|---|---|---|
| Baby shampoos | — | 2 | — | — |
| Bubble baths | — | 7 | — | — |
| Bath preparations (other) | — | 8 | — | 0.3,[h] 1,[f] 2[l] |
| Eyeliner | — | 4 | — | — |
| Eye shadow | — | 2 | — | 2[f] |
| Eye lotions | — | — | — | 1[d] |
| Eye makeup remover | — | — | — | 2[m] |
| Mascara | — | 1 | — | 1[j] |
| Eye makeup (other) | — | 2 | — | — |
| Colognes and toilet waters | 1 | 2 | >0.1–1 | 0.5,[l] 1[j] |
| Powders | — | 1 | — | 3[f] |
| Fragrance preparation (other) | 2 | 3 | >0.1–1 | 0.05,[f] 0.5[l] |
| Hair conditioners | 11 | 74 | ≤1 | 0.2[e] |
| Hair sprays (aerosol fixatives) | 60 | 89 | ≤1 | 0.006,[g] 0.2,[a] 0.3,[d,e] 0.8,[n] |
| Hair straighteners | — | — | — | 0.5,[l] 1[d] |
| Permanent waves | — | 1 | — | — |
| Rinses (noncoloring) | — | 3 | — | — |
| Shampoos (noncoloring) | 7 | 41 | >0.1–5 | 0.01,[e] 0.3,[d] 1[l] |
| Hair tonics, dressings, etc. | 2 | 145 | ≤0.1 | 0.02,[d] 0.08,[g] 0.1,[a] 0.2,[e] 0.5,[b] 0.9[l] |
| Wave sets | 25 | 9 | ≤5 | — |
| Hair preparations (other noncoloring) | 8 | 69 | ≤5 | — |
| Hair dyes and colors | — | 7 | — | — |
| Shampoos (coloring) | 6 | — | >0.1–1 | — |
| Hair bleaches | — | — | — | 1[a] |
| Hair coloring preparations (other) | — | 2 | — | — |
| Face powders | — | 3 | — | — |
| Foundations | 2 | 31 | >0.1–1 | 1,[l] 3[f] |
| Lipstick | — | 14 | — | 2[f] |
| Makeup bases | 1 | 5 | >5–10 | — |
| Rouges | 1 | — | >0.1–1 | — |
| Makeup fixatives | — | 1 | — | — |

*(Continued on next page)*

**TABLE 9**
Historical and current frequencies and concentrations of use for Dimethicone Copolyols *(Continued)*

| Product type | 1976 uses (Elder 1982) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1982) (%) | 2002 use concentrations (CTFA 2003) (%) |
|---|---|---|---|---|
| Makeup (other) | 2 | 10 | >0.1–1 | 2,[f] 4[l] |
| Nail polish and enamel | — | 1 | — | — |
| Manicuring preparations (other) | — | 1 | — | — |
| Bath soaps and detergents | — | 5 | — | 0.1,[h] 0.3,[d] 0.5,[l] 1[j] |
| Underarm deodorants | 2 | 9 | >0.1–1 | 1[j] |
| Personal cleanliness products (other) | 1 | 11 | >0.1–1 | 0.5,[f,l] |
| Aftershave lotion | 2 | 7 | >0.1–1 | 0.2,[f] 0.5,[l] 1,[j] |
| Shaving cream | 6 | 8 | >0.1–1 | — |
| Shaving preparations (other) | 2 | 7 | >0.1–1 | 0.2,[f] 1[l] |
| Skin-cleansing creams, lotions, liquids, and pads | — | 20 | — | 0.2,[h] 0.5[d,f,j,l] |
| Face and neck skin care preparations | 1* | 8 | >0.1–1* | — |
| Body and hand skin care preparations | | 22 | | 0.5,[d] 1,[j] 3[l] |
| Foot powders and sprays | — | 1 | — | — |
| Moisturizers | 2 | 29 | >1–5 | 0.5,[c] 1,[a,d,n] 2[l] |
| Night skin care preparations | — | 8 | — | — |
| Paste masks/mud packs | 8 | 7 | >0.1–5 | — |
| Skin fresheners | 1 | — | >0.1–1 | 0.005,[i] 0.2,[b,l] 0.5,[d,n] |
| Skin care preparations (other) | 1 | 26 | >0.1–1 | 0.005,[i] 0.5,[f,j] |
| Suntan gels, creams, and liquids | 6 | 1 | >1–5 | 21[k] |
| Indoor tanning preparations | — | 1 | — | 10[f] |
| Suntan preparations (other) | — | 2 | — | — |
| **Total uses/ranges for Dimethicone Copolyols** | **164** | **710** | **≤1–10** | **0.005–21** |

*These categories were combined when the original safety assessment was performed and are now separate categories.

[a]Reported as Dimethicone Copolyol; [b]reported as Dimethicone PEG-7 Phosphate; [c]reported as Dimethicone PEG-8 Benzoate; [d]reported as PEG/PPG-14/4 Dimethicone; [e]reported as PEG/PPG-17/18 Dimethicone; [f]reported as PEG/PP G-18/18 Dimet hicone; [g]reported as PEG/PP G-20/15 Dimet hicone; [h]reported as PEG/PPG-20/6 Dimethicone; [i]reported as PEG/PPG-22/23 Dimethicone; [j]reported as PEG/PPG-4/12 Dimethicone; [k]reported as PEG-10 Dimethicone; [l]reported as PEG-12 Dimethicone; [m]reported as PEG-7 Dimethicone; [n]reported as PEG-8 Dimethicone.

## REFERENCES


CTFA. 2003. Concentrations of use-dimethicone copolyols. Unpublished data submitted by CTFA on February 6, 2003.[10]

DiSapio, A. J. and M. S. Starch. 1981. New silicone emulsifier technology. *Cosmet. Toiletries* 96:55–57.

Elder, R. L. 1982. Final report on the safety assessment of dimethicone copolyol. *J. Am. Col. Toxicol*. 1:33–54.

FDA. 2002. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

National Industrial Chemical Notification and Assessment Scheme (NICNAS). 1997. Full Public Report: Abmil EM90. Unpublished data available at the URL http://www.nicnas.gov.au/publications/CAR/new/NA/NAFULLR/NA0400FR/NA460FR.pdf

Pepe, R. L., J. A. Wenninger, and G. N. McEwen, Jr. eds. 2002. *International cosmetic ingredient dictionary and handbook*, 9th ed. Washington, DC: Cosmetic, Toiletry, and Fragrance Association.

Starch, M., and C. De Vries. 1986. Dimethicone copolyol compounds and their contribution to diminish irritating effects on the rabbit eye. *Parfuem. Kosmet*. 67:148, 151–152, 154.

Wendel, S. R., and A. J. DiSapio. 1983. Organofunctional silicones for personal care applcations. *Cosmet. Toiletries* 98:103–106.

Yahagi, K. 1992. Silicones as conditioning agents in shampoos. *J. Soc. Cosmet. Chem*. 43:275–284.


[10]Available from Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036.

## DIOCTYL AND DIISOPROPYL ADIPATE

A safety assessment of Dioctyl Adipate (CAS no. 103-23-1) and Diisopropyl Adipate (CAS no. 6938-94-9) was published in 1984 with the conclusion that these ingredients are safe as presently used in cosmetics (Elder 1984). New studies given at the end of this section, along with updated information regarding products in which these ingredients are used and at what concentrations, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

In cosmetic product labeling, Dioctyl Adipate is currently given as Diethylhexyl Adipate (Pepe 2002).

Diethylhexyl Adipate was used in 27 product categories in 1981, with maximum concentrations in the >10% to 25% range.

In 2002 there were 49 reported uses of Diethylhexyl Adipate, with a current maximum concentration of use of 38%. Diisopropyl Adipate was used in 112 product categories in 1981, with a maximum concentration in the >10% to 25% range. In 2002, there were 66 reported uses of Diisopropyl Adipate at a current maximum concentration of 15%.

The Panel noted that a new use in aerosols is reported. The effects of inhaled aerosols depend on the specific chemical species, the concentration, the duration of exposure, and site of deposition within the respiratory system. Particle size is the most important factor affecting the location of deposition (Jensen and O'Brien 1993). The mean aerodynamic diameter of pump hair spray particle is $\geq$80 $\mu$ and the diameter of anhydrous spray particles is 60 to 80 $\mu$. Typically, less than 1% are below 10 $\mu$, which is the upper limit for respirable particles (Bower 1999). Although there are no inhalation toxicity data specific to these ingredients, based on the particle size, lanolin and related compounds would not be respirable in formulation.

Although the maximum reported concentration of use for Diethylhexyl Adipate has increased to 38% (in suntan preparations), the Panel stated that the available skin data support the safety of this leave-on use concentration.

The Panel did express initial concern over a Diethylhexyl Adipate fetotoxicity study in which the NOAEL was 200 mg/kg. An exposure assessment that assumed 40 g of use per day at concentrations up to 40% for a 60-kg individual resulted in a maximum exposure of 250 mg/kg, which is higher than the NOAEL. Based on a calculated octanol/water partition coefficient and the information that Diethylhexyl Adipate is not soluble in water, however, the Panel concluded that this ingredient would not be substantially absorbed and the actual exposure would be at least two orders of magnitude below the NOAEL.

Table 10 presents the current and historic frequencies and concentrations of use for Diethylhexyl Adipate and Diisopropyl Adipate.

**TABLE 10**
Historical and current frequencies and concentrations of use for Diethylhexyl and Diisopropyl Adipate

| Product category | 1981 use (Elder, 1984) | 2002 use (FDA, 2002) | 1981 use concentration (Elder, 1984) (%) | 2003 use concentration (CTFA, 2003) (%) |
|---|---|---|---|---|
| | *Diethylhexyl Adipate* | | | |
| Bath oils, tablets, salts | 4 | — | >10–25 | — |
| Eye lotion | — | — | — | 0.6 |
| Eye makeup (other) | — | 2 | — | 0.4–2 |
| Colognes and toilet waters | 6 | — | >1–5 | |
| Blushers | 1 | 3 | ≤0.1 | 13 |
| Makeup foundations | 4 | 2 | >0.1–10 | 16 |
| Makeup bases | — | 6 | — | 6 |
| Lipstick | 5 | 1 | >1–5 | — |
| Makeup (other) | 1 | 2 | >1–5 | — |
| Fragrance preparations (other) | — | 5 | — | — |
| Cuticle softeners | — | 1 | — | — |
| Nail creams and lotions | — | 1 | — | — |
| Nail polish and enamel remover | 2 | — | >1–5 | — |
| Underarm deodorants | 1 | — | >0.1–1 | 8 |
| Personal cleanliness products (other) | — | 4 | — | — |
| Shaving cream | — | 5 | — | — |
| Aftershave lotions | 1 | — | >1–5 | 1 |
| Face and neck skin care preparations | 1* | 2 | >1–5* | — |
| Body and hand skin care preparations | | 2 | | — |
| Skin care preparations (other) | — | 5 | — | — |
| Moisturizers | — | 4 | — | — |
| Suntan gels, creams, and liquids | — | 1 | — | 38 |
| Indoor tanning preparations | — | 2 | — | 12 |
| Suntan preparations (other) | 1 | 1 | >0.1–1 | — |
| **Total uses/ranges for Diethylhexyl Adipate** | **27** | **49** | **≤0.1–25** | **0.4–38** |

*(Continued on next page)*

**TABLE 10**
Historical and current frequencies and concentrations of use for Diethylhexyl and Diisopropyl Adipate *(Continued)*

| Product category | 1981 use (Elder, 1984) | 2002 use (FDA, 2002) | 1981 use concentration (Elder 1984) (%) | 2003 use concentration (CTFA 2003) (%) |
|---|---|---|---|---|
| | *Diisopropyl Adipate* | | | |
| Bath oils, tablets, and salts | 7 | 5 | >1–25 | 5 |
| Bubble baths | 1 | — | >1–5 | — |
| Bath preparations (other) | — | 1 | — | 8 |
| Eyeliner | 1 | — | >1–5 | — |
| Eye shadow | 1 | — | >10–25 | — |
| Colognes and toilet waters | 15 | 16 | >0.1–5 | 8 |
| Perfumes | 20 | 14 | >1–25 | 8 |
| Sachets | 1 | — | >10–25 | — |
| Fragrance preparations (other) | 9 | 2 | >0.1–25 | 15 |
| Hair conditioners | 3 | — | ≤0.1–1 | 0.1 |
| Hair sprays (aerosol fixatives) | 1 | 1 | >1–5 | 3 |
| Tonics, dressings, and other hair-grooming aids | 4 | 2 | >1–5 | — |
| Wave sets | 2 | — | — | — |
| Blushers (all types) | 1 | — | >1–5 | — |
| Face powders | 1 | — | >1–5 | — |
| Makeup foundations | 1 | — | >0.1–1 | 5 |
| Nail polish and enamel removers | — | 1 | — | 3 |
| Personal cleanliness products (other) | 1 | — | >0.1–1 | — |
| Underarm deodorants | — | — | — | 0.01 |
| Aftershave lotions | 16 | 10 | >0.1–5 | 1 |
| Preshave lotions (all types) | 1 | — | >5–10 | 5 |
| Skin-cleansing creams, lotions, liquids, etc. | 5 | 1 | >0.1–1 | — |
| Face and neck creams, lotions, etc. | —* | 1 | —* | — |
| Body and hand creams, lotions, etc. | | 1 | | 2–3 |
| Foot powders and sprays | 1 | — | >0.1–1 | — |
| Moisturizers | 2 | 5 | >0.1–5 | 0.2 |
| Night skin care preparations | 1 | — | >5–10 | — |
| Skin fresheners | 11 | 2 | ≤0.1–10 | — |
| Skin care preparations (other) | 2 | — | >1–10 | 4 |
| Suntan gels, creams, and liquids | 2 | 3 | >5–10 | 4 |
| Indoor tanning preps. | 2 | — | >1–5 | — |
| Suntan preparations (other) | — | 1 | — | — |
| **Total uses/ranges for Diisopropyl Adipate** | **112** | **66** | **≤0.1–25** | **0.01–15** |

*These categories were combined when the original safety assessment was performed and are now separate categories.

## REFERENCES


Astill, B. D., R. Gingell, D. Guest, et al. 1996. Oncogenicity Testing of 2-Ethylhexanol in Fischer 344 Rats and B6 C3F1 Mice. *Fundam. Appl. Toxicol.* 31:29–41.

Bell, F. P. 1983. Effect of the plasticizer di(2-ethylhexyl) adipate (dioctyladipate, DOA) on lipid metabolism in the rat: I. Inhibition of cholesterolgenesis and modification of phospholipid synthesis. *Lipids* 18:211–215.

Bell, F. P. 1984. Di(2-ethylhexyl)adipate (DEHA): effect on plasma lipids and hepatic cholesterolgenesis in the rat. *Bull. Environ. Contam. Toxicol.* 32:20–26.

Bergman, K., and L. Albanus. 1987. Di-(2-ethylhexyl)adipate: Absorption, autoradiographic distribution and elimination in mice and rats. *Food Chem. Toxicol.* 25:309–316.

Bower, D. 1999. Unpublished information on hair spray particle sizes provided at the September 9, 1999 CIR Expert Panel meeting.[11]

British Industrial Biological Research Association. 1985. Rat liver and lipid effects of representative phthalate esters. NTIS Report No. OTS0509538.

Busser M. T., and W. K. Lutz. 1987. Stimulation of DNA synthesis in rat and mouse liver by various tumor promoters. *Carcinogenesis* 8:1433–1437.

Chemical Manufacturer Association. 1989. A study of the hepatic effects of di-(2-ethylhexyl)adipate in the mouse and rat with appendices and cover letter dated 11/17/89. NTIS Report No. OTS0000731.


[11]Available from Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

Cornu, M. C., Y. Keith, C. R. Elcombe, and J. C. Lhuguenot. 1988. In Vivo and In Vitro Metabolism of Di-(2-ethylhexyl) Adipate, a Peroxisome Proliferator, in the Rat. *Arch. Toxicol. Suppl. 12 Target Organ. Toxic. Process.* 265–268.

Cornu, M. C., J. C. Lhuguenot, A. M. Brady, R. Moore, and C. R. Elcombe. 1992. Identification of the proximate peroxisome proliferator(s) derived from di (2-ethylhexyl) adipate and species differences in response. *Biochem. Pharmacol*. 43:2129–2134.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2003. Unpublished data regarding current concentrations of cosmetic uses of Diethylhexyl Adipate and Diisopropyl Adipate.[11]

Dalgaard, M., H. Ulla, A. M. Vinggaard, et al. 2003. Di(2-ethylhexyl)adipate (DEHA) induced developmental toxicity but not antiandrogenic effects in pre- and postnatally exposed Wistar rats. *Reprod. Toxicol.* 17:163–170.

Divincenzo, G. D., W. H. Donish, K. R. Mueller, M. L. Hamilton, and E. D. Barber. 1983. Mutagenicity testing of urine from rats dosed with 2-ethylhexanol derived plasticizers. *Environ. mutagen.* 5:471.

Dirven, H. A., P. H. van den Broek, J. G. Peters, J. Noordhoek, and F. J. Jongeneelen. 1992. Microsomal lauric acid hydroxylase activities after treatment of rats with three classical cytochrome P450 inducers and peroxisome proliferating compounds. *Biochem. Pharmacol.* 43:2621–2629.

Eastman Kodak Co. 1984. Bacterial mutagenicity testing of urine from rats dosed with 2-ethylhexanol derived plasticizers. NTIS Report No. OTS0206391.

Eastman Kodak Co. 1992. Submission summary: Synopsis of teratology study in rats (final report) using di(2-ethylhexyl)adipate with cover letter dated 091391. NTIS Report No. OTS0533689-1.

Elder, R. L., ed. 1984. Final report on the safety assessment of dioctyl adipate and diisopropyl adipate. *J. Am. Col. Toxicol.* 2:101–130.

Food and Drug Administration (FDA). 2002. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

Gupta, B. N., and A. K. Mathur. 1985. Effect of dermal application of a skin barrier cream on skin enzymes in rabbits and guinea-pigs. *Biol. Membrane* 11:157–160.

Gupta, B. N., R. Shanker, P. N. Viswanath, A. K. Mathur, L. Shukla, and A. Singh. 1987. Safety evaluation of a barrier cream. *Contact Dermatitis* 17:10–12.

International Agency for Research on Cancer (IARC). 2000. Di(2-ethylhexyl) adipate entry. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* 77:149–175.

Jensen P. A., and D. Obrien. 1993. Industrial Hygiene. In *Aerosol measurement. Principles techniques and applications*, ed. K. Willeke and P. A. Baron, 538–540. New York: John Wiley and Sons.

Katch, H., S. Nakajima, Y. Kawashima, H. Kozuka, and M. Uchiyama. 1984. Induction of rat hepatic long-chain acyl-CoA hydrolases by various peroxisome proliferators. *Biochem. Pharmacol.* 33:1081–1085.

Kawashima, Y., N. Hanioka, M. Matsumura, and H. Kozuka. 1983a. Induction of microsomal stearoyl-CoA desaturation by the administration of various peroxisome proliferators. *Biochim. Biophys. Acta* 752:259–264.

Kawashima, Y., S. Nakagawa, Y. Tachibana, and H. Kozuka. 1983b. Effects of peroxisome proliferators on fatty acid-binding protein in rat liver. *Biochim. Biophys. Acta* 754:21–27.

Keith, Y., M. C. Cornu, P. M. Canning, J. Foster, J. C. Lhuguenot, and C. R. Elcombe. 1992. Peroxisome proliferation due to di(2-ethylhexyl) adipate, 2-ethylhexanol and 2-ethylhexanoic acid. *Arch. Toxicol.* 66:321–326.

Kluwe, W. M. 1986. Carcinogenic potential of phthalic acid esters and related compounds: Structure-activity relationships. *Environ. Health Perspect*. 65:271–278.

Kluwe, W. M., J. E. Huff, H. B. Matthews, R. Irwin, and J. K. Haseman. 1985. Comparative chronic toxicities and carcinogenic potentials of 2-ethylhexyl-containing compounds in rats and mice. *Carcinogenesis* 6:1577–1583.

Kolmar Research Center. 1984. Toxicological examination of di-a-ethyl-hexyl-adipate (wickenol 158). NTIS Report No. OTS0000286-1.

Korhonen, A., K. Hemminki, and H. Vainio. 1983. Embryotoxic effects of phthalic acid derivatives, phosphates and aromatic oils used in the manufacturing of rubber on three day chicken embryos. *Drug Chem. Toxicol.* 6:191–207.

Lake, B. G., R. J. Price, M. E. Cunninghame, and D. G. Walters. 1997. Comparison of the effects of di-(2-ethylhexyl)adipate on hepatic peroxisome proliferation and cell replication in the rat and mouse. *Toxicology* 123:217–226.

Litton Bionetics, Inc. 1984. Evaluation of di-2-ethylhexyl-adipate in the in vitro transformation of balb/3t3 cells assay. NTIS Report No. OTS0000286-0.

Litton Bionetics, Inc. 1989. Mutagenicity evaluation of di-2-ethyl hexyl adipate in the Ames Salmonella/microsome plate test (final report) with attachments, cover sheet and letter dated 06/06/89. NTIS Report No. OTS0520392.

Litton Bionetics, Inc. 2000. Evaluation of di-2-ethylhexyl-adipate in the in vitro transformation of balb/3t3 cells assay addendum to the final report of September 1982. Contract no. Pe-140 -mut-lb. NTIS Report No. OTS0508486.

Loftus, N. J., W. J. Laird, G. T. Steel, M. F. Wilks, and B. H. Woollen. 1993. Metabolism and pharmacokinetics of deuterium-labelled di-2-(ethylhexyl) adipate(DEHA) in humans. *Food Chem. Toxicol.* 31:609–614.

Loftus, N. J., B. H. Woollen, G. T. Steel, M. F. Wilks, and L. Castle. 1994. An assessment of the dietary uptake of di-2-(ethylhexyl)adipate (DEHA) in a limited population study. *Food Chem. Toxicol.* 32:1–5.

Microbiological Assc. 1984. Submission of unpublished balb/3t3 cell transformation assays on Di-2-ethylhexyl adipate with attached reports. NTIS Report No. 0000286-0.

National Toxicology Program (NTP) 1984. Carcinogenesis bioassay of di(2-ethylhexyl) adipate (cas no. 103-23-1)F344 rats and B6C3f1 mice (feed study). NTIS Report No. OTS0000286-0.

Pepe, R. C., J. A. Wenninger, and G. N. McEwen, Jr., eds. 2002. *International Cosmetic Ingredient Dictionary and Handbook*, 8th ed., vol. 1. Washington, DC: CTFA.

Registry of Toxic Effects of Chemical Substances (RTECS). 1997. Diisopropyl Adipate entry. *RTECS database*. Bethesda, MD: National Library of Medicine.

Registry of Toxic Effects of Chemical Substances (RTECS). 1999. Diethylhexyl Adipate entry. *RTECS database*. Bethesda, MD: National Library of Medicine.

Reisenbichler, H., and P. M. Eckl. 1993. Genotoxic effects of selected peroxisome proliferators. *Mutat. Res.* 286:135–144.

Rhodes, C., T. Soames, M. D. Stonard, M. G. Simpson, A. J. Vernall, and C. R. Elcombe. 1984. The absence of testicular atrophy and in vivo and in vitro effects on hepatocyte morphology and peroxisomal enzyme activities in male rats following the administration of several alkanols. *Toxicol. Lett.* 21:103–109.

Takagi, A., K. Sai, T. Umemura, R. Hasegawa, and Y. Kurokawa. 1990. Significant increase of 8-hydroxydeoxyguanosine in liver DNA of rats following short-term exposure to the peroxisome proliferators di(2-ethylhexyl)phthalate and di(2-ethylhexyl)adipate. *Jpn. J. Cancer Res.* 81:213–215.

Takahashi, K., H. Sakano, N. Numata, S. Kuroda, and N. Mizuno. 2002. Effect of fatty acid diesters on permeation of anti-inflammatory drugs through rat skin. *Drug Dev. Ind. Pharm.* 28:1285–1294.

Takahashi, K., T. Suzuki, H. Sakano, and N. Mizuno. 1995. Effect of vehicles on diclofenac permeation across excised rat skin. *Biol. Pharm. Bull.* 18:571–575.

Tomaszewski, K. E., D. K. Agarwal, and R. L. Melnick. 1986. In vitro steady-state levels of hydrogen peroxide after exposure of male F344 rats and female B6C3F1 mice to hepatic peroxisome proliferators. *Carcinogenesis* 7:1871–1876.

von Daniken, A., W. K. Lutz, R. Jackh, and C. Schlatter. 1984. Investigation of the potential for binding of Di(2-ethylhexyl)phthalate (DEHP) and Di(2-ethylhexyl)adipate (DEHA) to liver DNA in vivo. *Toxicol. Appl. Pharmacol.* 73:373–387.

Yanagita, T., M. Satoh, H. Nomura, N. Enomot, and M. Sugano. 1987. Alteration of hepatic phospholipids in rats and mice by feeding di-(2-ethylhexyl)adipate and di-(2-ethylhexyl)phthalate. *Lipids* 22:572–577.

Zeiger, E., S. Haworth, K. Mortelmans, and W. Speck. 1985. Mutagenicity testing of di(2-ethylhexyl)phthalate and related chemicals in *Salmonella*. *Environ. Mutagen.* 7:213–232.

## EUPHORBIA CERIFERA (CANDELILLA) WAX, COPERNICA CERIFERA (CARNAUBA) WAX, RHUS SUCCEDANEA FRUIT WAX, AND BEESWAX

A CIR Final Report on these ingredients was published in 1984 (Elder 1984) with the conclusion that they are safe as used in cosmetics under present practices of concentration and use. In that report, the names for the first three ingredients was Candelilla Wax, Carnauba Wax, and Japan Wax, respectively. New studies given at the end of this section, along with updated information regarding products in which these ingredients are used and at what concentrations, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

**Euphorbia Cerifera (Candelilla) Wax** was used in 1703 products in 1976, mostly in lipsticks at a maximum concentration of 25%, although it was used in mascara products at a maximum concentration of 50% (Elder 1984). In 2002, this ingredient reportedly had 701 uses (FDA 2002), mostly in lipsticks at a maximum current concentration of 27% (CTFA 2003)—no higher current concentrations of use were reported.

**Copernica Cerifera (Carnauba) Wax** was used in 2109 products in 1976, again mostly in lipsticks at a maximum concentration of 25%, although it was used in eye makeup products at a maximum concentration of 50% (Elder 1984). In 2002, this ingredient reportedly had 1194 uses (FDA 2002), mostly in lipsticks in the 1% to 9% range, although it was used in foundations in the 6% to 20% range (CTFA 2003).

**Rhus Succedanea Fruit Wax** was used in 244 products in 1976, again mostly in lipsticks at concentrations up to 50%, although it was used in eye makeup products in the 5% to 50% range (Elder 1984). In 2002, this ingredient reportedly had 528 uses (FDA 2002), mostly in eyeliner products at a maximum current concentration of 11%, although it was used in eyebrow pencils at 34% (CTFA 2003).

**Beeswax** was used in 2437 products in 1976, again mostly in lipsticks in the 0.1% to 25% concentration range—no higher use concentrations were reported (Elder 1984). In 2002, this ingredient reportedly had 145 uses (FDA 2002), mostly in lipstick products in the 3% to 25% concentration range—no higher use concentrations were reported (CTFA 2003).

Table 11 lists the historical and current use and concentration data for these ingredients.

The Panel reminded manufacturers that cosmetic products containing plant-derived ingredients should be formulated to limit the presence of heavy metal/pesticide residues as follows: lead $\leq$10 ppm, arsenic $\leq$3 ppm, mercury $\leq$1 ppm, and total PCB/pesticide contamination $\leq$40 ppm, with $\leq$10 ppm for any specific residue.

**TABLE 11**
Historical and current cosmetic product uses and concentrations for Euphorbia Cerifera (Candelilla) Wax, Copernica Cerifera (Carnauba) Wax, Rhus Succedanea Fruit Wax, and Beeswax

| Product category | 1976 uses (Elder 1984) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1984) (%) | 2003 use concentrations (CTFA 2003) (%) |
|---|---|---|---|---|
| | *Euphorbia Cerifera (Candelilla) Wax* | | | |
| Eyebrow pencil | 6 | 4 | 1–10 | — |
| Eyeliner | 18 | 17 | 1–10 | 5–12 |
| Eye shadow | 183 | 16 | 0.1–25 | 3–5 |
| Mascara | 66 | 44 | 0.1–50 | 3–8 |
| Eye makeup (other) | 20 | 12 | 0.1–50 | 2–18 |
| Colognes and toilet waters | 1 | — | 1–5 | — |
| Perfumes | 3 | 3 | 5–25 | — |
| Fragrance preparations (other) | 5 | — | 1–25 | — |
| Hair conditioners | 1 | — | 0.1–1 | — |
| Hair tonics, dressings, etc. | 4 | 2 | 0.1–1 | — |
| Hair preparations (other) | — | — | — | 2 |
| Hair dyes and colors | 1 | — | 1–5 | — |
| Hair-coloring preparations (other) | — | — | — | 0.4 |
| Blushers | 55 | 12 | 0.1–25 | 2–8 |
| Face powders | — | 1 | — | 3 |
| Foundations | 24 | 14 | 0.1–10 | 3–10 |
| Lipsticks | 1144 | 504 | 0.1–25 | 5–27 |

*(Continued on next page)*

**TABLE 11**
Historical and current cosmetic product uses and concentrations for Euphorbia Cerifera (Candelilla) Wax, Copernica Cerifera (Carnauba) Wax, Rhus Succedanea Fruit Wax, and Beeswax *(Continued)*

| Product category | 1976 uses (Elder 1984) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1984) (%) | 2003 use concentrations (CTFA 2003) (%) |
|---|---|---|---|---|
| Makeup bases | 37 | 13 | 0.1–25 | — |
| Rouges | 30 | 2 | 1–25 | 5–8 |
| Makeup fixatives | 4 | — | 1–5 | — |
| Makeup (other) | 65 | 41 | 0.1–25 | 6–10 |
| Nail polish and enamel | — | 1 | — | 9 |
| Nail care preparations (other) | — | 1 | — | — |
| Oral hygiene products (other) | — | — | — | 0.03–12 |
| Skin-cleansing creams, lotions, liquids, and pads | 7 | 2 | 1–5 | 1 |
| Face and neck skin care preparations | | — | | — |
| Body and hand skin care preparations | 3* | — | Unknown* | 0.3 |
| Moisturizers | 14 | 4 | 1–25 | — |
| Night skin care preparations | 5 | 2 | 1–5 | 2 |
| Paste masks/mud packs | — | 3 | — | 2 |
| Skin care preparations (other) | 2 | 2 | 10–25 | 0.3–5 |
| Suntan gels, creams, and liquids | 4 | 1 | 1–10 | 8 |
| Suntan preparations (other) | 1 | — | 1–5 | 0.2–4 |
| Total uses/ranges for **Euphorbia Cerifera (Candelilla) Wax** | **1703** | **701** | **0.1–50** | **0.03–27** |
| *Copernica Cerifera (Carnauba) Wax* | | | | |
| Baby lotions, oils, powders, and creams | — | — | — | 0.8–1 |
| Bath oils, tablets, and salts | — | 1 | — | — |
| Eyebrow pencil | 10 | 36 | 0.1–10 | — |
| Eyeliner | 44 | 317 | 1–25 | 1 |
| Eye shadow | 297 | 59 | ≤0.1–50 | — |
| Eye lotion | 2 | — | ≤0.1–5 | — |
| Mascara | 162 | 143 | 0.1–50 | 2–6 |
| Eye makeup (other) | 26 | 48 | 0.1–10 | 5 |
| Colognes and toilet waters | — | 1 | — | — |
| Perfumes | 1 | — | 0.1–1 | — |
| Fragrance preparations (other) | 5 | 1 | 1–10 | — |
| Hair conditioners | 1 | — | 0.1–1 | — |
| Shampoos (noncoloring) | — | 1 | — | — |
| Hair tonics, dressings, etc. | 1 | — | Unknown | — |
| Hair dyes and colors | 1 | — | 1–5 | — |
| Hair-coloring preparations (other) | 4 | 8 | 1–10 | — |
| Blushers | 130 | 10 | ≤0.1–25 | 4 |
| Face powders | — | 1 | — | — |
| Foundations | 42 | — | 1–25 | 6–20 |
| Lipsticks | 1144 | 479 | ≤0.1–25 | 1–9 |
| Makeup bases | 66 | 7 | 0.1–10 | — |
| Rouges | 23 | — | 1–25 | — |
| Makeup fixatives | 12 | 2 | 1–5 | — |
| Makeup (other) | 92 | 45 | 0.1–25 | 2–6 |
| Nail creams and lotions | 1 | — | 1–5 | — |

*(Continued on next page)*

**TABLE 11**
Historical and current cosmetic product uses and concentrations for Euphorbia Cerifera (Candelilla) Wax, Copernica Cerifera (Carnauba) Wax, Rhus Succedanea Fruit Wax, and Beeswax *(Continued)*

| Product category | 1976 uses (Elder 1984) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1984) (%) | 2003 use concentrations (CTFA 2003) (%) |
|---|---|---|---|---|
| Nail polish and enamel | — | 1 | — | — |
| Nail care preparations (other) | 1 | 1 | 1–5 | — |
| Oral hygiene products (other) | — | 2 | — | 0.07 |
| Skin-cleansing creams, lotions, liquids, and pads | 5 | 3 | 5–10 | 0.2 |
| Depilatories | 1 | 1 | 1–5 | — |
| Face and neck skin care preparations | 3* | 2 | Unknown* | — |
| Body and hand skin care preparations | | 2 | | — |
| Moisturizers | 13 | 5 | 0.1–10 | — |
| Night skin care preparations | 6 | 5 | 1–5 | 0.2 |
| Paste masks/mud packs | — | 1 | — | — |
| Skin care preparations (other) | 12 | 9 | 1–25 | — |
| Suntan gels, creams, and liquids | 2 | 1 | 0.1–5 | 0.1 |
| Suntan preparations (other) | 2 | 2 | 1–10 | 4 |
| **Total uses/ranges for Copernica Cerifera (Carnauba) Wax** | **2109** | **1194** | **≤0.1–50** | **0.07–20** |
| | *Rhus Succedanea Fruit Wax* | | | |
| Bath oils, tablets, and salts | — | 1 | — | — |
| Eyebrow pencil | 47 | 56 | 5–50 | 34 |
| Eyeliner | 30 | 276 | 5–50 | 11 |
| Eye shadow | 1 | 23 | 10–25 | — |
| Eye makeup (other) | 5 | 7 | Unknown | — |
| Hair tonics, dressings, etc. | 2 | 1 | 1–10 | — |
| Blushers | 1 | — | 1–5 | — |
| Lipsticks | 158 | 143 | 0.1–25 | — |
| Makeup (other) | — | 19 | — | 7 |
| Face and neck skin care preparations | — | — | — | 1 |
| Skin care preparations (other) | — | 2 | — | — |
| **Total uses/ranges for Rhus Succedanea Fruit Wax** | **244** | **528** | **0.1–50** | **1–34** |
| | *Beeswax* | | | |
| Baby lotions, oils, powders, creams | 2 | 4 | 0.1–10 | — |
| Bath preparations (other) | — | — | — | — |
| Eyebrow pencil | 12 | 15 | 1–25 | — |
| Eyeliner | 28 | 29 | 1–25 | 2 |
| Eye shadow | 342 | 23 | 0.1–25 | 2 |
| Eye lotion | 4 | 1 | 1–10 | — |
| Eye makeup remover | 2 | — | 1–10 | — |
| Mascara | 182 | 116 | 1–50 | 19 |
| Eye makeup (other) | 43 | 38 | 0.1–50 | 3 |
| Colognes and toilet waters | 2 | — | 10–25 | — |
| Perfumes | 26 | 18 | 10–50 | 1 |
| Sachets | 26 | 9 | 0.1–50 | — |
| Fragrance preparations (other) | 10 | 6 | 1–50 | — |
| Hair conditioners | 14 | 4 | 0.1–25 | — |
| Hair straighteners | 3 | — | 10–25 | — |

*(Continued on next page)*

**TABLE 11**
Historical and current cosmetic product uses and concentrations for Euphorbia Cerifera (Candelilla) Wax, Copernica Cerifera (Carnauba) Wax, Rhus Succedanea Fruit Wax, and Beeswax *(Continued)*

| Product category | 1976 uses (Elder 1984) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1984) (%) | 2003 use concentrations (CTFA 2003) (%) |
|---|---|---|---|---|
| Rinses (noncoloring) | 1 | — | 0.1–1 | — |
| Shampoos (noncoloring) | 1 | — | 0.1–1 | — |
| Hair tonics, dressings, etc. | 26 | 17 | ≤0.1–25 | — |
| Wave sets | 1 | — | 0.1–1 | — |
| Hair preparations (other noncoloring) | 2 | — | 5–10 | 1 |
| Hair dyes and colors | 4 | 20 | 0.1–10 | — |
| Hair tints | — | 1 | — | — |
| Hair color sprays | — | 1 | — | — |
| Hair-coloring preparations (other) | 8 | 2 | 1–5 | — |
| Blushers | 66 | 11 | ≤0.1–25 | 19 |
| Face powders | 17 | 2 | 0.1–1 | 2 |
| Foundations | 80 | 14 | 0.1–10 | 5 |
| Lipstick | 799 | 224 | ≤0.1–50 | 56 |
| Makeup bases | 89 | 25 | 0.1–10 | 3 |
| Rouges | 33 | 2 | 0.1–10 | — |
| Makeup fixatives | 6 | — | 1–25 | — |
| Makeup (other) | 106 | 27 | 0.1–50 | 9 |
| Oral hygiene products (other) | — | — | — | 2 |
| Cuticle softeners | 5 | 5 | 1–10 | — |
| Nail creams and lotions | 4 | 5 | 1–25 | — |
| Bath soaps and detergents | 4 | 2 | ≤0.1–1 | — |
| Underarm deodorants | 1 | 1 | 1–5 | — |
| Personal cleanliness products (other) | 1 | 2 | 5–10 | — |
| Aftershave lotions | 2 | 8 | Unknown | — |
| Men's talcum | — | — | — | — |
| Shaving soaps | — | — | — | — |
| Shaving preparations (other) | 2 | 1 | 0.1–1 | |
| Skin-cleansing creams, lotions, liquids, and pads | 154 | 72 | ≤0.1–25 | 2 |
| Depilatories | 5 | 1 | 1–50 | 2 |
| Face and neck skin care preparations | 92* | 32 | ≤0.1–25* | 1 |
| Body and hand skin care preparations | | 93 | | 10 |
| Hormone products | 3 | N/A** | 1–25 | N/A** |
| Moisturizers | 91 | 102 | 0.1–25 | 1 |
| Night skin care preparations | 78 | 48 | 0.1–25 | 4 |
| Paste masks (mud packs) | 1 | 11 | 1–5 | 1 |
| Skin lighteners | 1 | N/A** | 25–50 | N/A** |
| Skin fresheners | 1 | — | Unknown | — |
| Skin care preparations (other) | 37 | 74 | 1–25 | 4 |
| Suntan gels, creams, liquids | 18 | 7 | 1–10 | — |
| Indoor tanning prep | — | 1 | — | — |
| Suntan preparations (other) | 2 | — | 1–5 | — |
| **Total uses/ranges for Beeswax** | **2437** | **1074** | **≤0.1–50** | **1–56** |

*These categories were combined when the original safety assessment was performed and are now separate categories.
**No longer considered a cosmetic product category.

## REFERENCES


Bogdanov, S., V. Kilchenmann, and A. Imdorf. 1998. Agaricide residues in some bee products. *J. Apicul. Res.* 37:57–67.

Brusick, D. 1976. Mutagenic evaluation of compound FDA 75-43, MX8006-44-8 candelilla wax, L.F. refined. Project No. 2468, Litton Bionetics, Inc. (Cited in FAO and WHO, 1993.)

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2003. Unpublished data regarding current concentrations of cosmetic uses of Euphorbia Cerifera (Candelilla) Wax, Copernica Cerifera (Carnauba) Wax, Rhus Succedanea Fruit Wax, and Beeswax.[12]

Elder, R. L., ed. 1984. Final report on the safety assessment of Candelilla Wax, Carnauba Wax, Japan Wax, and Beeswax. *J. Am. Col. Toxicol.* 3:1–41.

FAO and WHO. 1993a. Beeswax. WHO food additive series. Pages 230–234.

FAO and WHO. 1993b. Candelilla wax. WHO food additives series. Pages 235–243.

FASEB. 1975. Evaluation of the health aspects of beeswax (yellow or white) as a food ingredient. Federation of American Societies for Experimental Biology. Prepared for FDA. Contract No. FDA 223-75-2004. Unpublished report. (Cited in FAO and WHO, 1993a.)

FASEB. 1981. Evaluation of the health aspects of candelilla wax as a food ingredient. Federaton of American Societies for Experimental Biology. Prepared for FDA, Contract No. FDA 223-78-210. Unpublished report. (Cited in FAO and WHO, 1993b.)

Food and Drug Administration (FDA). 2002. Frequency of use of cosmetic ingredients *FDA Database*. Washington, DC: FDA.

Garcia, M., M. D. del Pozo, J. Diez, D. Munoz, and L. F. de Corres. 1995. Allergic contact dermatitis from a beeswax nipple-protective. *Contact Dermatitis* 33:440–441.

Harrisson, J. W. E. 1946. Product No. 12, type III GRS. Rubber and candelilla wax. Report No. 36731. LaWall and Harrisson, Consultants, Unpublished report. (Cited in FAO and WHO, 1993b.)

Harrisson, J. W. E. 1948. Product No. 16, 50/50 mixture candelilla wax and haveatex (Styrene and Butadiene) Polymer N-1017. Report 38222. LaWall and Harrisson, Consultants. Unpublished report. (Cited in FAO and WHO, 1993b.)

Harrisson, J. W. E. 1953. Long-term safety studies. Resume of studies on young dogs and albino rats. LaWall and Harrisson, Consultants. Unpublished report. (Cited in FAO and WHO, 1993b.)

Hodge, H. C. 1973. A critical review at the 1) Feeding studies of candelilla wax incorporated in gum base, 2) together with studies of the possible carcinogenic potential by other routes of administration. University of California, San Francisco. (Cited in FAO and WHO, 1993b.)

Lucente, P., M. Cavalli, C. Vezzani, C. Orlandi, and C. Vincenzi. 1996. Contact cheilitis due to beeswax. *Contact Dermatitis* 35:258.

Mortelmans, K. E., and S. L. Eckford. 1979. Microbial mutagenesis testing of substances compound report: F76-048, candelilla wax. Final Report, Project No. LSU-6909. SRI International. (Cited in FAO and WHO, 1993b.)

Nakamura, T. 1985. Contact dermatitis to Rhus succedanea. *Contact Dermatitis* 12:279.

Prival, M. J., V. F. Simmon, and K. E. Mortelmans. 1991. Bacterial mutagenicity testing of 49 food ingredients gives very few positive results. *Mutat. Res*. 260:321–329.

Rivera, R. F., J. O. Moffett, and R. L. Cox. 1987. Menthol residues in honey beeswax and honey bees. *Am. Bee J.* 127:850.

Rowland, I. R., K. R. Butterworth, I. F. Gaunt, P. Grasso, and S. D. Gangolli. 1982. Short-term toxicity study of carnauba (Copernica cerifera) wax in rats. *Food Chem. Toxicol.* 20:467–472.

Valsecchi, R., and T. Cainelli. 1984. Dermatits from propolis. *Contact Dermatitis* 11:317.

Van Ketel, W. G., and D. P. Bruynzeel. 1992. Occupational dermatitis in an accordion repairer. *Contact Dermatitis* 27:186.


[12] Available from Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

## ISOBUTANE, ISOPENTANE, n-BUTANE, AND PROPANE

A safety assessment of Isobutane, Isopentane, n-Butane, and Propane was published in 1982 with the conclusion that these compounds "are considered safe as cosmetic ingredients under present conditions of concentration and use" (Elder 1982). New studies, along with updated information regarding products in which these ingredients are used and at what concentrations were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

The Panel did note that concentrations of use have increased for this group of ingredients, but that the available safety test data adequately address even these higher concentrations.

**Isobutane** functions as a propellant in a wide variety of cosmetic products. Historically, the highest concentration of use of Isobutane in cosmetics was 50% in underarm deodorants. Currently, the highest concentration of use of Isobutane is 83% in powders. Historical and current uses of Isubutane in cosmetic products are listed in Table 12.

**Isopentane** functions as a propellant, solvent, and a viscosity decreasing agent in cosmetic products. Historically, the highest concentration of use of Isopentane in cosmetics was 50% in other personal cleanliness products. Currently, the highest concentration of use of Isopentane is 37% in underarm deodorants. Historical and current uses of Isopentane in cosmetic products are listed in Table 12.

**n-Butane** functions as a propellant in cosmetic products. Historically, the highest concentration of use of n-Butane in cosmetics was 25% in personal cleanliness products (other). Currently, the highest concentration of use of n-Butane is 92% in underarm deodorants. Historical and current uses of n-Butane in cosmetic products are listed in Table 12.

**Propane** functions as a propellant in cosmetic products. Historically, the highest concentration of use of Propane in cosmetics was 1% in face, neck, body, and hand skin care preparations. Currently, the highest concentration of use of Propane is 24% in nail basecoats and undercoats. Historical and current uses of Propane in cosmetic products are listed in Table 12.

## REFERENCES


American Conference of Governmental Industrial Hygienists (ACGIH). 2000. *2000 TLSs and BEIs. Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices.* Cincinnati, OH: ACGIH.

Avis, S. P., and J. T. Archibald. 1994. Asphyxial suicide by propane inhalation and plastic bag suffocation. *J. Forensic Sci.* 39:253–256.

Bowen, S. E., J. Daniel, and R. L. Balster. 1999. Deaths associated with inhalant abuse in Virginia from 1987 to 1996. *Drug Alcohol Dependance*. 53:239–245.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2002. Concentration of use—isobutane, isopentane, propane, and butane. Unpublished data submitted by CTFA on February 15, 2002.[13]

Elder, R. L. 1982. Final report of the safety assessment of isobutane, isopentane, n-butane and propane. *J. Am. Col. Toxicol*. 1:127–142.

Food and Drug Administration (FDA). 1976. Cosmetic product formulation data. *FDA database*. Washington, DC: FDA.

FDA. 2001. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.


[13] Available from Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

**TABLE 12**
Historical and current cosmetic product uses and concentrations for Isobutane, Isopentane, n-Butane, and Propane

| Product category | 1976 uses (Elder 1982) | 2001 uses (FDA 2001) | 1976 use concentrations (Elder 1982) (%) | 2001 use concentrations (CTFA 2001) (%) |
|---|---|---|---|---|
| | | *Isobutane* | | |
| Bath preparations (other) | 1 | — | >1–5 | — |
| Colognes and toilet waters | — | 12 | — | 54 |
| Powders | — | — | — | 83 |
| Sachets | — | 4 | — | 32 |
| Fragrance preparations (other) | — | 6 | — | 51–60 |
| Hair conditioners | 3 | 2 | >1–5 | — |
| Hair sprays (aerosol fixatives) | 103 | 107 | >5–25 | 13–32 |
| Hair tonics, dressings, etc. | — | 37 | — | 8–20 |
| Wave sets | — | 1 | — | — |
| Hair preparations (other noncoloring) | — | 11 | — | — |
| Hair tints | — | 17 | — | — |
| Hair color sprays (aerosol) | — | 1 | — | — |
| Blushers (all types) | 1 | — | ≤0.1 | — |
| Foundations | 1 | — | >0.1–1 | 3 |
| Makeup bases | 1 | — | >0.1–1 | — |
| Nail basecoats and undercoats | — | — | — | 30 |
| Mouthwashes and breath fresheners | — | 5 | — | 38 |
| Underarm deodorants | 6 | 20 | >1–50 | 25–70 |
| Feminine deodorants | 3 | 2 | >10–25 | — |
| Personal cleanliness products (other) | 13 | 13 | >0.1–25 | 2–16 |
| Aftershave lotion | — | 6 | — | — |
| Shaving cream | 51 | 67 | 0.1–5 | 0.6–5 |
| Shaving preparations (other) | — | 19 | — | 5 |
| Skin-cleansing creams, lotions, liquids, and pads | 1 | 2 | >1–5 | 0.9 |
| Depilatories | — | — | — | 4 |
| Face and neck skin care preparations | 2* | 1 | >1–5* | 5 |
| Body and hand skin care preparations | | 1 | | 1–75 |
| Foot powders and sprays | 1 | 2 | >1–5 | 26–82 |
| Moisturizers | 2 | 1 | >1–5 | 0.5–6 |
| Skin fresheners | 1 | — | >1–5 | 21 |
| Skin care preparations (other) | 1 | — | >0.1–1 | 2–24 |
| Indoor tanning preparations | — | 2 | — | — |
| **Totals uses/ranges for Isobutane** | **191** | **338** | **≤50** | **0.5–83** |
| | | *Isopentane* | | |
| Hair tonics, dressings, etc. | — | 1 | — | — |
| Hair sprays (aerosol fixatives) | — | — | — | 15 |
| Hair preparations (other noncoloring) | — | 1 | — | — |
| Mouthwashes and breath fresheners | — | — | — | 35 |
| Underarm deodorants | — | — | — | 0.5–37 |
| Personal cleanliness products (other) | 2 | 1 | >25–50 | 0.05 |
| Shaving cream | — | 6 | — | 1–5 |
| Shaving preparations (other) | — | 19 | — | — |
| Skin-cleansing creams, lotions, liquids, and pads | — | 1 | — | — |
| **Total uses/ranges for Isopentane** | **2** | **29** | **>25–50** | **0.5–37** |

*(Continued on next page)*

**TABLE 12**
Historical and current cosmetic product uses and concentrations for Isobutane, Isopentane, n-Butane, and Propane *(Continued)*

| Product category | 1976 uses (Elder 1982) | 2001 uses (FDA 2001) | 1976 use concentrations (Elder 1982) (%) | 2001 use concentrations (CTFA 2001) (%) |
|---|---|---|---|---|
| | | *n-Butane* | | |
| Colognes and toilet waters | — | 26 | — | 29 |
| Perfumes | — | 5 | — | — |
| Fragrance preparations (other) | — | 1 | — | 54 |
| Hair conditioners | 3 | 6 | >1–5 | 21 |
| Hair sprays (aerosol fixatives) | — | 47 | — | 12–14 |
| Hair tonics, dressings, etc. | — | 19 | — | — |
| Hair preparations (other noncoloring) | — | 24 | — | — |
| Hair tints | — | 3 | — | — |
| Blushers (all types) | 5 | — | >1–5 | — |
| Foundations | 3 | — | >1–5 | — |
| Makeup bases | 1 | — | >1–5 | — |
| Underarm deodorants | — | 5 | — | 17–92 |
| Personal cleanliness products (other) | 1 | 12 | >10–25 | 52 |
| Shaving cream | 14 | 24 | ≤1 | 1–5 |
| Skin-cleansing creams, lotions, liquids, and pads | 1 | — | >0.1–1 | — |
| Body and hand skin care preparations | — | — | — | 4–29 |
| Skin care preparations (other) | — | — | — | 55 |
| Indoor tanning preparations | — | 1 | — | — |
| **Total uses/ranges for n-Butane** | **28** | **173** | **≤25** | **1–92** |
| | | *Propane* | | |
| Colognes and toilet waters | — | 17 | — | 11 |
| Sachets | — | 4 | — | — |
| Fragrance preparations (other) | — | 5 | — | 7–21 |
| Hair conditioners | — | 6 | — | 3 |
| Hair sprays (aerosol fixatives) | — | 72 | — | 6–20 |
| Hair tonics, dressings, etc. | — | 19 | — | 3–9 |
| Wave sets | — | 1 | — | — |
| Hair preparations (other) | — | 16 | — | — |
| Hair tints | — | 3 | — | — |
| Hair color sprays (aerosol) | — | 1 | — | — |
| Foundations | — | — | — | 2–3 |
| Nail basecoats and undercoats | — | — | — | 24 |
| Underarm deodorants | — | 21 | — | 14–16 |
| Personal cleanliness products (other) | — | 12 | — | 13 |
| Shaving cream | 37 | 66 | ≤5 | 0.4–4 |
| Shaving preparation products (other) | — | — | — | 0.8 |
| Skin-cleansing creams, lotions, liquids and pads | — | 1 | — | 2 |
| Depilatories | — | — | — | 1 |
| Face and neck skin care preparations | 2* | — | >0.1–1* | 2 |
| Body and hand skin care preparations | | — | | 0.5–9 |
| Moisturizers | — | 1 | — | 0.2–0.4 |
| Skin fresheners | 1 | — | ≤0.1 | 0.8 |
| Other skin care preparations | — | — | — | 2–7 |
| Indoor tanning preparations | — | 2 | — | — |
| Other suntan preparations | — | — | — | 1 |
| **Total uses/ranges for Propane** | **40** | **248** | **≤1** | **0.2–24** |

*These categories were combined when the original safety assessment was performed and are now two separate categories.

Hartop, P. J., T. L. Cook, and M . G. Adams. Simulated consumer exposure to dimethyl ether and propane/butane in hairsprays. *Intl. J. Cosmet. Sci.* 13:161–167.

McLennan, J. J., A. Sekula-Perlman, M. B. Lippstone, and R. T. Callery. Propane-associated autoerotic fatalities. *Am. J. Forensic Med. Pathol.* 19:381–386.

American Pertoleum Institute. 1984. Thirteen week inhalation toxicity study of C4/C5 hydrocarbon blends in rats with 2 cover letters dated 10/30/84 and 11/08/84. NTIS Report No. OTS0000332-1.

Rohrig, T. P. 1997. Sudden death due to butane inhalation. *Am. J. Forensic Med. Pathol*. 18:299–302.

Siegel, E., and S. Wason. 1990. Sudden death caused by inhalation of butane and propane. *N. Engl. J. Med.*. 232:1838.

Stewart, R. D., A. A. Hermann, E. D. Baretta, H. V. Forster, J. J. Sikora, P. E. Newton, and R. J. Soto. 1977. Acute and repetitive human exposure to isobutane. *Scand. J. Environ. Health* 3:234–243.

Stewart, R. D., P. E. Newton, E. D. Baretta, A. A. Hermann, H. V. Forster, and R. J. Soto. 1978. Physiological response to aerosol propellants. *Environ. Health Perspect*. 26:275–285.

## ISOSTEARIC ACID

A safety assessment of Isostearic Acid was published in 1983 with the conclusion: "safe as a cosmetic ingredient in the present practices of use" (Elder 1983). Studies available since that safety assessment was completed, along with updated information regarding uses and concentrations were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

Isostearic Acid (CAS no. 2724-58-5) is a mixture of fatty esters consisting mainly of methyl branched isomers of octadecanoic acid; it functions as binders and surfactants (cleansing agents) in a wide variety of cosmetic products.

In 1981, there were 142 formulations reported to the FDA that contained Isostearic Acid at concentrations from ≤0.1% to 10%. Currently there are 119 total formulations reported at concentrations from 0.003% to 26%. Table 13 presents the use and concentration data.

**TABLE 13**
Historical and current cosmetic product uses and concentrations for Isostearic Acid

| Product category | 1981 uses (Elder 1983) | 2002 uses (FDA 2002) | 1981 use concentrations (Elder 1983) (%) | 2002 use concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| Eyeliner | 2 | 2 | >0.1–5 | 1 |
| Eye shadow | 17 | — | ≤0.1–5 | 0.02 |
| Mascara | 9 | 11 | >1–5 | 0.01–3 |
| Eye makeup (other) | — | — | — | 0.01 |
| Powders | — | — | — | 0.3 |
| Hair conditioners | — | — | — | 1 |
| Shampoos (noncoloring) | — | 1 | — | — |
| Hair tonics, dressings, etc. | — | 2 | — | 2 |
| Other hair preparations | — | 1 | — | — |
| Hair dyes and colors | — | — | — | 18 |
| Hair bleaches | — | — | — | 26 |
| Blushers (all types) | 20 | 5 | ≤0.1–5 | 4 |
| Face powders | 13 | 3 | ≤0.1–5 | 3 |
| Makeup foundations | 12 | 26 | >0.1–5 | 0.02–3 |
| Lipstick | 8 | 6 | >0.1–10 | 10 |
| Makeup bases | 17 | 9 | >0.1–5 | — |
| Rouges | 1 | | >1–5 | — |
| Makeup (other) | — | 2 | — | 3 |
| Cuticle softeners | — | 2 | — | — |
| Nail creams and lotions | — | — | — | 16 |
| Nail polish and enamel | — | — | — | 2 |
| Bath soaps and detergents | 3 | — | >1–5 | 2–9 |
| Underarm deodorants | — | 2 | — | — |
| Other personal cleanliness products | 2 | — | >0.1–1 | — |
| Aftershave lotions | — | — | — | 0.003 |

*(Continued on next page)*

**TABLE 13**
Historical and current cosmetic product uses and concentrations for Isostearic Acid *(Continued)*

| Product category | 1981 uses (Elder 1983) | 2002 uses (FDA 2002) | 1981 use concentrations (Elder 1983) (%) | 2002 use concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| Shaving cream | 2 | 2 | >1–5 | — |
| Shaving soap | — | — | — | 5 |
| Shaving preparation products (other) | 1 | — | >0.1–1 | — |
| Skin-cleansing creams, lotions, liquids, and pads | 5 | 3 | >0.1–5 | 2 |
| Face and neck skin care preparations | | 4 | | 2 |
| Body and hand skin care preparations | 6* | 5 | >0.1–5* | 0.3–2 |
| Moisturizers | 19 | 26 | >0.1–5 | 0.5–3 |
| Night skin care preparations | 2 | 1 | >0.1–5 | — |
| Skin lighteners | 1 | N/A** | >1–5 | N/A** |
| Skin fresheners | — | 1 | — | — |
| Skin care preparations (other) | — | 3 | — | 0.6–3 |
| Suntan gels, creams, and liquids | 1 | 2 | >5–10 | — |
| Suntan preparations (other) | 1 | — | >1–5 | — |
| **Total uses/ranges for Isostearic Acid** | **142** | **119** | **≤0.1–10** | **0.003–26** |

*In 1976, many categories were grouped into one; e.g., one category, bath preparations, represented all of what are currently divided into discrete product categories: bath oils, tablets, and salts; bubble baths; bath capsules; and bath preparations (other).

**No longer considered a cosmetic product category.

## REFERENCES


Aungst, B. J. 1989. Structure-effect studies of fatty acid isomers as skin penetration enhancers and skin irritants. *Pharm. Res.* 6:244–247.

Bagley, D. M., J. R. Gardner, G. Holland, R. W. Lewis, J. F. Regnier, D. A. Stringer, and A. P. Walker. 1996. Skin irritation: Reference chemicals data bank. *Toxicol. In Vitro* 10:1–16.

Bagley, D. M., J. R. Gardner, G. Holland, R. W. Lewis, H. Vrijhof, and A. P. Walker. 1999. Eye irritation: Updated reference chemicals data bank. *Toxicol. In Vitro* 13:505–510.

Chollet, J. L., E. S. Goebl, C. S. Moeckly, and K. R. Phares. 1997. The effect of temperature on the solubility of imiquimod in isostearic acid. *Pharmaceut. Res.* 14:S483.

Chollet, J. L., M. J. Jozwiakowski, K. R. Phares, M. J. Reiter, P. J. Roddy, H. J. Shultz, Q. V. Ta, and M. A. Tomai. 1999. Development of a topically active imiquimod formulation. *Pharm. Dev. Technol.* 4:35–43.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2002. Concentration of use of Isostearic Acid in cosmetic products. Unpublished data submitted by CTFA.[14]

Elder, R. L., ed. 1983. Final report on the Safety Assessment of Isostearic Acid. *J. Am. Col. Toxicol.* 1:1-23.

Elmaleh, D. R., E. Livini, S. Levy, D. Varnum, H. W. Strauss, and G. L. Brownell. 1983. Comparison of 11C and 14C-labeled fatty acids and their beta-methyl analogs. *Int. J. Nucl. Med. Biol.* 10:181–187.

Fentem, J. H., G. E. B. Archer, M. Balls, P. A. Bontham, R. D. Curren, L. K. Earl, D. J. Esdaile, H.-G. Holzhutter, and M. Liebsch. 1998. The ECVAM International Validation Study on in vitro tests for skin corrosivity. 2. Results and evaluation by management team. *Toxicol. In Vitro* 12:483–524.

FDA. 2002. Cosmetic product formulation data. FDA database. Washington, DC: FDA.

Kawaji, T., and M. Yamaji. 2001. Oily patches for external use containing diclofenac sodium. US Patent 6262121.


[14]Available from Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.


Kubota, K., T. Takahashi, T. Fujiwara, S. Yamada, T. Sato, R. Kubota, R. Iwata, K. Ishiwata, T. Ido, and T. Matsuzawa. 1991. Possibility for tumor detection with fatty acid analogs. *Int. J. Rad. Appl. Instrum. B* 18:191–195.

Nadathur, S. R., J. R. Carney, S. J. Gould, and A. T. Bakalinsky. 1996. Palmitic acid is the major fatty acid responsible for significant anti-*N*-methyl-*N′*-nitro-*N*-nitroguanidine (MNNG) activity in yogurt. *Mutat. Res.* 359:179–189.

Roehl, E. L., P. J. Sakers, and H. M. Brand. 1989. Isostearic acid and its derivatives as new raw materials in cosmetics. *Parfuem. Kosmet.* 70:140–144.

Roehl, E. L., P. J. Sakers, and H. M. Brand. 1990. Isostearic acid and isosteric acid derivatives. *Cosmet Toiletries* 105:79–87.

Suhaimi, H., F. B. Ahmad, and S. E. Friberg. 1995. Curcumin in a model skin lotion formulation. *J. Pharm. Sci.* 84:376–380.

Suzuki, K., K. Nagao, J. Tokunaga, N. Katayama, and M. Uyeda. 1996. Inhibition of DNA methyltransferase by microbial inhibitors and fatty acids. *J. Enzyme Inhib.* 10:271–280.

Takahashi, K., T. Suzuki, H. Sakano, and N. Mizuno. 1995. Effect of vehicles on diclofenac permeation across excised rat skin. *Biol. Pharmaceu. Bull.* 18:571–575.

Whitehouse, M. W. 1982. Rat polyarthritis: Induction with adjuvants constituted with mycobacteria (and oils) from the environment. *J. Rheumatol.* 9:494–501.

Worth, A. P., and M. T. D. Cronin. 2001. The use of pH measurements to predict the potential of chemicals to cause acute dermal and ocular toxicity. *Toxicology* 169:119–131.


## LANETH-10 ACETATE, LANETH-9 ACETATE, LANETH-5, LANETH-16, AND LANETH-25

A safety assessment of Laneth-10 Acetate, Laneth-9 Acetate, Laneth-5, Laneth-16, and Laneth-25 was published in 1982 (Elder 1982). New studies since then are listed at the end of this review. These new studies, along with the updated

information below regarding types and concentrations of use, were considered by the CIR Expert Panel. After this review, the Panel determined to not reopen this safety assessment.

**Laneth-5** was used in 46 cosmetic products in 1976, with the highest concentration of 10% in face body, and hand skin care preparations. Currently, Laneth-5 is reportedly used in 42 cosmetic preparations, with the highest concentration of 2% in mascara.

**Laneth-16** was used in 39 cosmetic products in 1976, with the highest concentration of 5% in a variety of preparations. Currently, Laneth-16 is reportedly used in 44 cosmetic preparations, with the highest concentration of 3% in mascara and in foundations.

**Laneth-25** was used in 49 cosmetic products in 1976, with the highest concentration of 10% in blushers. Currently, Laneth-25 is reportedly used in three cosmetic preparations; however, no current concentrations of use were reported.

**Laneth-9 Acetate** was used in three cosmetic products in 1976, with the highest concentration of 10% in other skin care preparations. Currently, Laneth-9 Acetate is not reported to FDA as used in cosmetic preparations, nor were any current concentrations of use reported.

**Laneth-10 Acetate** was used in 234 cosmetic products in 1976, with the highest concentration of 25% in perfumes. Currently, Laneth-10 Acetate is reportedly used in 43 cosmetic preparations; however, no current concentrations of use were reported.

Table 14 shows the historical and current cosmetic product uses and concentrations for Laneth-5 Laneth-16, Laneth-25, Laneth-9 Acetate, and Laneth-10 Acetate.

**TABLE 14**

Historical and current cosmetic product uses and concentrations for Laneth-5, Laneth-16, Laneth-25, Laneth-9 Acetate, and Laneth-10 Acetate

| Product category | 1976 use (Elder 1982) | 2001 use (FDA 2001) | 1976 concentrations (Elder 1982) (%) | 2001 concentrations (CTFA 2001) (%) |
|---|---|---|---|---|
| | *Laneth-5* | | | |
| Baby shampoos | — | 1 | — | — |
| Mascara | — | 2 | — | 2 |
| Fragrance preparations (other) | 1 | — | >1–5 | — |
| Hair conditioners | 1 | — | >1–5 | — |
| Hair straighteners | — | 3 | — | — |
| Shampoos (noncoloring) | 1 | — | >1–5 | — |
| Hair dyes and colors | 31 | 21 | >0.1–5 | 0.8 |
| Hair tints | — | 9 | — | — |
| Makeup (other) | 1 | — | >1–5 | — |
| Bath soaps and detergents | — | 1 | — | — |
| Skin-cleansing creams, lotions, liquids, and pads | 1 | — | >1–5 | — |
| Face and neck skin care preparations | 3* | — | >0.1–10* | — |
| Body and hand skin care preparations | | 1 | | 1 |
| Moisturizers | 5 | 2 | >0.1–5 | — |
| Night skin care preparations | — | 2 | — | — |
| Skin fresheners | 1 | — | >1–5 | — |
| Skin care preparations (other) | 1 | — | >1–5 | — |
| **Total uses/ranges for Laneth-5** | **46** | **42** | **>0.1–10** | **0.8–2** |
| | *Laneth-16* | | | |
| Bath oils, tablets, and salts | 1 | — | >1–5 | — |
| Bath preparations (other) | 2 | 1 | >1–5 | — |
| Mascara | — | 5 | — | 3 |
| Sachets | 4 | — | >1–5 | — |
| Fragrance preparations (other) | 1 | — | >0.1–1 | — |
| Hair conditioners | 4 | 1 | ≤0.1–5 | 0.1 |
| Hair sprays (aerosol fixatives) | 1 | — | ≤0.1–1 | — |
| Hiar straighteners | — | — | — | 0.3 |
| Permanent waves | 3 | — | >0.1–1 | — |
| Shampoos (noncoloring) | 3 | 1 | >0.1–1 | — |

*(Continued on next page)*

**TABLE 14**
Historical and current cosmetic product uses and concentrations for Laneth-5, Laneth-16, Laneth-25, Laneth-9 Acetate, and Laneth-10 Acetate *(Continued)*

| Product category | 1976 use (Elder 1982) | 2001 use (FDA 2001) | 1976 concentrations (Elder 1982) (%) | 2001 concentrations (CTFA 2001) (%) |
|---|---|---|---|---|
| Hair tonics, dressings, etc. | 1 | 4 | >0.1–1 | — |
| Wave sets | 1 | — | >0.1–1 | — |
| Hair bleaches | 1 | — | >1–5 | — |
| Blushers (all types) | 2 | 1 | >0.1–5 | — |
| Foundations | — | — | — | 3 |
| Lipsticks | — | 1 | — | — |
| Makeup bases | — | 18 | — | — |
| Makeup (other) | — | 1 | — | — |
| Underarm deodorants | 2 | — | >0.1–5 | 0.3 |
| Personal cleanliness products (other) | 2 | — | >0.1–5 | — |
| Aftershave lotions | 1 | — | >0.1–1 | — |
| Shaving preparation products (other) | — | 1 | — | — |
| Skin-cleansing creams, lotions, liquids, and pads | — | 1 | — | — |
| Face and neck skin care preparations | 2* | — | >0.1–1* | — |
| Body and hand skin care preparations | | 1 | | — |
| Moisturizers | 7 | 8 | >0.1–5 | 1 |
| Paste masks/mud packs | 2 | — | >0.1–1 | — |
| **Total uses/ranges for Laneth-16** | **39** | **44** | **≤0.1–5** | **0.1–3** |
| | *Laneth-25* | | | |
| Bubble baths | 1 | — | >1–5 | — |
| Sachets | 5 | — | >0.1–1 | — |
| Hair conditioners | 1 | — | >1–5 | — |
| Wave sets | 1 | — | >0.1–1 | — |
| Blushers (all types) | 1 | — | >5–10 | — |
| Skin care preparations (other) | — | 2 | — | — |
| Suntan gels, creams, and liquids | — | 1 | — | — |
| **Total uses/ranges for Laneth-25** | **9** | **3** | **>0.1–10** | **—** |
| | *Laneth-9 Acetate* | | | |
| Rinses (noncoloring) | 1 | — | >1–5 | — |
| Aftershave lotions | 1 | — | >1–5 | — |
| Skin care preparations (other) | 1 | — | >5–10 | — |
| **Total uses/ranges for Laneth-9 Acetate** | **3** | **0** | **>1–10** | **—** |
| | *Laneth-10 Acetate* | | | |
| Baby lotions, oils, powders, and creams | 2 | — | >0.1–1 | — |
| Baby products (other) | 1 | 2 | >0.1–1 | — |
| Bath oils, tablets, and salts | 6 | — | >0.1–1 | — |
| Bubble baths | 3 | — | >0.1–5 | — |
| Bath preparations (other) | 1 | — | >1–5 | — |
| Eye shadow | 5 | — | >0.1–1 | — |
| Colognes and toilet waters | 5 | — | >1–5 | — |
| Perfumes | 2 | — | >5–25 | — |
| Sachets | 2 | — | >1–5 | — |
| Fragrance preparations (other) | 6 | — | >0.1–5 | — |
| Hair conditioners | 4 | — | >0.1–5 | — |
| Hair sprays (aerosol fixatives) | 26 | 5 | ≤1 | — |

*(Continued on next page)*

**TABLE 14**
Historical and current cosmetic product uses and concentrations for Laneth-5, Laneth-16, Laneth-25, Laneth-9 Acetate, and Laneth-10 Acetate *(Continued)*

| Product category | 1976 use (Elder 1982) | 2001 use (FDA 2001) | 1976 concentrations (Elder 1982) (%) | 2001 concentrations (CTFA 2001) (%) |
|---|---|---|---|---|
| Rinses (noncoloring) | 1 | — | ≤0.1 | — |
| Shampoos (noncoloring) | 59 | 2 | >0.1–5 | — |
| Permanent waves | 2 | — | >0.1–1 | — |
| Hair tonics, dressings, etc. | 3 | 1 | >0.1–5 | — |
| Wave sets | 2 | — | ≤0.1 | — |
| Hair preparations (other) | 1 | — | ≤0.1 | — |
| Blushers (all types) | 9 | — | >0.1–10 | — |
| Face powders | 1 | — | >0.1–1 | — |
| Foundations | 4 | 3 | >0.1–5 | — |
| Makeup bases | 9 | 1 | >0.1–5 | — |
| Makeup (other) | 4 | — | >0.1–5 | — |
| Nail creams and lotions | 1 | — | >1–5 | — |
| Nail polish and enamel removers | 12 | 1 | >0.1–5 | — |
| Bath soaps and detergents | — | 7 | — | — |
| Personal cleanliness products (other) | 7 | 4 | >0.1–5 | — |
| Aftershave lotions | 4 | 3 | >0.1–5 | — |
| Shaving cream | 2 | — | >1–5 | — |
| Shaving preparations (other) | 1 | — | >1–5 | — |
| Skin-cleansing creams, lotions, liquids, and pads | 6 | 3 | >0.1–10 | — |
| Face and neck skin care preparations | 25* | — | ≤0.1–5* | — |
| Body and hand skin care preparations | | 9 | | — |
| Moisturizers | 6 | — | >0.1–5 | — |
| Night skin care preparations | 1 | — | >1–5 | — |
| Paste masks/mud packs | 3 | — | >0.1–1 | — |
| Skin fresheners | 3 | 1 | >0.1–1 | — |
| Skin care preparations (other) | 3 | 2 | >1–5 | — |
| Suntan gels, creams, and liquids | 1 | — | >1–5 | — |
| **Total uses/ranges for Laneth-10 Acetate** | **234** | **43** | **≤0.1–25** | **—** |

*This category was combined when the original safety assessment was performed and is now two separate categories.

## REFERENCES

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2001. Concentration of Use—Laneth-10 Acetate, Laneth-9 Acetate, Laneth-5, Laneth-16, and Laneth-25. Unpublished data submitted by CTFA on December 11, 2001.[15]

Elder, R. L. 1982. Final report on the Safety Assessment of Laneth-10 Acetate Group. *J. Am. Col. Toxicol.* 1:1–23.

Food and Drug Administration (FDA). 2001. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

Wenninger, J. A., R. C. Canterbery, and G. N. McEwen, Jr., eds. 2000. *International cosmetic ingredient dictionary and handbook*, 8th ed., vol. 1., 132. Washington, DC: CTFA.

[15]Available from the Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

## LAURETH-4 AND LAURETH-23

A safety assessment of Laureth-4 and Laureth-23 was published in 1983 with the conclusion "safe as cosmetic ingredients in the present practices of use and concentration" (Elder 1983). Studies available since that safety assessment was completed (listed at the end of this section), along with the updated information regarding uses and use concentrations, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

The Panel acknowledged the medical uses of other Laureths, i.e., Laureth-7 and -9, as sclerosing agents for the treatment of varicose veins, but noted that these uses are not cosmetic uses and the safety of such uses is not addressed.

**Laureth-4** was used in 202 products in 1981, with the largest single use in eye shadow in the concentration range of >0.1%

to 5%. In 2002, Laureth-4 was reportedly used in 152 preparations, with the largest single use in hair dyes and colors in the concentration range of >10% to 25% (CTFA 2002). Data submitted in 2002 indicate the use of Laureth-4 in two additional product categories, baby products and suntan products. Complete information is shown in Table 15.

**Laureth-23** was used in 218 products in 1981, with the largest single use in permanent waves in the concentration range of ≤0.1% to 5%. In 2002, Laureth-23 was reportedly used in 289 preparations, with the largest single use in hair dyes and colors at a concentration of 3%, reduced to 1.5% after dilution (CTFA 2002). Data submitted in 2002 indicate the use of Laureth-23 in two additional product categories, suntan products and indoor tanning preparations. Complete information is shown in Table 15.

**TABLE 15**
Historical and current cosmetic product uses and concentrations for Laureth-4 and Laureth-23

| Product category | 1981 use (Elder 1983) | 2002 use (FDA 2002) | 1981 use concentrations (Elder 1983) (%) | 2002 use concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| | | *Laureth-4* | | |
| Baby products (other) | — | 1 | — | 2 |
| Bath oils, tablets, and salts | 5 | 3 | >0.1–10 | — |
| Bubble baths | 1 | — | >1–5 | 3 |
| Bath preparations (other) | 2 | 1 | >0.1–1 | 3 |
| Eyeliner | 1 | 9 | >1–5 | 2 |
| Eye shadow | 85 | 12 | >0.1–5 | — |
| Eye makeup preparations | — | 3 | — | 2 |
| Powders | — | — | — | 0.004 |
| Fragrance preparations (other) | — | 2 | — | — |
| Hair conditioners | 2 | 7 | >0.1–1 | 0.07–1 |
| Hair sprays (aerosol fixatives) | 2 | — | ≤0.1 | — |
| Permanent waves | 10 | 2 | ≤0.1–1 | — |
| Rinses (noncoloring) | 6 | 5 | ≤0.1–5 | — |
| Shampoos (noncoloring) | 4 | 8 | >0.1–10 | 3 |
| Hair tonics, dressings, etc. | 2 | 1 | >1–5 | — |
| Wave sets | 2 | — | ≤0.1–1 | — |
| Hair preparations (other noncoloring) | — | 4 | — | — |
| Hair dyes and colors | 17 | 27 | >10–25 | 0.02–5 (0.01–2.5 after dilution) |
| Hair bleaches | 3 | 16 | >0.1–25 | — |
| Hair-coloring preparations (other) | 1 | — | >1–5 | — |
| Blushers (all types) | 4 | 19 | >0.1–1 | — |
| Face powders | — | 2 | — | — |
| Foundations | 3 | 1 | >0.1–1 | 0.5 |
| Lipsticks | — | — | — | — |
| Makeup bases | 10 | — | >0.1–5 | — |
| Rouges | — | 1 | — | — |
| Makeup (other) | 1 | — | ≤0.1 | 0.5 |
| Nail creams and lotions | 1 | — | >1–5 | — |
| Nail polish and enamel | — | — | — | — |
| Nail polish and enamel removers | — | — | — | — |
| Nail care preparations (other) | 1 | — | >1–5 | 5 |
| Bath soaps and detergents | — | 2 | — | 0.4 |
| Underarm deodorants | 15 | 6 | >0.1–10 | — |
| Personal cleanliness products (other) | 6 | 7 | >0.1–5 | — |
| Aftershave lotion | 1 | 2 | >1–5 | — |
| Beard softeners | 1 | — | >1–5 | — |
| Shaving cream | — | — | — | 1–5 |
| Shaving preparation products (other) | 1 | 1 | >1–5 | — |

*(Continued on next page)*

**TABLE 15**
Historical and current cosmetic product uses and concentrations for Laureth-4 and Laureth-23 *(Continued)*

| Product category | 1981 use (Elder 1983) | 2002 use (FDA 2002) | 1981 use concentrations (Elder 1983) (%) | 2002 use concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| Skin-cleansing creams, lotions, liquids, and pads | 6 | 2 | >1–10 | 3 |
| Face and neck skin care preparations | 2* | — | >0.1–10* | — |
| Body and hand skin care preparations | | — | | 1–4 |
| Moisturizers | 1 | 2 | >0.1–1 | 8 |
| Skin fresheners | 2 | 1 | >0.1–1 | — |
| Skin care preparations (other) | 3 | 4 | >0.1–5 | 0.2–6 |
| Suntan gels, creams, and liquids | — | 1 | — | — |
| **Total uses/ranges for Laureth-4** | **202** | **152** | **≤0.1–25** | **0.004–6** |
| | | *Laureth-23* | | |
| Baby lotions, oils, powders, and creams | 1 | — | >0.1–1 | — |
| Bath oils, tablets, and salts | 1 | 1 | >0.1–1 | — |
| Bath preparations | 2 | 2 | >0.1–1 | 3 |
| Eye makeup remover | 1 | — | >1–5 | — |
| Eye makeup (other) | 1 | — | >1–5 | — |
| Colognes and toilet waters | 6 | — | >1–5 | — |
| Perfumes | 3 | — | >1–5 | — |
| Powders | — | — | — | 0.001 |
| Hair conditioners | 6 | 7 | ≤0.1–5 | 0.04–0.1 |
| Hair sprays (aerosol fixatives) | 2 | — | ≤0.1 | — |
| Hair straighteners | 1 | — | >1–5 | — |
| Permanent waves | 94 | 41 | ≤0.1–5 | — |
| Rinses (noncoloring) | 4 | 6 | ≤0.1–1 | — |
| Shampoos (noncoloring) | 11 | 2 | ≤0.1–5 | 2 |
| Hair tonics, dressings, etc. | 5 | 17 | ≤0.1–1 | 0.3 |
| Wave sets | 12 | 3 | ≤0.1–1 | — |
| Hair preparations (other noncoloring) | 12 | 3 | ≤0.1–5 | — |
| Hair dyes and colors | 1 | 76 | >0.1–1 | 3 (1.5% after dilution) |
| Hair shampoos (coloring) | — | 1 | — | — |
| Hair bleaches | 3 | 14 | ≤0.1–5 | — |
| Hair-coloring preparations (other) | 2 | 2 | >0.1–5 | 0.02 |
| Makeup bases | 1 | — | >0.1–1 | — |
| Cuticle softeners | 3 | — | ≤0.1–1 | — |
| Nail polish and enamel removers | — | — | — | — |
| Nail care preparations (other) | 2 | — | >0.1–1 | — |
| Bath soaps and detergents | 3 | 2 | >1–5 | 6 |
| Underarm deodorants | 10 | 7 | >0.1–5 | — |
| Personal cleanliness products (other) | 6 | 7 | ≤0.1–5 | 3 |
| Aftershave lotions | 1 | 2 | >1–5 | 2 |
| Shaving cream | 3 | 26 | >1–5 | 2 |
| Shaving preparation products (other) | 1 | 1 | >1–5 | — |
| Skin-cleansing creams, lotions, liquids, and pads | 3 | 4 | >0.1–5 | 0.3–2 |
| Face and neck skin care preparations | —* | 4 | —* | 0.2 |
| Body and hand skin care preparations | | 20 | | 1 |
| Moisturizers | 5 | 22 | >0.1–5 | 0.2–3 |
| Night skin care preparations | 4 | 1 | >0.1–5 | — |
| Skin fresheners | 1 | — | >0.1–1 | — |
| Skin care preparations (other) | 7 | 17 | ≤0.1–5 | 1 |
| Suntan gels, creams, and liquids | — | — | — | 0.4 |
| Indoor tanning preparations | — | 1 | — | — |
| **Total uses/ranges for Laureth-23** | **218** | **289** | **≤0.1–5** | **0.001–6** |

*This category was combined when the original safety assessment was performed and is now two separate categories.

## REFERENCES


Aungst, B. J., and N. J. Rogers. 1988. Site dependence of absorption-promoting actions of laureth-9, Na salicylate, Na2EDTA, and aprotinin on rectal, nasal, and bucca insulin delivery. *Pharm. Res.* 5:305–308.

Bakale, G., and R. D. McCreary. 1992. Response to the ke test to NCI-screened chemicals: II. Genotoxic carcinogens and non-genotoxic non-carcinogens. *Carcinogenesis* 13:1437–1445.

Beissert, S., D. Presser, A. Rutter, D. Metze, T. A. Luger, and T. Schwarz. 1999. Embolia cutis medicamentosa (Nicolau syndrome) after intra-articular injection. *Hautarzt* 50:214–216.

Benea, G., R. Galeotti, S. Tartari, and P. Mannella. 1988. Percutaneous therapy of primary varicocele. 6 years' experience. *Radiol. Med.* 76:458–465.

Banque de Données Automatisée sur les Médicaments (BIAM). 2002. Donnez-nous votre avis. Lauromacrogol 400. http://www.biam2.org/www/Sub1333.html

Bergh, M., L. P. Shao, G. Hagelthorn, et al. 1998. Contact allergens from surfactants. Atmospheric oxidation of polyoxyethylene alcohols, formation of ethoxylated aldehydes, and their allergenic activity. *J. Pharm. Sci.* 87:276–282.

Brand, N., G. Mailhot, and M. Bolte. 2000. The interaction "light, Fe(III)" as a tool for pollutant removal in aqueous solution: Degradation of alcohol ethoxylates. *Chemosphere* 40:395–401.

Carlin, M. C., and J. L. Ratz. 1987. Treatment of telangiectasia: Comparison of sclerosing agents. *J. Dermatol. Surg. Oncol.* 13:1181–1184.

Cook, L., and B. Ternai. 1988. Deleterious effect of Brij 35 on alkyl 2-pyrones and other hydrophobic inhibitors of human sputum and leucocyte elastase. *Biochem. Int.* 17:637–646.

Cosmetic Physicians Society of Australasia. 2002. Sclerotherapy for veins. The technique of sclerotherapy for treating veins. http://www.cosmeticphysicians.org.au/Sclerotherapy.htm

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2002. Use concentration data on laureth-4 and laureth-23 from industry survey. Unpublished data submitted by CTFA, June 26, 2002. 2 pages.[16]

Donovan, M. D., G. L. Flynn, and G. L. Amidon. 1990. The molecular weight dependence of nasal absorption: The effect of absorption enhancers. *Pharm. Res.* 7:808–815.

Elder R. L., ed. 1983. Final report on the safety assessment of laureths-4 and -23. *J. Am. Col. Toxicol.* 2:1–15.

Feied, C. F., J. J. Jackson, T. S. Bren, et al. 1994. Allergic reactions to polidocanol for vein sclerosis. Two case reports. *J. Dermatol. Surg. Oncol.* 20:466–468.

Food and Drug Administration (FDA). 1992. Import alert IA6649. Automatic detention of polidocanol, also known as aetoxisclerol 0.5% and aethoxysklerol injection 1% and 3%. http://www.fda.gov/ora/fiars/ora_import_ia6649.html

FDA. 2002. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

Foureman, P., J. M. Mason, R. Valencia, and S. Zimmering. 1994. Chemical mutagenesis testing in Drosophila: X. Results of 70 coded chemicals tested for the National Toxicology Program. *Environ. Mol. Mutagen.* 23:208–227.

Frosch, P. J., and A. Schulze-Dirks. 1989. Contact allergy caused by polidocanol (thesit). *Hautarzt* 40:146–149.

Frullini, A., and A. Cavezzi. 2002. Sclerosing foam in the treatment of varicose veins and telangiectases: History and analysis of safety and complications. *Dermatol. Surg.* 28:11–15.

Gallo, R., M. Basso, S. Voltolini, and M. Guarrera. 2001. Allergic contact dermatitis from laureth-9 and polyquaternium-7 in a skin-care product. *Contact Dermatitis* 45:356–357.

Georgiev, M. 1993. Postsclerotherapy hyperpigmentations. Chromated glycerin as a screen for patients at risk (a retrospective study). *J. Dermatol. Surg. Oncol.* 19:649–652.

Geukens, J., E. Rabe, and T. Bieber. 1999. Embolia cutis medicamentosa of the foot after sclerotherapy. *Eur. J. Dermatol.* 9:132–133.

Goldman, M. P. 2002. Treatment of varicose and telangiectatic leg veins: Double-blind prospective comparative trial between aethoxyskerol and sotradecol. *Dermatol. Surg.* 28:52–55.

Goossens, A., M. H. Beck, E. Haneke, et al. 1999. Adverse cutaneous reactions to cosmetic allergens. *Contact Dermatitis* 40:112–113.

Guex, J. J. 1993. Indications for the sclerosing agent polidocanol (aetoxisclerol dexo, aethoxisklerol kreussler). *J. Dermatol. Surg. Oncol.* 19:959–961.

Hamann, K., P. S. Skov, and C. Avnstorp. 1981. Aethoxysklerol. A histamine liberator? *Ugeskr. Laeger.* 143:822–823.

Hayakawa, E., A. Yamamoto, Y. Shoji, and V. H. Lee. 1989. Effect of sodium glycocholate and polyoxyethylene-9-lauryl ether on the hydrolysis of varying concentrations of insulin in the nasal homogenates of the albino rabbit. *Life Sci.* 45:167–174.

Ikeda, T., K. Ninomiya, K. Sugi, et al. 1993. An experimental study on transcoronary chemical ablation: Comparison of ventricular tachyarrhythmias induced by chemical ablation according to different chemical materials. *Kokyu To Junkan* 41:459–462.

Imperiali, G., V. Terruzzi, D. Spotti, and G. Minoli. 1986. Heart failure as a side effect of polidocanol given for oesophageal variceal sclerosis. *Endoscopy* 18:207.

Institut Fresnius. 2002. Polidocanol. http://enius.de/schadstoffe/polidocanol.html

Jaganathan, L., and R. Boopathy. 1998. Interaction of Triton X-100 with acyl pocket of butyrylcholinesterase: Effect on esterase activity and inhibitor sensitivity of the enzyme. *Indian J. Biochem. Biophys.* 35:142–147.

Jain, R., S. Bandhu, S. Sawhney, and R. Mittal. 2002. Sonographically guided percutaneous sclerosis using 1% polidocanol in the treatment of vascular malformations. *J. Clin. Ultrasound* 30:416–423.

James, M. P., and H. Grech. 2002. Subclinical, primary antiphospholipid syndrome unmasked by sclerotherapy. *Br. J. Dermatol.* 146:527–528.

Kerr, D. J., T. E. Wheldon, J. G. Russell, et al. 1987. The effect of the non-ionic surfactant Brij 30 on the cytotoxicity of adriamycin in monolayer, spheroid and clonogenic culture systems. *Eur. J. Cancer Clin. Oncol.* 23:1315–1322.

Kimura, M., and A. Kawada. 2000. Follicular contact dermatitis due to polyoxyethylene laurylether. *J. Am. Acad. Dermatol.* 42:879–880.

Kojima, H., A. Hanamura, S. Miyamoto, A. Sato, H. Konishi, and I. Yoshimura. 1995. Evaluation of seven alternative assays on the main ingredients in cosmetics as predictors of Draize eye irritation scores. *Toxicology In Vitro* 9:333–340.

Li, G. L., R. van der Geest, L. Chanet, et al. 2002. In vitro iontophoresis across human stratum corneum. Structure-transport relationship of penetration enhancement. *J. Control Release* 84:49–57.

Loveday, K. S., B. E. Anderson, M. A. Resnick, and E. Zeiger. 1990. Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro. 5. Results with 46 chemicals. *Environ. Mol. Mutagen.* 16:272–303.

Macias Rodriguez, M. A., M. J. Soria de la Cruz, M. Iglesias Arrabal, and L. Martin Herrera. 1992. Esophageal carcinoma after the endoscopic sclerotherapy of varices. *Rev. Esp. Enferm. Dig.* 82:43–46.

Matthews, E. J., J. W. Spalding, and R. W. Tennant. 1993. Transformation of BALB/c-3T3 cells: V. Transformation responses of 168 chemicals compared with mutagenicity in Salmonella and carcinogenicity rodent bioassays. *Environ. Health Perspect.* 101(Suppl. 2):347–482.

Meissner, K., and B. Jirikowski. 1993. Stomach wall slough and ulcer perforation following endoscopic injection hemostasis with polidocanol. *Endoscopy* 25:185–187.

Merenciano Cortina, F. J., W. Rafie Mazketli, M. Amat Cecilia, and P. Romero Perez. 2001. Sclerotherapy of hydrocele and cord cyst with polidocanol. Efficiency study. *Acta Urol. Esp.* 25:704–709.

Metz, K. A., J. Erhard, E. Gross, and K. Donhuijsen. 1986. Effect of various sclerosing drugs on the rat esophagus. *Z. Gastroenterol.* 24:605–611.


[16]Available from the Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

Ministry of Health, Labor and Welfare (MHLW). June 2001. Unofficial translation of MHW Ordinance No. 331, Attached Table 2 [Restri cted list]. Ministry of Health, Labor and Welfare, Pharmaceutical and Medical Safety Bureau, Inspection and Guidance Division, 2-2, 1-chome, Kasumigaseki, Chiyoda-ku, Tokyo 100-8045, Japan.

Myhr, B. C., and W. J. Caspary. 1991. Chemical mutagenesis at the thymidine kinase locus in L5178Y mouse lymphoma cells: Results for 31 coded compounds in the National Toxicology Program. *Environ. Mol. Mutagen.* 18:51–83.

National Toxicology Program (NTP). 2002a. Ethoxylated dodecyl alcohol (9002-92-0). http://ntp-server.niehs.nih.gov

NTP. 2002b. Carcinogenicity study on ethoxylated dodecyl alcohol. Personal communication with NTP's Central Data Management, December 4.

Nishida, R., R. Inoue, Y. Takimoto, and T. Kita. 1999. A sclerosant with astringent properties developed in China for oesophageal varices: Comparison with ethanolamine oleate and polidocanol. *J. Gastroenterol. Hepatol.* 14:481–488.

Noppeney, T., A. Scheidt, and I. Kurth. 2001. Indications and technique for sclerotherapy of varicose veins. *Zentralbl. Chir.* 126:546–550.

Norris, M. J., M. C. Carlin, and J. L. Ratz. 1989. Treatment of essential telangiectasia: Effects of increasing concentrations of polidocanol. *J. Am. Acad. Dermatol.* 20:643–649.

Oexle, B., J. Weirich, K. Haverkampf, and H. Antoni. 1988. Effects of polidocanol as a constituent of a venous sclerosing agent on cardiac electrical activity. Studies on the isolated perfused heart and pa pillary muscle of the guinea pig and on the isolated sinus node of the rabbit. *Arzneimuttekfirschung* 38:1578–1582.

Olesch B. 1952. Neuere Erkenntisse zur Pharmakokinetik von polidocanol (aethoxysklerol). *Arzneimittelforsche* 2:109.

Olivares, J. L., G. Rodriguez, J. A. Fernandez, and M. A. de Gregorio. 2001. Jugular venous malformation in an 8-year-old boy: Treatment with endovascular sclerotherapy. *Eur. J. Pediatr.* 160:392–394.

Orikasa, K. 1989. Studies on the damage of the cultured endothelial cells and K-562 cells by sclerosants (ethanolamine oleate, Aethoxysklerol and absolute ethanol) used in the treatment of esophageal varices. *Nippon Shokakibyo Gakkai Zasshi* 86:2365–2372.

Ormeci, N., I. Soykan, M. Palabiyikoglu, et al. 2002. A new therapeutic approach for treatment of hydatid cysts of the spleen. *Dig. Dis. Sci.* 47:2037–2044.

Pepe, R. C., J. A. Wenninger, and G. N. Jr. McEwen, eds. 2002. *International cosmetic ingredient dictionary and handbook*. 9th ed., 878–879, 882. Washington, DC: CTFA.

Potzi, R., P. Ferenci, and A. Gangl. 1991. Endoscopic sclerotherapy of esophageal varices during pregnancy—case report. *Z. Gastroenterol.* 29:246–247.

Procter & Gamble Company. 1984. Initial submission: Letter from Procter & Gamble Company to USEPA submitting information on alkylethoxylates enclosed study with attachments. NTIS Report No. OTS0543795.

Pundzius, J., and M. Jievaltas. 1998. Experimental studies of injection agents for peptic ulcer bleeding endoscopic control. *Int. Surg.* 83:280–282.

Registry of Toxic Effects of Chemical Substances (RTECS). 2002. Laureth-4 entry. RTECS database. Columbus, OH: Scientific and Technical Information Network (STN) International.

Shelby, M. D., G. L. Erexson, G. J. Hook, and R. R. Tice. 1993. Evaluation of a three-exposure mouse bone marrow micronucleus protocol: Results with 49 chemicals. *Environ. Mol. Mutagen.* 21:160–179.

Shirai, H. 1999. Experimental study of intraarterial injection of polidocanol as an embolic agent. *Nippon Igaku Hoshasen Gakkai Zasshi* 59:853–859.

Stricker, B. H., J. A. van Oijen, C. Kroon, and A. H. Ovink. 1990. Anaphylaxis following use of polidocanol. *Ned. Tijdschr. Geneeskd.* 134:240–242.

Suzuki, S., H. Atai, and F. Y. Hatakeyama. 1989. Mutagenicity test on Polidocanol. *Jitchuken Zenrinsho Kenkyuho* 15:1–9.

Suzuki, M., M. Machida, K. Adachi, et al. 2000. Histopathological study of the effects of a single intratracheal instillation of surface active agents on lung in rats. *J. Toxicol. Sci.* 25:49–55.

Svensson, A. 1988. Allergic contact dermatitis to laureth-4. *Contact Dermatitis* 18:113–114.

Tang, J., N. Esmon, I. Ferlan, and A. Fesmire. 1981. The enhancement of streptokinase activation of plasminogen by nonionic detergents and by serum albumin. *Thromb. Res.* 24:359–365.

Tennant, R. W., B. H. Margolin, M. D. Shelby, et al. 1987. Prediction of chemical carcinogenicity in rodents from in-vitro genetic toxicity assays. *Science* 236:933–941.

Trenkwalder, P., and H. Lydtin. 1994. Ischaemic neurological deficit after sclerotherapy. *Lancet* 343:794.

Utter, W., J. Geier, and T. Fuchs. 2000. Contact allergy to polidocanol. *J. Allergy Clin. Immunol.* 106:1203–1204.

Van der Plas, J. P., J. C. Lambers, J. W. Van Wersch, and P. J. Koehler. 1994. Reversible ischaemic neurological deficit after sclerotherapy of varicose veins. *Lancet* 343:428.

Vian, L., J. Vincent, J. Maurin, I. Fabre, J. Giroux, and J.P. Cano. 1995. Comparison of three in vitro cytotoxicity assays for estimating surfactant ocular irritation. *Toxicol. In Vitro* 9:185–190.

Weiss, R. A., and M. A. Weiss. 1990. Incidence of side effects in the treatment of telangiectasias by compression sclerotherapy: Hypertonic saline vs. polidocanol. *J. Dermatol. Surg. Oncol.* 16:800–804.

Zeiger, E., B. Anderson, S. Haworth, T. Lawlor, K. Mortelmans, and W. Speck. 1987. *Salmonella* mutagenicity tests: III. Results from the testing of 255 chemicals. *Environ. Mol. Mutagen.* 9(Suppl. 9):1–110.

Zhou, M., and M. D. Donovan. 1996. Recovery of the nasal mucosa following laureth 9 induced damage. *Int. J. Pharm.* 130:93–102.

Zipper, S. G. 2000. Peroneal nerve damage after varicose vein sclerotherapy with ethoxysclerol. Single case description with malpractice relevant questions. *Versicherungsmedizin* 52:185–187.

## MYRISTYL MYRISTATE AND ISOPROPYL MYRISTATE

A safety assessment of Myristyl Myristate and Isopropyl Myristate was published in 1982 (Elder 1982). New studies since then are listed at the end of this review. These new studies along with the updated information below regarding types and concentrations of use were considered by the CIR Expert Panel. After this review, the Panel determined to not reopen the safety assessment.

**Myristyl Myristate** was used in 160 cosmetic preparations at concentrations less than 0.1% to 25% in 1976. In 2002, Myristyl Myristate was used in 244 cosmetic preparations with concentrations of 0.01% to 20% (CTFA 2002; FDA 2002).

There were 26 new product categories in which there was use of Myristyl Myristate in 2002. In addition, use concentrations increased in the perfume and other fragrances categories.

**Isopropyl Myristate** was reported in 2198 cosmetic formulations in 1976. In 2002, it was used in 881 cosmetic preparations. Five new categories were reported in 2002.

Isopropyl Myristate had concentrations reported in 1976 that ranged from less that 0.1% to greater than 50%. Concentration of use increased from 1976 to 2002 in the following categories: eyeliner from 0.1–5% in 1976 to 31% in 2001, eye makeup remover from 1–50% to 78%, other manicuring preparations from 1–5% to 38%, and deodorant from 0.1–25% to 0.001–52%.

Table 16 presents the historical and current use of Myristyl and Isopropy Myristate.

**TABLE 16**
Historical and current cosmetic product uses and concentrations for Myristyl Myristate and Isopropyl Myristate

| Product category | 1976 uses (Elder 1982) | 2002 uses (FDA 2002) | 1976 concentrations (Elder 1982) (%) | 2002 concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| | *Myristyl Myristate* | | | |
| Baby lotions, oils, powders, and creams | 2 | 3 | >0.1–5 | 2–3 |
| Baby products (other) | — | 1 | — | — |
| Bath oils, tablets, and salts | — | 5 | — | — |
| Eyebrow pencil | — | 5 | — | — |
| Bubble bath | — | — | — | 2 |
| Bath preparations (other) | — | — | — | 2 |
| Eyeliner | — | 1 | — | 5 |
| Eye shadow | 26 | 4 | >0.1–10 | 0.01–7 |
| Eye lotion | — | 1 | — | 0.5–1 |
| Eye makeup remover | 1 | 2 | >5–10 | — |
| Mascara | — | — | — | 1 |
| Eye makeup (other) | 2 | 22 | >5–10 | 2–6 |
| Colognes and toilet waters | — | 1 | — | — |
| Perfumes | 30 | 16 | >5–10 | 20 |
| Powders | — | 4 | — | — |
| Sachets | — | — | — | 2 |
| Fragrance preparations (other) | 1 | 6 | >1–5 | 17 |
| Hair conditioners | 1 | 7 | >0.1–1 | 3–4 |
| Rinses (noncoloring) | — | 1 | — | — |
| Shampoos (noncoloring) | — | 3 | — | 0.7 |
| Hair tonics, dressings, etc. | — | 2 | — | 2 |
| Blushers (all types) | 1 | 1 | >1–5 | 0.01–5 |
| Face powders | — | — | — | 0.5 |
| Foundations | 4 | 5 | >1–10 | 2–6 |
| Lipsticks | 6 | 3 | >0.1–5 | 8 |
| Makeup bases | 1 | 8 | >10–25 | 2 |
| Rouges | 9 | — | >5–10 | — |
| Makeup (other) | — | 12 | — | 2–4 |
| Cuticle softeners | 1 | 3 | >1–5 | 1.4 |
| Nail creams and lotions | — | — | — | 4 |
| Nail care preparations (other) | — | 2 | — | 2 |
| Underarm deodorants | — | — | — | 1–5 |
| Aftershave lotions | 1 | 9 | >1–5 | 3 |
| Shaving cream | — | 6 | — | — |
| Shaving preparation products (other) | 1 | — | >1–5 | — |
| Skin-cleansing creams, lotions, liquids, and pads | 9 | 2 | ≤1–10 | 2 |
| Face and neck skin care preparations | 11* | 7 | >1–5* | 2–7 |
| Body and hand skin care preparations | | 34 | | 1–8 |
| Foot powders and sprays | — | 4 | — | — |
| Moisturizers | 42 | 53 | >0.1–10 | 0.6–9 |
| Night skin care preparations | 7 | 2 | >0.1–10 | 3–4 |
| Paste masks/mud packs | 2 | 3 | >0.1–1 | 4 |
| Skin fresheners | — | 1 | — | — |
| Skin care preparations (other) | — | 12 | — | 3–7 |
| Suntan gels, creams, and liquids | — | — | — | 6 |

*(Continued on next page)*

**TABLE 16**
Historical and current cosmetic product uses and concentrations for Myristyl Myristate and Isopropyl Myristate *(Continued)*

| Product category | 1976 uses (Elder 1982) | 2002 uses (FDA 2002) | 1976 concentrations (Elder 1982) (%) | 2002 concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| Indoor tanning preparations | — | 2 | — | — |
| Suntan preparations (other) | — | 1 | — | — |
| **Total uses/ranges for Myristyl Myristate** | **160** | **244** | **>0.1–25** | **0.01–20** |
| | *Isopropyl Myristate* | | | |
| Baby lotions, oils, powders, and creams | 3 | 3 | >1–10 | 3 |
| Bath oils, tablets, and salts | 137 | 19 | ≤0.1–>50 | 20 |
| Bubble baths | 3 | — | >1–50 | 1 |
| Bath capsules | 3 | — | >10–25 | 22 |
| Bath preparations (other) | 24 | 3 | ≤0.1–>50 | 20 |
| Eyebrow pencil | 15 | 12 | >1–5 | 6 |
| Eyeliner | 4 | 53 | >0.1–5 | 31 |
| Eye shadow | 246 | 39 | ≤0.1–50 | 4–18 |
| Eye lotion | 1 | 1 | >25–50 | 2 |
| Eye makeup remover | 4 | 3 | >1–50 | 78 |
| Mascara | 23 | 1 | >0.1–10 | 0.4 |
| Eye makeup (other) | 24 | 6 | ≤0.1–50 | 0.007–7 |
| Colognes and toilet waters | 29 | 11 | ≤0.1–25 | 0.06–21 |
| Perfumes | 57 | 4 | ≤0.1–>50 | 12–39 |
| Powders | 100 | 3 | ≤0.1–5 | 5 |
| Sachets | 26 | 10 | >0.1–5 | — |
| Fragrance preparations (other) | 38 | 26 | >0.1–>50 | 21–30 |
| Hair conditioners | 12 | 28 | ≤0.1–5 | 0.003–2 |
| Hair sprays (aerosol fixatives) | 5 | 1 | >0.1–5 | 0.002 |
| Hair straighteners | 6 | 5 | >0.1–5 | — |
| Permanent waves | 1 | 1 | >1–5 | — |
| Rinses (noncoloring) | 5 | — | ≤0.1–5 | — |
| Shampoos (noncoloring) | 1 | 4 | ≤0.1 | 0.0007 |
| Hair tonics, dressings, etc. | 10 | 26 | >0.1–50 | 0.002–7 |
| Hair preparations (other noncoloring) | 3 | 2 | ≤0.1–10 | — |
| Hair shampoos (coloring) | 1 | 1 | >0.1–1 | — |
| Hair color sprays (aerosol) | — | 1 | — | — |
| Hair bleaches | 1 | — | >1–5 | — |
| Blushers (all types) | 82 | 38 | >0.1–50 | 0.00008–18 |
| Face powders | 85 | 13 | ≤0.1–25 | 5 |
| Foundations | 159 | 35 | >0.1–>50 | 6–14 |
| Lipstick | 225 | 43 | >0.1–25 | 0.05–29 |
| Makeup bases | 220 | 7 | >0.1–50 | 2–12 |
| Rouges | 19 | 1 | >0.1–50 | 4 |
| Makeup fixatives | 4 | — | >5–25 | — |
| Makeup (other) | 31 | 17 | >0.1–25 | 6 |
| Nail basecoats and undercoats | — | 1 | — | — |
| Cuticle softeners | 2 | 3 | ≤0.1–1 | — |
| Nail creams and lotions | 2 | 1 | >5–25 | — |
| Nail polish and enamel removers | — | 1 | | 3 |
| Manicuring preparations (other) | 1 | 2 | >1–5 | 38 |
| Bath soaps and detergents | 1 | 1 | >1–5 | 0.003–3 |

*(Continued on next page)*

**TABLE 16**
Historical and current cosmetic product uses and concentrations for Myristyl Myristate and Isopropyl Myristate *(Continued)*

| Product category | 1976 uses (Elder 1982) | 2002 uses (FDA 2002) | 1976 concentrations (Elder 1982) (%) | 2002 concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| Underarm deodorants | 15 | 6 | >0.1–25 | 0.001–52 |
| Feminine deodorants | 19 | 3 | >0.1–25 | — |
| Personal cleanliness products (other) | 22 | 14 | >0.1–25 | 0.3–21 |
| Aftershave lotion | 11 | 10 | >0.1–25 | 0.003–1 |
| Men's talcum | 1 | — | >0.1–1 | — |
| Preshave lotions | 31 | 7 | >1–25 | 15 |
| Shaving cream | 1 | 4 | >1–5 | 0.004–0.5 |
| Other shaving preparations | 3 | 5 | >1–10 | — |
| Skin-cleansing creams, lotions, liquids, and pads | 36 | 37 | ≤0.1–25 | 0.002–10 |
| Depilatories | — | 1 | — | — |
| Face and neck skin care preparations | 133* | 27 | ≤0.1–>50* | 0.2–10 |
| Body and hand skin care preparations | | 120 | | 0.4–10 |
| Foot powders and sprays | 6 | 3 | >0.1–1 | 0.08–7 |
| Moisturizers | 125 | 98 | ≤0.1–50 | 0.02–16 |
| Night skin care preparations | 46 | 25 | ≤0.1–>50 | 0.01–8 |
| Paste masks (mud packs) | 4 | 10 | >1–25 | 15 |
| Skin fresheners | 5 | 2 | ≤0.1–5 | 0.003 |
| Skin lighteners | 3 | N/A** | >1–5 | N/A** |
| Hormone preparations | 3 | N/A** | ≤0.1–5 | N/A** |
| Other skin care preparations | 34 | 50 | ≤0.1–>50 | 2–61 |
| Suntan gels, creams, and liquids | 86 | 22 | >0.1–50 | 9–10 |
| Indoor tanning preparations | — | 7 | — | 3 |
| Other suntan preparations | 2 | 4 | >1–25 | — |
| **Total uses/ranges for Isopropyl Myristate** | **2198** | **881** | **≤0.1–>50** | **0.00008–78** |

*This category was combined when the original safety assessment was performed and is now two separate categories.
**No longer considered a cosmetic product category.

The Panel considered data in the original safety assessment suggesting that Isopropyl Myristate may be a tumor promoter. The CIR Expert Panel concluded that the data are more indicative of cocarcinogenesis in which Isopropyl Myristate has to be administered with a carcinogen all of the time, but produces only a slight enhancing effect. The large dose of Isopropyl Myristate required in order to bring about a cocarcinogenic effect suggests that, under cosmetic use conditions, no enhancing or potentiating effect of Isopropyl Myristate would be anticipated.

The Panel did recall the data in the original safety assessment regarding the comedogenicity of Isopropyl Myristate, data that have been confirmed in subsequent studies, and reminded formulators to consider this, especially in view of the increase in use concentration from 1976 to 2002 in eye products.

## REFERENCES


Bechgaard, E. 1985. Acnegenicity Testing in Rabbits. An Objective Quantification Method. *Acta Derm. Venereol*. 65:282–286.

Blevins, R. D., and D. E. Taylor. 1982. Mutagenicity screening of twenty-five cosmetic ingredients with the Salmonella/microsome test. *J. Environ. Sci. Health A* 17:214–239.

Campbell, R. L., and R. D. Bruce. 1981. Comparative dermatoxicology. I. Direct comparison of rabbit and human primary skin irritation responses to isopropyl myristate. *Toxicol. Appl. Pharmacol.* 59:555–563.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2002. Concentration of use of Myristyl and Isopropyl Myristate. Unpublished data submitted by CTFA.[17]

Elder, R. L., ed. 1982. Final Report on the Safety Assessment of Myristyl Myristate and Isopropyl Myristate. *J. Am. Col. Toxicol.* 1:55–80.

Food and Drug Administration (FDA). 2002. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

Fulton, J. E., and S. R. Pay. 1984. Comedogenicity of current therapeutic products, cosmetics, and ingredients in the rabbit ear. *J. Am. Acad. Dermatol*. 10:96–105.

Guillot, J. P., M. C. Martini, and J. Y. Giauffret. 1977. Safety evaluation of cosmetic raw materials. *J. Soc. Cosmet. Chem*. 28:377–393.

Komatsu, H., K. Asaba, and M. Suzuki. 1979. Some biochemical effects of isopropyl myristate and squalane on rabbit skin. *J. Soc. Cosmet. Chem*. 30:263–278.

Motoyoshi, K. 1983. Enhanced comedone formation in rabbitear skin by squalene and oleic acid peroxides. *Br. J. Dermatol*. 109:191–198.


[17]Available from the Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

Pepe, R. C., J. A. Wenninger, G. N. McEwen, Jr. eds. 2002. *International cosmetic ingredient dictionary and handbook*, 9th ed., vols. 1–4. Washington, DC: CTFA.

Suzuki, M., K. Asaba, H. Komatsu, and M. Mochizuka. 1978. Autoradiographic study on percutaneous absorption of several oils useful for cosmetics. *J. Soc. Cosmet. Chem*. 29:265–282.

Tucker, S. B., S. A. Flannigan, M. Dunbar, and R. B. Drotman. 1986. Development of an objective comedogenicity assay. *Arch. Dermatol*. 122:660–665.

## OZOKERITE, CERESIN, MONTAN WAX, PARAFFIN, MICROCRYSTALLINE WAX, EMULSIFYING WAX N.F., SYNTHETIC WAX, AND SYNTHETIC BEESWAX

A safety assessment of these fossil and synthetic waxes was published in 1984 with the conclusion that these ingredients are "safe as cosmetic ingredients in the practices and concentrations of use" (Elder 1984). New studies listed at the end of this section, with updated information regarding types and concentrations of use, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

**Ozokerite** was used in 1269 cosmetic products in 1976, with the largest use occurring in moisturizing products at concentrations of >1% to 50%. In 2002, Ozokerite was used in 680 cosmetic products (FDA 2002), at a maximum use concentration of 22% in other eye makeup preparations (CTFA 2003).

**Ceresin** was used in 403 cosmetic products in 1976, with the largest use occurring in makeup bases; rouges; other makeup preparations; cleansing; face, body, and hand skin care; moisturizing; night, wrinkle smoothers; and other skin care preparations at concentrations of ≤25%. In 2002, Ceresin was used in 404 cosmetic products (FDA 2002), at a maximum use concentration of 20% in other makeup preparations and suntan gels, creams, and liquids (CTFA 2003).

**Montan Wax** was used in 355 cosmetic products in 1976, with the largest use occurring in eyebrow pencil and lipsticks at concentrations of >0.1% to 25%. In 2002, Montan Wax was used in 13 cosmetic products (FDA 2002), at a maximum use concentration of 11% in foundations (CTFA 2003).

**Paraffin** was used in 1238 cosmetic products in 1976, with the largest use occurring in other eye makeup preparations; perfumes; other fragrance preparations; other hair coloring preparations; other makeup preparations; face, body, and hand skin care; moisturizers; and other skin care preparations at concentrations of ≤50%. In 2002, Paraffin was used in 481 cosmetic products (FDA 2002), at a maximum use concentration of 99% in other skin care preparations (CTFA 2003).

**Microcrystalline Wax** was used in 868 cosmetic products in 1976, with the largest use occurring in other fragrance preparations at concentrations of >25% to 50%. In 2002, Microcrystalline Wax was used in 581 cosmetic products (FDA 2002), at a maximum use concentration of 50% in other hair preparations (CTFA 2003).

**Emulsifying Wax N.F.** was used in 12 cosmetic products in 1976, with the only use occurring in other skin care preparations at concentrations of >0.1% to 10%. In 2002, Emulsifying Wax N.F. was used in 102 cosmetic products (FDA 2002), at a maximum use concentration of 21% in hair straighteners (CTFA 2003). This ingredient is no longer listed as a cosmetic ingredient in the *International Cosmetic Ingredient Dictionary and Handbook* (Pepe et al. 2002).

**Synthetic Beeswax** was used in 146 cosmetic products in 1976, with the largest use occurring in foundations and rouges at concentrations of >1% to 5%. In 2002, Synthetic Beeswax was used in 179 cosmetic products (FDA 2002), at a maximum use concentration of 18% in mascara (CTFA 2003).

**Synthetic Wax** was used in five cosmetic products in 1976, with the largest use occurring in lipstick at concentrations of >1 to 10%. In 2002, Synthetic Wax was used in 215 cosmetic products (FDA 2002), at a maximum use concentration of 29% in lipstick (CTFA 2003).

Table 17 presents the historical and current cosmetic product uses and use concentrations of these fossil and synthetic waxes.

**TABLE 17**
Historical and current cosmetic product uses and concentrations for fossil and synthetic waxes

| Product type | 1976 uses (Elder 1984) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1984) (%) | 2003 use concentrations (CTFA 2003) (%) |
|---|---|---|---|---|
| | | *Ozokerite* | | |
| Baby lotions, oils, powders, and creams | 3 | 1 | >1–5 | 2 |
| Bath preparations (other) | — | — | — | 15 |
| Eyebrow pencil | — | 8 | — | — |
| Eyeliner | — | 11 | — | 7–10 |
| Eye shadow | 152 | 10 | >0.1–25 | 6–14 |
| Eye makeup remover | 2 | 3 | >10–25 | 2–4 |
| Mascara | 71 | 25 | >1–25 | 7–9 |
| Eye makeup (other) | 17 | 26 | >0.1–25 | 2–22 |
| Colognes and toilet waters | — | 1 | — | 15 |

*(Continued on next page)*

**TABLE 17**
Historical and current cosmetic product uses and concentrations for fossil and synthetic waxes *(Continued)*

| Product type | 1976 uses (Elder 1984) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1984) (%) | 2003 use concentrations (CTFA 2003) (%) |
|---|---|---|---|---|
| Perfumes | 41 | 10 | >25–50 | 15 |
| Sachets | 3 | — | >1–5 | — |
| Fragrance preparations (other) | 7 | 2 | >10–25 | 15 |
| Hair Conditioners | 1 | 1 | >5–10 | — |
| Hair tonics, dressings, etc. | — | 3 | — | — |
| Hair preparations (other noncoloring) | 1 | 2 | >0.1–1 | — |
| Hair dyes and colors | — | 46 | — | — |
| Hair-coloring preparations (other) | — | — | — | 0.3 |
| Blushers (all types) | 65 | 10 | >0.1–25 | 2–21 |
| Face powders | 1 | 1 | >5–10 | 1 |
| Foundations | 45 | 33 | >0.1–25 | 4–15 |
| Leg and body paint | 1 | — | >1–5 | 8 |
| Lipsticks | 559 | 374 | >0.1–25 | 2–21 |
| Makeup bases | 149 | 11 | >0.1–25 | — |
| Rouges | 35 | 2 | >1–25 | — |
| Makeup fixatives | 1 | — | >0.1–1 | — |
| Makeup (other) | 36 | 37 | >1–25 | 3–21 |
| Cuticle softeners | 1 | 1 | >5–10 | — |
| Nail polish and enamel | — | — | — | 3 |
| Bath soaps and detergents | — | — | — | 0.08 |
| Personal cleanliness products (other) | — | 1 | — | — |
| Skin-cleansing creams, lotions, liquids, and pads | 17 | 4 | >0.1–10 | 1–5 |
| Face and neck skin care preparations | 18* | 2 | >0.1–50* | — |
| Body and hand skin care preparations | | 10 | | 7 |
| Hormone preparations** | 1 | — | >1–5 | — |
| Moisturizers | 17 | 15 | >0.1–25 | 1–5 |
| Night skin care preparations | 9 | 7 | >1–50 | 2 |
| Paste masks/mud packs | — | 4 | — | — |
| Skin care preparations (other) | 8 | 7 | >1–25 | 6 |
| Suntan gels, creams, and liquids | 5 | 9 | >1–25 | 8–15 |
| Suntan preparations (other) | 3 | 3 | >1–5 | 3–12 |
| **Total uses/ranges for Ozokerite** | **1269** | **680** | **>0.1–50** | **1–22** |
| | | *Ceresin* | | |
| Baby lotions, oils, powders, and creams | 1 | — | >5–10 | — |
| Bath preparations (other) | 2 | — | >10–25 | — |
| Eyebrow pencil | — | 29 | — | 8 |
| Eyeliner | 3 | 43 | >1–5 | 5–12 |
| Eye shadow | 48 | 31 | >25–50 | 11 |
| Eye lotion | 2 | 2 | >5–10 | — |
| Eye makeup remover | 2 | 3 | >5–10 | — |
| Mascara | 32 | 9 | >0.1–25 | 4 |
| Eye makeup (other) | 17 | 4 | >1–25 | 4–11 |
| Colognes and toilet waters | 6 | — | >5–10 | — |
| Perfumes | 8 | 1 | >10–25 | — |
| Fragrance preparations (other) | 33 | — | >10–25 | — |
| Hair conditioners | 1 | — | >5–10 | — |

*(Continued on next page)*

**TABLE 17**
Historical and current cosmetic product uses and concentrations for fossil and synthetic waxes *(Continued)*

| Product type | 1976 uses (Elder 1984) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1984) (%) | 2003 use concentrations (CTFA 2003) (%) |
|---|---|---|---|---|
| Hair tonics, dressings, etc. | 7 | 4 | >0.1–25 | 2 |
| Wave sets | 1 | — | >5–10 | — |
| Hair preparations (other noncoloring) | 2 | 1 | >1–10 | 17 |
| Hair-coloring preparations (other) | — | 1 | — | — |
| Blushers (all types) | 19 | 11 | >0.1–25 | 6 |
| Face powders | 4 | — | >5–10 | 6 |
| Foundations | 7 | 6 | >1–25 | 4–7 |
| Lipsticks | 109 | 191 | >0.1–25 | 0.8–20 |
| Makeup bases | 7 | 2 | ≤0.1–25 | — |
| Rouges | 1 | 2 | >10–25 | — |
| Makeup fixatives | — | — | — | 3 |
| Makeup (other) | 19 | 15 | >0.1–25 | 4–13 |
| Nail creams and lotions | — | 2 | — | — |
| Nail polish and enamel | — | 1 | — | 4 |
| Underarm deodorant | 1 | — | >1–5 | — |
| Skin-cleansing creams, lotions, liquids, and pads | 29 | 13 | ≤0.1–25 | — |
| Face and neck skin care preparations | 5* | 1 | >0.1–25* | 5–8 |
| Body and hand skin care preparations | | 5 | | 8 |
| Hormone preparations** | 1 | — | >1–5 | — |
| Moisturizers | 13 | 11 | >1–25 | 5 |
| Night skin care preparations | 12 | 4 | >1–25 | 5 |
| Paste masks/mud packs | — | 1 | — | — |
| Skin care preparations (other) | 9 | 9 | >5–25 | — |
| Suntan gels, creams, and liquids | — | 2 | — | 13 |
| Other suntan preparations | 1 | — | >5–10 | — |
| **Total uses/ranges for Ceresin** | **403** | **404** | **≤0.1–25** | **0.8–20** |
| | | *Montan Wax* | | |
| Eyebrow pencil | 5 | — | >10–25 | — |
| Eyeliner | — | — | — | 2 |
| Eye Shadow | 18 | — | >1–5 | 9 |
| Mascara | — | — | — | 3 |
| Eye makeup (other) | — | — | — | 0.5 |
| Perfumes | 1 | — | >0.1–1 | — |
| Hair-coloring preparations (other) | — | 1 | — | — |
| Foundations | — | 5 | — | 11 |
| Lipsticks | 323 | 7 | >0.1 — 25 | 0.5 |
| Makeup (other) | — | — | — | 0.5 |
| Nail polish and enamel | — | — | — | 0.5 |
| Rouges | 7 | — | >5–10 | — |
| Face and neck skin care preparations | 1* | — | >0.1–1* | — |
| Body and hand skin care preparations | | — | | — |
| **Total uses/ranges for Montan Wax** | **355** | **13** | **>0.1–25** | **0.5–11** |
| | | *Paraffin* | | |
| Baby shampoos | 1 | — | >1–5 | — |
| Baby lotions, oils, powders, and creams | — | — | — | 1 |
| Eyebrow pencil | — | 4 | — | 6 |

*(Continued on next page)*

**TABLE 17**
Historical and current cosmetic product uses and concentrations for fossil and synthetic waxes *(Continued)*

| Product type | 1976 uses (Elder 1984) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1984) (%) | 2003 use concentrations (CTFA 2003) (%) |
|---|---|---|---|---|
| Eyeliner | — | 7 | — | 4–20 |
| Eye shadow | 127 | 5 | >0.1–25 | 3–8 |
| Eye lotion | — | 1 | — | 1–6 |
| Eye makeup remover | 3 | 3 | >1–10 | — |
| Mascara | 3 | 28 | >1–5 | 6–20 |
| Other eye makeup preparations | 20 | 4 | >0.1–50 | 4 |
| Colognes and toilet waters | 3 | — | >10–25 | — |
| Perfumes | 30 | — | >25–50 | — |
| Sachets | 6 | — | >5–10 | — |
| Other fragrance preparation | 15 | 1 | >25–50 | — |
| Hair conditioners | 14 | 7 | >5–10 | 2 |
| Hair rinses (noncoloring) | 3 | — | >1–5 | — |
| Shampoos (noncoloring) | 2 | 1 | >0.1–1 | — |
| Tonics, dressings, and other hair-grooming aids | 29 | 23 | >0.1–25 | 2–20 |
| Wave sets | 1 | 1 | >10–25 | — |
| Other hair preparations | 3 | 1 | >1–10 | 2 |
| Hair tints | — | 1 | — | — |
| Hair colors sprays (aerosol) | — | 2 | — | — |
| Other hair-coloring preparations | 3 | 10 | >10–50 | — |
| Blushers (all types) | 65 | 4 | >0.1–25 | — |
| Face powders | 15 | — | >0.1–1 | — |
| Foundations | 76 | 33 | >0.1–10 | 2–6 |
| Lipstick | 439 | 134 | ≤0.1–25 | 2–10 |
| Makeup bases | 95 | 37 | >0.1–10 | — |
| Rouges | 29 | — | >0.1–25 | — |
| Makeup fixatives | 3 | 1 | >1–5 | — |
| Other makeup preparations | 44 | 18 | >0.1–50 | 2–21 |
| Cuticle softeners | 3 | 1 | >1–5 | — |
| Nail creams and lotions | 2 | 3 | >1–25 | — |
| Nail polish and enamel | — | 5 | — | 0.03–2 |
| Other manicuring preparations | 1 | — | >1–5 | 0.03 |
| Bath soaps and detergents | 3 | 7 | ≤0.1 | — |
| Deodorants (underarm) | 1 | 2 | >5–10 | — |
| Other personal cleanliness products | 3 | 16 | >1–10 | — |
| Aftershave lotion | 3 | — | >0.1–1 | — |
| Shaving cream | 1 | 1 | >1–5 | 1 |
| Cleansing | 69 | 26 | >0.1–25 | 12–20 |
| Depilatories | 1 | 1 | >5–10 | — |
| Face and neck (excluding shave) | 31* | 4 | ≤0.1–50* | — |
| Body and hand (excluding shave) | | 19 | | 3 |
| Hormone preparations** | 2 | — | ≤0.1–1 | — |
| Foot powders and sprays | — | 1 | — | — |
| Moisturizers | 28 | 24 | >1.0–50 | 2 |
| Night skin care preparations | 11 | 6 | >1–10 | 0.3–8 |
| Paste masks/mud packs | 4 | 7 | >0.1–5 | 32 |
| Skin lighteners** | 4 | — | >1–5 | — |

*(Continued on next page)*

**TABLE 17**
Historical and current cosmetic product uses and concentrations for fossil and synthetic waxes *(Continued)*

| Product type | 1976 uses (Elder 1984) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1984) (%) | 2003 use concentrations (CTFA 2003) (%) |
|---|---|---|---|---|
| Skin fresheners | 1 | — | >10–25 | — |
| Skin care preparations (other) | 22 | 27 | >1–50 | 99 |
| Suntan gels, creams, and liquids | 13 | 3 | >0.1–10 | 2–10 |
| Indoor tanning preparations | — | — | — | 2 |
| Suntan preparations (other) | 6 | 2 | >1–25 | 20 |
| **Total uses/ranges for Paraffin** | **1238** | **481** | **≤0.1–50** | **0.03–99** |
| | *Microcrystalline Wax* | | | |
| Baby products (other) | — | — | — | 3 |
| Bath oils, tablets, and salts | — | 1 | — | — |
| Bath preparations (other) | — | — | — | 0.5 |
| Eyebrow pencil | 2 | 15 | >0.1–10 | 6 |
| Eyeliner | — | 126 | — | 2–18 |
| Eye shadow | 37 | 16 | >0.1–25 | 2–6 |
| Eye lotion | — | — | — | 0.3 |
| Eye makeup remover | 2 | 1 | >1–5 | — |
| Mascara | 5 | 20 | >1–25 | 3–6 |
| Eye makeup (other) | 23 | 33 | >0.1–25 | 8–19 |
| Perfumes | 17 | 1 | >10–25 | — |
| Fragrance preparations (other) | 9 | 1 | >25–50 | — |
| Hair conditioners | 2 | 3 | >1–5 | 4 |
| Hair straighteners | — | 1 | — | 0.4 |
| Hair tonics, dressings, etc. | 14 | 15 | >1–25 | 0.8 |
| Hair preparations (other noncoloring) | 2 | 1 | >1–10 | 3–50 |
| Hair-coloring preparations (other) | 1 | 1 | >1–5 | — |
| Blushers (all types) | 38 | 8 | >1–25 | 6–10 |
| Face powders | 1 | 1 | >1–5 | — |
| Foundations | 9 | 35 | >0.1–10 | 9–12 |
| Lipstick | 640 | 229 | >0.1–25 | 0.5–10 |
| Makeup bases | 6 | 2 | ≤0.1–10 | — |
| Rouges | — | — | — | 7 |
| Makeup fixatives | — | 1 | — | — |
| Makeup (other) | 17 | 33 | >0.1–10 | 3–13 |
| Cuticle softeners | 1 | — | >5–10 | — |
| Oral hygiene products (other) | — | — | — | 10 |
| Shaving preparation products (other) | — | — | — | 0.5 |
| Nail creams and lotions | 1 | — | >1–5 | — |
| Nail polish and enamel | — | 1 | — | — |
| Personal cleanliness products (other) | — | 1 | — | — |
| Skin-cleansing creams, lotions, liquids, and pads | 12 | 6 | >0.1–10 | 2 |
| Depilatories | — | 1 | — | 4 |
| Face and neck skin care preparations | 10* | 2 | >0.1–25* | — |
| Body and hand skin care preparations | | 5 | | — |
| Moisturizers | 8 | 5 | >0.1–25 | — |
| Night skin care preparations | 7 | 4 | >0.1–25 | 2 |
| Paste masks/mud packs | — | 2 | — | — |
| Skin care preparations | 4 | 10 | >5–25 | 1 |

*(Continued on next page)*

**TABLE 17**
Historical and current cosmetic product uses and concentrations for fossil and synthetic waxes *(Continued)*

| Product type | 1976 uses (Elder 1984) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1984) (%) | 2003 use concentrations (CTFA 2003) (%) |
|---|---|---|---|---|
| Suntan gels, creams, and liquids | — | — | — | 1–15 |
| Indoor tanning products | — | — | — | 15 |
| Suntan preparations (other) | — | — | — | 0.2–0.5 |
| **Total uses/ranges for Montan Wax** | **868** | **581** | **≤0.1–50** | **0.2–50** |
| | *Emulsifying Wax N.F.* | | | |
| Baby lotions, oils, powders, and creams | — | 2 | — | — |
| Eyeliners | — | 2 | — | — |
| Eye makeup (other) | — | 1 | — | — |
| Fragrance preparation (other) | — | 4 | — | — |
| Hair conditioners | — | 14 | — | 0.8–2 |
| Hair straighteners | — | 10 | — | 21 |
| Hair tonics, dressings, etc. | — | — | — | 9 |
| Rinses (noncoloring) | — | 1 | — | — |
| Permanent waves | — | 1 | — | — |
| Hair bleaches | — | 1 | — | — |
| Hair coloring preparations (other) | — | 6 | — | — |
| Foundations | — | 2 | — | — |
| Cuticle softeners | — | 2 | — | 0.5 |
| Nail creams and lotions | — | 1 | — | — |
| Skin-cleansing creams, lotions, liquids, and pads | — | 2 | — | 1 |
| Face and neck skin care preparations | —* | — | —* | 1 |
| Body and hand skin care preparations | | 12 | | 2–10 |
| Moisturizers | — | 25 | — | 12 |
| Night skin care preparations | — | 4 | — | 1 |
| Paste masks/mud packs | — | 1 | — | 1 |
| Skin care preparations (other) | 12 | 5 | >0.1–10 | — |
| Indoor tanning preparations | — | 5 | — | — |
| Suntan preparations (other) | — | 1 | — | — |
| **Total uses/ranges for Emulsifying Wax N.F.** | **12** | **102** | **>0.1–10** | **0.5–21** |
| | *Synthetic Beeswax* | | | |
| Baby lotions, oils, powders, and creams | — | 1 | — | 0.5 |
| Baby products (other) | — | 1 | — | — |
| Eyebrow pencils | — | 6 | — | — |
| Eyeliner | — | 9 | — | 0.06–14 |
| Eye shadow | 119 | 1 | >0.1–1 | — |
| Mascara | — | 6 | — | 0.05–18 |
| Eye makeup (other) | — | 1 | — | 0.06–9 |
| Fragrance preparations (other) | — | 1 | — | — |
| Hair tonics, dressings, etc. | — | — | — | 12 |
| Blushers | 14 | — | >0.1–1 | — |
| Face powders | 10 | — | >0.1–1 | — |
| Foundations | 1 | 2 | >1–5 | — |
| Leg and body paints | — | — | — | 13 |
| Lipstick | — | 131 | — | 4–7 |
| Makeup bases | — | 1 | — | — |
| Rouges | 2 | — | >1–5 | — |

*(Continued on next page)*

**TABLE 17**
Historical and current cosmetic product uses and concentrations for fossil and synthetic waxes *(Continued)*

| Product type | 1976 uses (Elder 1984) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1984) (%) | 2003 use concentrations (CTFA 2003) (%) |
|---|---|---|---|---|
| Makeup (other) | — | 9 | — | 1 |
| Skin-cleansing creams, lotions, liquids, and pads | — | 1 | — | — |
| Face and neck skin care preparations | —* | 1 | —* | — |
| Body and hand skin care preparations | | 2 | | 1–3 |
| Moisturizers | — | 5 | — | 0.5 |
| Skin care preparations (other) | — | 1 | — | — |
| **Total uses/ranges for Synthetic Beeswax** | **146** | **179** | **>0.1–5** | **0.05–18** |
| | | *Synthetic Wax* | | |
| Baby lotions, oils, powders, and creams | — | — | — | 4 |
| Eyebrow pencils | — | 2 | — | — |
| Eyeliner | — | 28 | — | 0.8–27 |
| Eye shadow | — | 9 | — | — |
| Mascara | — | 10 | — | 2–11 |
| Eye makeup (other) | — | 1 | — | — |
| Perfumes | — | 1 | — | — |
| Fragrance preparation (other) | — | 2 | — | — |
| Hair conditioners | — | 1 | — | — |
| Blushers (all types) | 1 | 10 | >1–5 | — |
| Face powders | — | 2 | — | 0.5 |
| Foundations | 1 | 6 | >1–5 | 9 |
| Lipsticks | 3 | 134 | >1–10 | 3–29 |
| Makeup bases | — | 2 | — | — |
| Rouges | — | 1 | — | 2 |
| Makeup (other) | — | 4 | — | — |
| Cuticle softeners | — | — | — | 0.1 |
| Aftershave lotions | — | — | — | 1 |
| Skin-cleansing creams, lotions, liquids, and pads | — | — | — | 5 |
| Face and neck skin care preparations | —* | — | —* | 3 |
| Body and hand skin care preparations | | — | | 2–4 |
| Moisturizers | — | 1 | — | — |
| Night skin care preparations | — | — | — | 3 |
| Personal cleanliness products (other) | — | 1 | — | — |
| Suntan preparations (other) | — | — | — | 1 |
| **Total uses/ranges for Synthetic Wax** | **5** | **215** | **>1–10** | **0.1–29** |

*This category was combined when the original safety assessment was performed and is now two separate categories.
**No longer considered a cosmetic product category.

## REFERENCES


Benedetto, G. D., M. Pierangeli, A. Scalise, and A. Bertani. 2002. Paraffin oil injection in the body: An obsolete and destructive prodecure. *Ann. Plastic Surg*. 49:391–396.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2003. Concentrations of use—mineral waxes. Unpublished data submitted by CTFA on January 21, 2003. 6 pages.[18]

Elder, R. L. 1984. Final report on the safety assessment of fossil and synthetic waxes. *J. Am. Col. Toxicol*. 3:43–99.

[18]Available from the Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

Food and Drug Administration (FDA). 2002. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

Heimbach, J. T., A. R. Bodor, J. S. Douglas, et al. 2002. Dietary exposures to mineral hydrocarbons from food-use applications in the United States. *Food Chem. Toxicol*. 40:555–571.

Hintschich, C. R., C. K. Beyer-Machule, and F. H. Stefani. 1995. Paraffinoma of the periorbit—a challenge for the oculoplastic surgeon. *Ophthal. Plastic Reconstr. Surg*. 11:39–44.

Joint FAO/WHO Expert Committee on Food Additives (JECFA). 1993. Microcrystalline wax and paraffin wax. *WHO Food Addit. Ser.* 30:253–260.

JECFA. 1996. Mineral oils (food grade), paraffin waxes and microcrystalline waxes. *WHO Food Addi. Ser.* 35:193–206.

Pepe, R. C., J. A. Wenninger, and G. N. McEwen, Jr. 2002. *International cosmetic ingredient dictionary and handbook*. 9th ed. Washington, DC: CTFA.
Smith, J. H., A. K. Mallett, A. J. Preston, et al. 1996. Ninety-day feeding study in Fischer-344 rats of highly refined petroleum-derived food-grade white oils and waxes. *Toxicol. Pathol*. 24:214–230.
Vigneswaran, W. T., and S. S. Ramasastry. 1996. Paraffin plombage of the chest revisited. *Ann. Thorac. Surg*. 62:1837–1839.
Witschel, H., and K. Geiger. 1994. Paraffin induced sclerosing lipogranuloma of eyelids and anterior orbit following endonasal sinus surgery. *Br. J. Ophthamol*. 78:61–65.

## PEG-2, -3, -4, -5, -6, -6-32, -7, -8, -9, -10, -12, -14, -15, -18, -20, -23, -25, -30, -32, -35, -36, -40, -45, -50, -55, -75, -90, -100, -120, AND -150 STEARATES

A safety assessment of PEG-2, -6, -8, -12, -20, -32, -40, -50, -100, and -150 Stearates was published in 1983 with the conclusion "safe as cosmetic ingredients in the present practices of concentration and use" (Elder 1983). Studies available since that safety assessment was completed, along with updated information regarding use concentrations, were considered by the CIR Expert Panel. The Panel determined not to reopen this safety assessment.

In 1979, PEG Stearates were used in 374 cosmetic products, typically at concentrations ranging from >0.1% to 10%. Currently, there are uses reported in 1459 products, typically at concentrations <4%. Table 18 presents the available use information.

### REFERENCES

Barany, E., M. Lindberg, and M. Loden. 2000. Unexpected skin barrier influence from nonionic emulsifiers. *Int. J. Pharm.* 195:189–195.
Bryan, A. J., R. Kaur, G. Robinson, N. W. Thomas, and C. G. Wilson. 1980. Histological and physiological studies on the intestine of the rat exposed to solutions of Myrj 52 and PEG 2000. *Int. J. Pharm.* 7:145–156.

**TABLE 18**
Historical and current cosmetic product uses and concentrations for PEG Stearates

| Product type | 1976 uses (Elder 1983) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1983) (%) | 2002 use concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| | *PEG-2 Stearate* | | | |
| Bath preparations (other) | 1 | — | >0.1–1 | — |
| Eye makeup (other) | — | — | — | 2 |
| Sachets | — | 1 | — | — |
| Fragrance preparations | 11 | — | >0.1–1 | — |
| Shampoos (noncoloring) | — | 2 | — | — |
| Hair tonics, dressings, etc. | — | 1 | — | — |
| Hair preparations (other noncoloring) | 4 | — | >0.1–10 | — |
| Hair-coloring preparations (other) | 1 | — | >0.1–1 | — |
| Foundations | — | 4 | — | 0.2–1 |
| Makeup bases | — | 1 | — | — |
| Makeup (other) | 16 | — | >0.1–10 | 2 |
| Manicuring preparations (other) | 1 | — | >1–5 | — |
| Personal cleanliness products (other) | 1 | — | >0.1–1 | — |
| Aftershave lotion | — | 3 | — | 0.4 |
| Shaving preparations (other) | 6 | — | >0.1–1 | — |
| Skin-cleansing creams, lotions, liquids, and pads | — | 6 | — | 2 |
| Face and neck skin care preparations | | 1 | | — |
| Body and hand skin care preparations | —* | 7 | —* | — |
| Moisturizers | — | 13 | — | — |
| Night skin care preparations | — | 9 | — | — |
| Paste masks/mud packs | — | 4 | — | — |
| Skin care preparations (other) | 20 | 8 | >0.1–10 | — |
| Suntan gels, creams, and liquids | 1 | 2 | >1–5 | 2 |
| Indoor tanning preparations | — | 1 | — | 1 |
| Suntan preparations (other) | — | 1 | — | — |
| **Total uses/ranges for PEG-2 Stearate** | **62** | **64** | **>0.1–10** | **0.2–2** |
| Body and hand skin care preparations | — | 5 | — | — |

*(Continued on next page)*

**TABLE 18**
Historical and current cosmetic product uses and concentrations for PEG Stearates *(Continued)*

| Product type | 1976 uses (Elder 1983) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1983) (%) | 2002 use concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| Paste masks/mud packs | — | 1 | — | — |
| Skin care preparations (other) | — | 2 | — | — |
| **Total uses/ranges for PEG-5 Stearate** | **—** | **8** | **—** | **—** |
| | *PEG-6 Stearate* | | | |
| Eyeliner | — | — | 2–2.5 | — |
| Mascara | — | 1 | — | — |
| Eye makeup (other) | — | — | 3 | — |
| Hair conditioners | — | 1 | — | — |
| Hair preparations (other noncoloring) | 1 | — | >1–5 | — |
| Hair-coloring preparations (other) | — | 1 | — | — |
| Foundations | — | 1 | — | — |
| Skin-cleansing creams, lotions, liquids, and pads | — | 1 | — | — |
| Face and neck skin care preparations | | — | | 3 |
| Body and hand skin care preparations | —* | 2 | —* | — |
| Moisturizers | — | 3 | — | 6 |
| Night skin care preparations | — | 3 | — | — |
| Paste masks (mud packs) | — | 1 | — | 2–3 |
| Skin care preparations (other) | 3 | 8 | >1–5 | — |
| **Total uses/ranges for PEG-6 Stearate** | **4** | **22** | **>1–5** | **2–6** |
| | *PEG-6-32 Stearate* | | | |
| Foundations | — | 1 | — | — |
| Skin-cleansing creams, lotions, liquids, and pads | — | 2 | — | — |
| Face and neck skin care preparations | | 1 | | — |
| Body and hand skin care preparations | —* | 1 | —* | — |
| Moisturizers | — | 6 | — | — |
| Night skin care preparations | — | 2 | — | — |
| Skin care preparations (other) | — | 5 | — | — |
| Suntan gels, creams, and liquids | — | 11 | — | — |
| Indoor tanning preparations | — | 4 | — | — |
| Suntan preparations (other) | — | 1 | — | — |
| **Total uses/ranges for PEG-6-32 Stearate** | **—** | **34** | **—** | **—** |
| | *PEG-8 Stearate* | | | |
| Mascara | — | 1 | — | — |
| Eye makeup (other) | 1 | — | >0.1–1 | — |
| Fragrance preparations (other) | 3 | — | >1–5 | — |
| Hair conditioners | — | 3 | — | — |
| Hair preparations (other noncoloring) | 13 | — | >0.1–10 | — |
| Foundations | — | 1 | — | — |
| Makeup (other) | 5 | 1 | >0.1–5 | — |
| Shaving cream | — | 1 | — | — |
| Shaving preparations (other) | 1 | — | >1–5 | — |
| Skin-cleansing creams, lotions, liquids, and pads | — | 1 | — | 2 |
| Depilatories | — | 1 | — | — |
| Face and neck skin care preparations | | — | | 0.5 |
| Body and hand skin care preparations | —* | 2 | —* | — |
| Moisturizers | — | 5 | — | 3 |

*(Continued on next page)*

**TABLE 18**
Historical and current cosmetic product uses and concentrations for PEG Stearates *(Continued)*

| Product type | 1976 uses (Elder 1983) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1983) (%) | 2002 use concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| Other skin care preparations | 3 | 1 | >0.1–5 | — |
| Suntan gels, creams, and liquids | 1 | 1 | >1–5 | — |
| **Total uses/ranges for PEG-8 Stearate** | **27** | **17** | **>0.1–5** | **0.5–3** |
| | *PEG-10 Stearate* | | | |
| Shampoos (noncoloring) | — | 2 | — | — |
| Skin-cleansing creams, lotions, liquids, and pads | — | 1 | — | — |
| **Total uses/ranges for PEG-10 Stearate** | **—** | **3** | **—** | **—** |
| | *PEG-12 Stearate* | | | |
| Eye makeup (other) | 1 | — | >0.1–1 | — |
| Shaving cream | — | 12 | — | — |
| Skin-cleansing creams, lotions, liquids, and pads | — | 1 | — | — |
| Face and neck skin care preparations | | 2 | | — |
| Body and hand skin care preparations | —* | 3 | —* | — |
| Suntan gels, creams, and liquids | — | 1 | — | — |
| **Total uses/ranges for PEG-12 Stearate** | **1** | **19** | **>0.1–1** | **—** |
| | *PEG-20 Stearate* | | | |
| Bath preparations (other) | — | 1 | — | — |
| Eye makeup remover | — | 1 | — | — |
| Eye makeup (other) | 4 | — | >0.1–10 | — |
| Fragrance preparations (other) | 4 | 2 | >1–5 | — |
| Hair conditioners | — | 2 | — | — |
| Hair preparations (other noncoloring) | 8 | — | >0.1–25 | — |
| Hair-coloring preparations (other) | 1 | — | >1–5 | — |
| Foundations | — | 1 | — | — |
| Makeup (other) | 3 | — | >0.1–1 | — |
| Personal cleanliness products (other) | 3 | 3 | >0.1–5 | — |
| Aftershave lotions | — | 1 | — | — |
| Shaving preparations (other) | 2 | 1 | >1–5 | — |
| Skin-cleansing creams, lotions, liquids, and pads | — | 6 | — | 2 |
| Face and neck skin care preparations | — | 2 | — | 0.5–2 |
| Body and hand skin care preparations | — | 6 | — | 0.2–4 |
| Moisturizers | — | 8 | — | 4 |
| Night skin care preparations | — | 1 | — | 3 |
| Paste masks/mud packs | — | 3 | — | — |
| Suntan gels, creams, and liquids | 10 | 4 | >0.1–5 | — |
| **Total uses/ranges for PEG-20 Stearate** | **35** | **42** | **>0.1–10** | **0.2–4** |
| | *PEG-30 Stearate* | | | |
| Moisturizers | — | 1 | — | — |
| Night skin care preparations | — | 1 | — | — |
| **Total uses/ranges for PEG-30 Stearate** | **—** | **2** | **—** | **—** |
| | *PEG-32 Stearate* | | | |
| Eye makeup preparations (other) | 3 | — | >5–10 | — |
| Personal cleanliness products (other) | 1 | 1 | >5–10 | — |
| Shaving preparation products (other) | 1 | 1 | >1–5 | — |
| Skin-cleansing creams, lotions, liquids and pads | — | 1 | — | 1 |
| Face and neck skin care preparations | | — | | 3 |

*(Continued on next page)*

**TABLE 18**
Historical and current cosmetic product uses and concentrations for PEG Stearates *(Continued)*

| Product type | 1976 uses (Elder 1983) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1983) (%) | 2002 use concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| Body and hand skin care preparations | —* | 1 | —* | 2 |
| Moisturizers | — | 5 | — | 6 |
| Paste masks (mud packs) | — | 1 | — | 3 |
| Skin care preparations (other) | 4 | 1 | >1–10 | — |
| **Total uses/ranges for PEG-32 Stearate** | **9** | **11** | **>1–10** | **1–6** |
| | *PEG-40 Stearate* | | | |
| Bath preparations (other) | 1 | — | >5–10 | 4 |
| Eyebrow pencil | — | — | — | 5 |
| Eye shadow | — | — | — | 2 |
| Eye lotion | — | — | — | 1–2 |
| Eye makeup remover | — | 1 | — | 0.8–2 |
| Mascara | — | 3 | — | 1 |
| Eye makeup (other) | 4 | 2 | >1–10 | 3–4 |
| Perfumes | — | 8 | — | — |
| Fragrance preparations (other) | 9 | 4 | >1–10 | 2 |
| Hair conditioners | — | 4 | — | 0.5–2 |
| Hair straighteners | — | 2 | — | — |
| Hair tonics, dressings, etc. | — | 1 | — | 2 |
| Hair preparations (other noncoloring) | 5 | — | >5–10 | — |
| Hair lighteners with color | — | — | — | 0.07 |
| Hair bleaches | — | 1 | — | — |
| Hair-coloring preparations (other) | — | 1 | — | — |
| Blushers (all types) | — | — | — | 2 |
| Foundations | — | 6 | — | 2–3 |
| Lipstick | — | — | — | 2 |
| Makeup bases | — | 1 | — | 2–3 |
| Makeup (other) | 42 | 1 | >1–10 | 3 |
| Manicuring preparations (other) | 2 | 1 | >5–10 | 3 |
| Bath soaps and detergents | — | 1 | — | 0.01 |
| Underarm deodorants | — | — | — | 3 |
| Personal cleanliness products (other) | 11 | 3 | >5–10 | |
| Aftershave lotion | — | 15 | — | — |
| Shaving cream | — | 1 | — | — |
| Shaving preparations (other) | 2 | 2 | >1–10 | 3 |
| Skin-cleansing creams, lotions, liquids, and pads | — | 9 | — | 0.8–7 |
| Face and neck skin care preparations | | 8 | | 0.8–3 |
| Body and hand skin care preparations | —* | 27 | —* | 0.8–5 |
| Foot powders and sprays | — | 1 | — | — |
| Moisturizers | — | 34 | — | 2–3 |
| Night skin care preparations | — | 6 | — | 2–3 |
| Paste masks (mud packs) | — | 7 | — | 0.8 |
| Skin care preparations (other) | 19 | 15 | >1–10 | 1–2 |
| Suntan gels, creams, and liquids | 5 | 1 | >5–10 | 0.5–2 |
| Indoor tanning preparations | — | 3 | — | 2 |
| Suntan preparations (other) | — | 1 | — | 2 |
| **Total uses/ranges for PEG-40 Stearate** | **100** | **170** | **>1–10** | **0.07–7** |

*(Continued on next page)*

**TABLE 18**
Historical and current cosmetic product uses and concentrations for PEG Stearates *(Continued)*

| Product type | 1976 uses (Elder 1983) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1983) (%) | 2002 use concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| | *PEG-50 Stearate* | | | |
| Eye makeup preparations (other) | 13 | — | >5–10 | — |
| Hair preparations (other) | 1 | — | >1–5 | — |
| Manicuring preparations (other) | — | — | — | 9 |
| Aftershave lotion | — | 1 | — | — |
| Face and neck skin care preparations | — | 1 | — | — |
| Moisturizers | — | 8 | — | — |
| Night skin care preparations | — | 1 | — | — |
| Skin care preparations (other) | 3 | — | >5–10 | — |
| **Total uses/ranges for PEG-50 Stearate** | **17** | **11** | **>1–10** | **9** |
| | *PEG-55 Stearate* | | | |
| Eyeliner | — | 1 | — | — |
| **Total uses/ranges for PEG-55 Stearate** | **—** | **1** | **—** | **—** |
| | *PEG-75 Stearate* | | | |
| Face and neck skin care preparations | —* | 2 | —* | — |
| Body and hand skin care preparations | | 1 | | — |
| Moisturizers | — | 1 | — | — |
| Night skin care preparations | — | 1 | — | — |
| Skin care preparations (other) | — | 1 | — | — |
| **Total uses/ranges for PEG-75 Stearate** | **—** | **6** | **—** | **—** |
| | *PEG-90 Stearate* | | | |
| Paste masks/mud packs | — | 1 | — | — |
| **Total uses/ranges for PEG-90 Stearate** | **—** | **1** | **—** | **—** |
| | *PEG-100 Stearate* | | | |
| Baby lotions, oils, powders, and creams | — | 5 | — | 1 |
| Baby products (other) | — | — | — | — |
| Bath preparations (other) | — | — | — | 3 |
| Eyebrow pencil | — | 1 | — | — |
| Eyeliner | — | 2 | — | 1 |
| Eye Lotion | — | 3 | — | 0.5–4 |
| Mascara | — | 8 | — | 2–3 |
| Eye makeup (other) | — | 5 | — | 1–3 |
| Perfumes | — | 1 | — | 3 |
| Fragrance preparations (other) | — | 14 | — | — |
| Hair conditioners | — | 30 | — | 0.2–4 |
| Rinses (noncoloring) | — | 2 | — | 0.6 |
| Hair tonics, dressings, etc. | — | 2 | — | — |
| Hair preparations (other noncoloring) | 7 | 5 | >1–10 | 3 |
| Hair dyes and colors | — | 2 | — | — |
| Hair tints | — | 1 | — | — |
| Hair color sprays (aerosol) | — | 1 | — | — |
| Hair lighteners with color | — | 1 | — | — |
| Hair bleaches | — | 2 | — | — |
| Hair-coloring preparations (other) | — | 2 | — | — |
| Foundations | — | 6 | — | 0.5–2 |
| Lipstick | — | — | — | 0.3–5 |

*(Continued on next page)*

**TABLE 18**
Historical and current cosmetic product uses and concentrations for PEG Stearates *(Continued)*

| Product type | 1976 uses (Elder 1983) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1983) (%) | 2002 use concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| Makeup bases | — | 1 | — | — |
| Makeup fixatives | — | 1 | — | — |
| Makeup (other) | — | — | — | 4 |
| Cuticle softeners | — | 2 | — | 3 |
| Nail creams and lotions | — | 1 | — | — |
| Bath soaps and detergents | — | — | — | 0.8 |
| Underarm deodorants | — | 3 | — | 0.5– 25 |
| Personal cleanliness products (other) | 2 | 24 | >5–25 | 2 |
| Aftershave lotion | — | 1 | — | 0.8–2 |
| Shaving preparations (other) | — | 1 | — | 0.8 |
| Skin-cleansing creams, lotions, liquids, and pads | — | 38 | — | 1–5 |
| Face and neck skin care preparations | —* | 25 | —* | 0.3–5 |
| Body and hand skin care preparations | — | 34 | — | 3 |
| Foot powders and sprays | — | 1 | — | — |
| Moisturizers | — | 85 | — | 1–3 |
| Night skin care preparations | — | 20 | — | 0.01–3 |
| Paste masks/mud packs | — | 22 | — | 2–6 |
| Skin fresheners | — | 2 | — | — |
| Skin care preparations (other) | — | 38 | — | 0.9–3 |
| Suntan gels, creams, and liquids | — | 14 | — | 3 |
| Indoor tanning preparations | — | 18 | — | 2–4 |
| **Total uses/ranges for PEG-100 Stearate** | **9** | **431** | **>1–25** | **0.01–25** |
| | *PEG-150 Stearate* | | | |
| Eyeliner | — | — | — | 3 |
| Eye lotion | — | 1 | — | |
| Eye makeup remover | — | — | — | 2 |
| Fragrance preparations (other) | — | 1 | — | — |
| Hair conditioners | — | 3 | — | — |
| Hair straighteners | — | 2 | — | — |
| Shampoos (noncoloring) | — | 3 | — | 0.2 |
| Hair preparations (other noncoloring) | 1 | — | >0.1–1 | 0.4 |
| Blushers (all types) | — | — | — | 1 |
| Rouges | — | — | — | 0.6 |
| Makeup (other) | — | — | — | 3 |
| Manicuring preparations (other) | — | 1 | — | — |
| Bath soaps and detergents | — | — | — | 0.5 |
| Skin-cleansing creams, lotions, liquids, and pads | — | — | — | 2–3 |
| Face and neck skin care preparations | | — | | 2 |
| Body and hand skin care preparations | —* | 3 | —* | 0.8 |
| Foot powders and sprays | — | 1 | — | — |
| Moisturizers | — | 4 | — | 0.8–1 |
| Night skin care preparations | — | 2 | — | 0.5–1 |
| Paste masks/mud packs | — | 1 | — | — |
| Skin fresheners | — | 1 | — | — |
| Skin care preparations (other) | 2 | — | >5–10 | 6 |
| **Total uses/ranges for PEG-150 Stearate** | **3** | **23** | **>0.1–10** | **0.2–6** |

*These categories were combined when the original safety assessment was performed and are now two separate categories.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2002. Use concentration data on peg stearates from industry survey. Unpublished data submitted by CTFA, September 13, 2002. 5 pages.[19]

Cutler, R. R., P. Wilson, and F. V. Clarke. 1987. The effect of polyoxyethylene stearate (POES) on the growth of mycobacteria in radiometric 7H12 Middlebrook TB medium. *Tubercle.* 68:209–220.

Dahlgren, C., and K. E. Magnusson. 1980. Modulation of polymorphonuclear leukocyte locomotion by synthetic amphiphiles. *Scand. J. Infect. Dis. Suppl.* 24:44–47.

Dahlgren, C., I. Rundqvist, O. Stendahl, and K. E. Magnusson. 1980. Modulation of polymorphonuclear leukocyte locomotion by synthetic amphiphiles: Effect of saturated fatty acid esters (C2-C18) of poly(ethyleneglycol) 6000. *Cell Biophys.* 2:253–267.

Elder, R. L., ed. 1983. Final report on the safety assessment of PEG-2, -6, -8, -12, -20, -32, -40, -50, -100, and -150 Stearates. *J. Am. Col. Toxicol.* 2:17–34.

Gowan, W. G., F. Tio, K. Lamp, C. Gowan, and S. Stavchansky. 1986. The effects of Tween 80 MYRJ-52 and polyethylene glycol 8000 on the rate of pentobarbital disappearance cumulative water flux and histological changes in the rat small intestine. *Int. J. Pharm.* 29:169–176.

Hachiya, N. 1987. Evaluation of chemical genotoxicity by a series of short-term tests. *Akita. Igaku.* 14:269–292.

Ismail, S., A. A. Mohamed, and M. G. Abd El-Mohsen. 1989. Modifying effects of polyoxyethylene stearates on the rate of acid-catalyzed hydrolysis of acetylsalicyclic acid. *Bull. Pharm. Sci.* 12:52–67.

Ivanchenko, O. B., O. N. I'inskaya, A. N. Fattakhova, I. M. Skipina, and IE. Cherepneva. 1992. Assessment of genotoxicity of non-ionogenic surfactants. *Biol. Nauki.* 10:75–80.

Kaur, R., D. J. W. Grant, and T. Eaves. 1980. Comparison of polyethylene glycol and polyoxyethylene stearate as excipients for solid dispersion systems of griseofulvin and tolbutamide. Part 1. Phase equilibria. Part 2. Dissolution and solubility studies. *J. Pharm. Sci.* 69:1317–1326.

Kilbanov, A. L., K. Maruyama, V. P Torchilin, and L. Huang. 1990. Ampipathic polyethyleneglycols effectively prolong the circulation time of liposomes. *FEBS Lett.* 268:235–237.

Kobayashi, I. 1989. The screening test for mutagenesis of surfactants, detergents and fluorescent whitening agents. *Gosei Senzai Kenkyukaishi* 12:19–28.

Lee, M. H., C. D. Kim, and H. J. Ahn. 1994. Evaluation of surfactant cytotoxicity potential by neutral red uptake assay, MTT assay and cell protein assay. *Korean J. Toxicol.* 10:215–220.

Lewis, R. W., J. C. McCall, P. A. Botham, and R. Trebilcock. 1994. A comparison of two cytotoxicity tests for predicting the ocular irritancy of surfactants. *Toxicol. In Vitro* 8:867–869.

Margarit, M. V., I. C. Rodriguez, and A. Cerezo. 1992. Myrj 51 as a suppository excipient in fluence on pharmaceutical availability and bioavailability of sodium valproate. *Int. J. Pharm.* 81:67–73.

Miller, M. A., L. Thibert, F. Desjardins, S. H. Siddiqi, and A. Dascal. 1996. Growth inhibition of Mycobacterium tuberculosis by polyoxyethylene stearate present in the BACTEC pyrazinamide susceptibility test. *J. Clin. Microbiol.* 34:84–86.

Pepe, R. C., J. A. Wenninger, and G. N. McEwen Jr., eds. 2002. *International cosmetic ingredient dictionary and handbook*, 9th ed., 1201–1207. Washington, DC: CTFA.

Pienaar, E. W., N. P. Kriek, B. Boneschans, and H. A. Koelman. 1994. Adverse effects of polyethylene glycol and phenytoin on the rectal mucosa of the rat. *Drug Dev. Ind. Pharm.* 20:1493–1502.

Realini, L., P. Van Der Stufyt, K. De Ridder, B. Hirschel, and F. Portaels. 1997. Inhibitory effects of polyoxyethylene stearate, PANTA, and neutral pH on growth of *Mycobacterium genavense* in BACTEC® primary cultures. *J. Clin. Microbiol.* 35:2791–2794.

Salminen, S., and E. Salminen. 1987. Urinary excretion of orally administered oxalic acid in MYRJ-45-treated NMRI mice. *Toxicol. Lett.* 37:91–94.

Satoh, S., Y. Horiguchi, K. Ito, N. Nambu, and T. Nagai. 1985. Irritative effects of suppository bases on the rectal membranes in rabbits. *Arch. Pract. Pharm.* 45:298–303.

Shen, W.-W., A. G. Danti, and F. N. Bruscato. 1976. Effect of nonionic surfactants on percutaneous absorption of salicylic acid and sodium salicylate in the presence of dimethyl sulfoxide. *J. Pharm. Sci.* 65:1780–1783.

Tassett, C., V. Preat, A. Bernard, and M. Roland. 1992. Comparison of nephrotoxicities of different polyoxyethylene formulations of amphotericin B in rats. *Antimicrob. Agent Chemother.* 36:1525–1531.

Tassett, C., V. Preat, and M. Roland. 1991. The influence of Myrj 59 on the solubility, toxicity and activity of amphotericin B. *J. Pharm. Pharmacol.* 43:297–302.

Tatsumi, H., and H. Ritsuko. 1991. A study on the relation between the result of guinea-pig skin irritation test and human patch test with cosmetic ingredients. *Hifu* 33:31–38.

Uraizee, S. A., A. M. McPhillips, A. A. Sakr, and W. A. Ritschel. 1999. Evaluation of absorption enhancers and enzyme inhibitors for the protection of human insulin: screening study. *Pharm. Ind.* 61:259–262.

## POLYAMINO SUGAR CONDENSATE

A safety assessment of Polyamino Sugar Condensate was published in 1982 (Elder 1982). New studies since then (listed at the end of this review), along with the updated information below regarding types and concentrations of use, were considered by the CIR Expert Panel. The Panel determined not to reopen this safety assessment.

In 1976 Polyamino Sugar Condensate was reported to be used in 111 cosmetic preparations with the largest single use occurring in moisturizers at concentrations of ≤0.1% to 1%. As reported to the FDA (FDA 2001), Polyamino Sugar Condensate is currently used in 25 cosmetic preparations; however, according to an industry survey (CTFA 2001), Polyamino Sugar Condensate is not currently used in cosmetic preparations. Table 19 presents the available use information.

A study by Peterson et al. (1986) demonstrated that Polyamino Sugar Condensate was absorbed into the stratum corneum and epidermis of athymic nude mice grafted with human skin. Although this information was new, the Expert Panel noted that Polyamino Sugar Condensate is a sugar–amino acid expected to be metabolized to sugars and amino acids. Because the original safety assessment fully discussed the potential production of nitrosamines during the manufacture of Polyamino Sugar Condensate, no further discussion was warranted.

## REFERENCES

CTFA. 2002. Product use concentration information for Polyamino Sugar Condensate; memorandum dated January 22. Unpublished data.[20]

Baker, C. G., R. D. Berg, and E. S. Curtis. 1987. Formulating with NMF (normal moisturizing factor). *Drug Cosmet. Ind.* 140:32–39.

Elder, R. L., ed., 1982. Final report on the safety assessment of Polyamino Sugar Condensate. *J. Am. Col. Toxicol.* 1:25–32.

[19]Available from the Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

[20]Available from the Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

**TABLE 19**
Historical and current cosmetic product uses and concentrations for Polyamino Sugar Condensate

| Product type | 1976 uses (Elder 1982) | 2001 uses (FDA 2001) | 1976 use concentrations (Elder 1982) (%) | 2001 use concentrations (CTFA 2001) (%) |
|---|---|---|---|---|
| Eye makeup (other) | 1 | 4 | ≤0.1 | — |
| Shampoos (noncoloring) | 1 | — | ≤0.1 | — |
| Blushers | 6 | — | ≤0.1 | — |
| Face powders | 2 | — | ≤0.1 | — |
| Foundations | 8 | — | ≤0.1–1 | — |
| Leg and body paints | 1 | — | >0.1–1 | — |
| Lipstick | 1 | — | >0.1–1 | — |
| Makeup bases | 5 | — | ≤0.1–1 | — |
| Rouges | 4 | — | ≤0.1 | — |
| Makeup fixatives | 1 | — | ≤0.1 | — |
| Makeup (other) | 1 | — | ≤0.1 | — |
| Cuticle softeners | 1 | — | >0.1–1 | — |
| Nail creams and lotions | 1 | — | ≤0.1 | — |
| Aftershave lotion | 2 | — | ≤0.1–1 | — |
| Skin-cleansing creams, lotions, liquids, and pads | 6 | 2 | >0.1–1 | — |
| Face and neck skin care preparations | 12* | 1 | ≤0.1–1* | — |
| Body and hand skin care preparations | | 4 | | — |
| Moisturizers | 26 | 9 | ≤0.1–1 | — |
| Night skin care preparations | 20 | 1 | ≤0.1–1 | — |
| Paste masks/mud packs | 3 | 1 | ≤0.1–1 | — |
| Skin fresheners | 1 | — | >0.1–1 | — |
| Skin care preparations (other) | 8 | 2 | ≤0.1–1 | — |
| Suntan gels, creams, and liquids | | 1 | | — |
| **Total uses/ranges for Polyamino Sugar Condensate** | **111** | **25** | **≤0.1–1** | **—** |

*This category was combined when the original safety assessment was performed and is now two separate categories.

Food and Drug Administration (FDA). 2001. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

Peterson, R. V., et al. 1986. Athymic nude mouse grafted with human skin as a model for evaluating the safety and effectiveness of radiolabeled cosmetic ingredients. *J. Soc. Cosmet. Chem.* 37:249–265.

Wenninger, J. A., R. C. Canterbery, and G. N. McEwen. Jr., eds. 2000. *International Cosmetic Ingredient Dictionary and Handbook*, 8th ed., 1114–1115. Washington, DC: CTFA.

## POLYBUTENE

In 1982, CIR issued a Final Report that Polybutenes are safe as presently used in cosmetics (Elder 1982). One new inhalation toxicity study was reported since then (Skyberg et al. 1990). This new study, along with the updated information below regarding types and concentrations of use, were considered by the CIR Expert Panel. The Panel determined not to reopen this safety assessment.

In 1976 Polybutene was reported to be used in 84 cosmetic preparations, with the largest single use occurring in lipstick at concentrations of >1% to >50%. As reported to the FDA (FDA 2001), Polybutene is currently used in 253 products, with lipstick again the largest category and highest concentration, according to an industry survey (CTFA 2001). Table 20 presents the available use information.

The Panel noted that use concentration has increased overall and may currently be as high as 92% in some lipstick products, but that the available data demonstrate that this ingredient is not absorbed in the skin or the gut. The levels of Polybutene that are toxic via an inhalation route are not reached in cosmetics, and there are no aerosolized cosmetic products that contain Polybutene.

## REFERENCES

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2002. Product use concentration information for Polybutene. Unpublished data submitted by CTFA.[21]

[21]Available from the Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036.

**TABLE 20**
Historical and current cosmetic product uses and concentrations for Polybutene

| Product type | 1976 uses (Elder 1982) | 2001 uses (FDA 2001) | 1976 use concentrations (Elder 1982) (%) | 2001 uses concentrations (CTFA 2001) (%) |
|---|---|---|---|---|
| Bath preparations (other) | — | — | — | 0.002 |
| Eyebrow pencil | — | 3 | — | 3 |
| Eyeliner | — | 3 | — | 4 |
| Eye shadow | 10 | 8 | >1–5 | 8.4–36 |
| Mascara | — | 51 | — | 2–5 |
| Eye makeup (other) | — | 6 | — | 2–36 |
| Fragrance preparations (other) | — | — | — | 14 |
| Noncoloring shampoos | 2 | — | >5–10 | 0.9 |
| Blushers | — | — | — | 10 |
| Face powders | — | 1 | — | 2–3 |
| Foundations | — | 5 | — | 8 |
| Lipstick | 70 | 151 | >1–>50 | 0.6–92 |
| Makeup preparations (other) | — | 19 | >10–25 | 6–87 |
| Personal cleanliness products (other) | — | — | — | 16 |
| Moisturizers | 1 | 3 | >1–5 | — |
| Night skin care preparations | 1 | — | >10–25 | — |
| Skin care preparations (other) | — | 2 | — | 6–16 |
| Suntan preparations (other) | — | 1 | — | — |
| **Total uses/ranges for Polybutene** | **84** | **253** | **>1–>50** | **0.002–92** |

Elder, R. L. ed. 1982. Final report on the safety assessment of Polybutene. *J. Am. Col. Toxicol.* 1:103–118.

Food and Drug Administration (FDA). 2001. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

Skyberg, K., V. Skaug, B., Gylseth, J. R. Pedersen, and O. H. Iversen. 1990. Subacute inhalation toxicity of mineral oils, C15-C20 alkylbenzenes, and polybutene in male rats. *Environ. Res.* 53:48–61.

Wenninger, J. A., R. C. Canterbery, and G. N. McEwen, Jr., eds. 2000. *International Cosmetic Ingredient Dictionary and Handbook*, 8th ed., 1114–1115. Washington, DC: CTFA.

## POLYQUATERNIUM-11

In 1983, CIR issued a Final Report that Polyquaternium-11 is safe as a cosmetic ingredient in the present practices of use (Elder 1983). A review of the recent literature on Polyquaternium-11 uncovered no new studies. Updated information below regarding types and concentrations of use were considered by the CIR Expert Panel. The Panel determined not to reopen this safety assessment.

In 1976 Polyquaternium-11 was reported to be used in 131 cosmetic preparations with the largest single use occurring in hair conditioners at concentrations of ≤25%. As reported to the FDA (FDA, 2001), Polyquaternium-11 is currently used in 254 products, with hair tonics, dressings, etc., as the largest category with a concentration range of 0.05–10%, according to an industry survey (CTFA 2001). Table 21 presents the available use information.

### REFERENCES

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2001. Product use concentration information for Polybutene. Unpublished data submitted by CTFA.[22]

Elder, R. L., ed. 1983. Final report on the safety assessment of Polyquaternium-11. *J. Am. Col. Toxicol.* 2:161–178.

Food and Drug Administration (FDA). 2001. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

## POTASSIUM COCOYL HYDROLYZED COLLAGEN AND TRIETHANOLAMINE COCOYL HYDROLYZED COLLAGEN

A Safety Assessment of Potassium-Coco-Hydrolyzed Animal Protein and Triethanolamine-Coco-Hydrolyzed Animal Protein was published in 1983 (Elder 1983). Based on the data available at that time, the Panel concluded that these compounds were "safe as cosmetic ingredients in the present practices of use."

The names these two compounds as listed in the *International Cosmetic Ingredient Dictionary and Handbook* have been

[22]Available from the Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

**TABLE 21**
Historical and current cosmetic product uses and concentrations for Polyquarternium-11

| Product type | 1976 uses (Elder 1983) | 2001 uses (FDA 2001) | 1976 use concentrations (Elder 1983) (%) | 2001 uses concentrations (CTFA 2001) (%) |
|---|---|---|---|---|
| Baby products (other) | 1 | — | 1–5 | — |
| Bath preparations (other) | — | 1 | — | — |
| Mascara | — | 1 | — | — |
| Hair conditioners | 49 | 69 | 0–25 | 0.8–3 |
| Hair sprays (aerosol fixatives) | 2 | — | 1–5 | 2 |
| Permanent waves | 7 | 14 | 0.1–10 | — |
| Rinses (noncoloring) | 5 | 1 | 0–5 | 0.8 |
| Shampoos (noncoloring) | 8 | 24 | 0.1–5 | 0.05–4 |
| Hair tonics, dressings, etc. | 3 | 88 | 1–5 | 0.05–10 |
| Wave sets | 23 | 8 | 0.1–50 | 2–3 |
| Hair preparations (other noncoloring) | 12 | 37 | 0–25 | 0.1–4 |
| Hair dyes and colors | 5 | — | 0.1–1 | — |
| Hair tints | — | 4 | — | — |
| Hair rinses (coloring) | 4 | — | 0.1–1 | — |
| Hair-bleaches | 1 | 3 | 0.1–1 | — |
| Hair-coloring preparations (other) | 1 | | 0.1–1 | 0.3 |
| Personal cleanliness products (other) | — | 1 | — | 12 |
| Shaving cream | 5 | 2 | 0.1–1 | — |
| Skin-cleansing creams, lotions, liquids, and pads | — | — | — | 0.4 |
| Face and neck skin care preparations | | — | — | 0.05 |
| Moisturizers | 1 | — | 0.1–1 | — |
| Night skin care preparations | 1 | — | 0.1–1 | 0.05 |
| Paste masks (mud packs) | 1 | — | 10–25 | 4 |
| Skin fresheners | 2 | 1 | 0–0.1 | — |
| **Total uses/ranges for Polyquaternium-11** | **131** | **254** | **$\leq$25** | **0.05–10** |

changed to Potassium Cocoyl Hydrolyzed Collagen (CAS no. 68920-65-0) and Triethanolamine Cocoyl Hydrolyzed Collagen (CAS no. 68952-16-9), respectively (Pepe et al. 2002).

A search of the scientific literature databases to identify any new safety data relevant to the cosmetic use of Potassium Cocoyl Hydrolyzed Collagen and Triethanolamine Cocoyl Hydrolyzed Collagen yielded no new safety or toxicity data on either compound. The only new information related to these compounds is the updated frequency of use, as voluntarily reported by the industry to the FDA and shown in Table 22. The CIR Expert Panel considered these new uses and determined to not reopen this safety assessment.

Potassium-Coco-Hydrolyzed Animal Protein was used in 251 cosmetic products in 1981, with the highest concentration at 50% in non-coloring shampoos. In 2002, Potassium Cocoyl Hydrolyzed Collagen was used in 64 cosmetic products, with the highest concentration at 20% in noncoloring shampoo.

Triethanolamine-Coco-Hydrolyzed was used in 18 cosmetic products in 1981, with the highest concentration at 50% in noncoloring shampoos. In 2002, Triethanolamine Cocoyl Hydrolyzed Collagen was reported to FDA as used in 21 cosmetic products (FDA 2002), but an industry survey of current use concentrations did not provide any information (CTFA 2002).

The CIR Expert Panel acknowledged the new use of Triethanolamine Cocoyl Hydrolyzed Collagen in aerosol hair sprays. The effects of inhaled aerosols depend on the specific chemical species, the concentration, the duration of exposure, and site of deposition within the respiratory system. Particle size is the most important factor affecting the location of deposition (Jensen and O'Brien 1993). The mean aerodynamic diameter of pump hair spray particles is $\geq$80 $\mu$, and the diameter of anhydrous hair spray particles is 60 to 80 $\mu$. Typically less than 1% are below 10 $\mu$, which is the upper limit for respirable particles (Bower 1999). Based on the particle size, Triethanolamine Cocoyl Hydrolyzed Collagen would not be respirable in formulation. Therefore, the Panel was not concerned about the lack of inhalation toxicity data.

The Panel also noted that the hydrolyzed protein would not absorb into human tissues, thus further reducing the risk of toxicity.

**TABLE 22**
Historic and current use of Potassium Cocoyl Hydrolyzed Collagen and Triethanolamine (TEA) Cocoyl Hydrolyzed Collagen

| Product type | 1976 uses (Elder 1983) | 2001 uses (FDA 2001) | 1976 use concentrations (Elder 1983) (%) | 2001 uses concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| *Potassium Cocoyl Hydrolyzed Collagen* | | | | |
| Bubble baths | 6 | — | >1–5 | — |
| Bath preparations (other) | 1 | — | >1–5 | — |
| Hair conditioners | 4 | — | >1–10 | — |
| Hair straighteners | 12 | 2 | ≤0.1–1 | — |
| Permanent waves | 55 | 18 | ≤0.1–5 | 1 |
| Shampoos (noncoloring) | 33 | 6 | ≤0.1–50 | 1–20 |
| Hair tonics, dressings, etc. | 6 | 2 | ≤0.1–5 | — |
| Wave sets | 1 | — | >1–5 | — |
| Hair preparations (other noncoloring) | 3 | 1 | >1–5 | — |
| Hair dyes and colors | 43 | 21 | >1–10 | 5 |
| Hair tints | — | 9 | — | — |
| Hair lighteners with color | 1 | — | >1–5 | — |
| Hair bleaches | 1 | — | >1–5 | — |
| Nail creams and lotions | — | — | — | 0.05 |
| Nail polish and enamel | 74 | — | ≤0.1 | — |
| Manicuring preparations (other) | 6 | — | ≤0.1–5 | — |
| Shaving preparations (other) | — | 1 | — | — |
| Skin cleansing creams, lotions, liquids, and pads | 3 | 3 | >1–50 | — |
| Face and neck skin care preparations | 1* | — | >1–5* | — |
| Body and hand skin care preparations | | — | | — |
| Moisturizers | — | 1 | — | 0.2 |
| Skin care preparations (other) | 1 | — | >0.1–1 | — |
| **Total uses/ranges for Potassium Cocoyl Hydrolyzed Collagen** | **251** | **64** | **≤0.1–50** | **0.05–20** |
| *Triethanolamine (TEA) Cocoyl Hydrolyzed Collagen* | | | | |
| Baby shampoos | — | 1 | — | — |
| Bath oils, tablets, and salts | — | 1 | — | — |
| Bubble Baths | — | 3 | — | 1 |
| Perfumes | — | 1 | — | — |
| Hair conditioners | 3 | 1 | >1–5 | — |
| Hair sprays (aerosol fixatives) | — | 1 | — | — |
| Permanent waves | — | 2 | — | — |
| Shampoos (noncoloring) | 11 | 3 | ≤0.1–50 | — |
| Hair tonics, dressings, etc. | 1 | — | >1–5 | — |
| Foundations | — | 1 | — | — |
| Cuticle softeners | 1 | — | ≤0.1 | — |
| Bath soaps and detergents | 1 | — | >1–5 | — |
| Personal cleanliness products (other) | — | 1 | — | — |
| Shaving cream | — | 1 | — | — |
| Skin-cleansing creams, lotions, liquids, and pads | — | 4 | — | — |
| Skin care preparations (other) | 1 | — | >1–5 | — |
| **Total uses/ranges for Triethanolamine (TEA) Cocoyl Hydrolyzed Collagen** | **18** | **20** | **0.1–50** | **—** |

*This category was combined when the original safety assessment was performed and is now two separate categories.

As with all cosmetic ingredients derived from animal tissues, Potassium Cocoyl Hydrolyzed Collagen and Triethanolamine Cocoyl Hydrolyzed Collagen, as used in cosmetic products, must be free of detectable pathogenic viruses, prions, or other pathogenic agents.

## REFERENCES

Bower, D. 1999. Unpublished information on hair spray particle size provided at the September 9, 1999, CIR Expert Panel meeting.[23]

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2002. Ingredient use data—potassium cocoyl hydrolyzed collagen. Unpublished data submitted by CTFA.[23]

Elder, R. L. 1983. Final report on the safety assessment of potassium-coco-hydrolyzed animal protein and triethanolamine-coco-hydrolyzed animal protein. *J. Am. Col. Toxicol.* 2:75–86.

FDA. 2002. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

Jensen, P. A., and D. O'Brien. 1993. Industrial Hygiene. In ed. K. Willeke, and P. A. Baron, 538–540. *Aerosol measurement. Principles techniques and applications*, New York: John Wiley and Sons.

Pepe, R. C., J. A. Wenninger, and G. N. McEwen, Jr., eds. 2002. *International Cosmetic Ingredient Dictionary and Handbook*, 9th ed., vol. 2, 1336, 1689. Washington, DC: CTFA.

## PROPYLENE GLYCOL STEARATE/PROPYLENE GLYCOL STEARATE SE

A Safety assessment of Propylene Glycol Stearate/Propylene Glycol Stearate Self-Emulsifying was published in 1983 (Elder 1983). Only one new study has been reported since then. This new study, along with the updated information below regarding types and concentrations of use, was considered by the CIR Expert Panel. After this review, the Panel determined that there was no need to reopen the safety assessment.

Data from the 1983 report on frequency of use and concentration of use (circa, 1976) is provided in Table 23, along with current frequency of use and total products in each category as provided by the FDA (FDA, 2002). An industry survey (CTFA 2002) uncovered no current concentrations of use of these ingredients.

In 1976, Propylene Glycol Stearate was used in 401 cosmetic preparations; currently Propylene Glycol Stearate is used in 193 cosmetic preparations. Eleven new product categories appeared in 2002.

Concentration of use in 1976 for Propylene Glycol Stearate ranged from 0.1% to 25%. In 1976, Propylene Glycol Stearate SE was reported in 131 cosmetic formulations; currently Propylene Glycol Stearate SE is used in 60 cosmetic formulations. Eight new product use categories appeared in 2002. Concentrations of use in 1976 for Propylene Glycol Stearate SE ranged from less than or equal to 0.1% to 25%.

[23]Available from the Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

## REFERENCES

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2002. Ingredient use data—potassium cocoyl hydrolyzed collagen. Unpublished data submitted by CTFA.[24]

Elder, R. L. ed. 1983. Final report on the safety assessment of Propylene Glycol Stearate and Propylene Glycol Stearate Self-Emulsifying. *J. Am. Col. Toxicol.* 2:101–124.

Fulton, J. E., and S. R. Pay. 1984. Comedogenicity of current therapeutic products, cosmetics, and ingredients in the rabbit ear. *J. Am. Acad. Dermatol*. 10:96–105.

Pepe, R. C., J. A. Wenninger, and G. N. McEwen, Jr. eds. 2002. *International Cosmetic Ingredient Dictionary and Handbook*, 9th ed., vol 1–4, 1418. Washington, DC: CTFA.

## SODIUM LAURETH SULFATE AND AMMONIUM LAURETH SULFATE

A Safety assessment of Sodium Laureth Sulfate and Ammonium Laureth Sulfate was published in 1982 (Elder 1982). New studies since then are listed at the end of this review. These new studies along with the updated information below regarding types and concentrations of use were considered by the CIR Expert Panel. After this review, the Panel determined that there was no need to reopen the safety assessment.

Data from the 1983 report on frequency of use and concentration of use (circa 1976) is provided in Table 24, along with current frequency of use and total products in each category as provided by the FDA (FDA 2002). Current concentration of use data from an industry survey are also provided (CTFA 2002).

In 1976, Sodium Laureth Sulfate was used in 282 cosmetic preparations, with the largest use in noncoloring shampoos at concentrations ranging from >1% to >50%. According to reports to FDA, Sodium Laureth Sulfate is reportedly now used in 952 cosmetic preparations (FDA 2002), with the largest use in shampoos at 11% to 50% (CTFA 2002). This ingredient is used in 23 product categories in 2002 that were not in the 1976 FDA data.

In 1976, Ammonium Laureth Sulfate was used in 63 cosmetic preparations, with the largest use in hair dyes and colors at >5% to 25%. Currently Ammonium Laureth Sulfate is used in 244 cosmetic preparations, with the largest use in shampoos at >0.1% to >50%. This ingredient was used in 11 product categories in 2002 that were not in the 1976 FDA data.

The Panel reiterated that the previously existing and the new data demonstrate the irritancy of Sodium Laureth Sulfate and Ammonium Laureth Sulfate in leave on products. The available data do suggest that these ingredients are toxic in animal tests via inhalation exposure and they are used in products that may be aerosolized.

The effects of inhaled aerosols in humans depend on the specific chemical species, the concentration, the duration of

[24]Available from the Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

**TABLE 23**
Historic and current use of Propylene Glycol Stearate and Propylene Glycol Stearate SE

| Product type | 1976 uses (Elder 1983) | 2001 uses (FDA 2001) | 1976 use concentrations (Elder 1983) (%) | 2002 uses concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| | *Propylene Glycol Stearate* | | | |
| Bath preparation (other) | 1 | 1 | >1–5 | — |
| Eyebrow pencil | 7 | — | >10–25 | — |
| Eyeshadow | 63 | 1 | >0.1–5 | — |
| Eye lotion | 13 | 3 | >1–5 | — |
| Mascara | 7 | 10 | >1–5 | — |
| Eye makeup (other) | 3 | 3 | >1–5 | — |
| Colognes and toilet waters | 1 | — | >0.1–1 | — |
| Perfume | — | 9 | — | — |
| Sachets | 4 | 4 | >1–5 | — |
| Fragrance preparations (other) | — | 13 | — | — |
| Hair conditioners | 1 | 4 | >1–5 | — |
| Rinses (noncoloring) | 4 | — | >0.1–1 | — |
| Shampoos (noncoloring) | 1 | — | >1–5 | — |
| Hair tonics, dressings, etc. | — | 1 | — | — |
| Hair preparations (other) | — | 1 | — | — |
| Blusher (all types) | 36 | — | >0.1–5 | — |
| Foundation | 28 | 19 | >0.1–10 | — |
| Leg and body paint | 15 | — | >1–5 | — |
| Lipstick | 3 | 2 | >1–25 | — |
| Makeup bases | 141 | 31 | >0.1–10 | — |
| Rouges | 3 | 1 | >1–10 | — |
| Makeup fixatives | — | 2 | — | — |
| Makeup (other) | 6 | 6 | >1–10 | — |
| Manicuring preparations | 1 | — | >5–10 | — |
| Personal cleanliness products (other) | — | 1 | — | — |
| Aftershave lotion | — | 2 | — | — |
| Shaving cream | 1 | 7 | >1–5 | — |
| Shaving preparations (other) | — | 2 | — | — |
| Skin-cleansing creams, lotions, liquids, and pads | — | 4 | — | — |
| Face and neck skin care preparations | | 3 | | — |
| Body and hand skin care preparations | 28* | 18 | >0.1–5* | — |
| Hormone skin preparations | 2 | N/A** | >1–5 | N/A** |
| Moisturizers | 22 | 31 | >0.1–5 | — |
| Night skin care preparations | 2 | 4 | >1–5 | — |
| Paste masks/mud packs | — | 2 | — | — |
| Skin care preparations (other) | 2 | 7 | >0.1–5 | — |
| Suntan gels, creams, and liquids | 2 | — | >0.1–5 | — |
| Indoor tanning preparations | — | 1 | — | — |
| **Total uses/ranges for Propylene Glycol Stearate** | **401** | **193** | **>0.1–25** | — |
| | *Propylene Glycol Stearate SE* | | | |
| Eyeshadow | 15 | 1 | >1–5 | — |
| Mascara | — | 3 | — | — |
| Eye makeup (other) | — | 1 | — | — |
| Hair tonics, dressings, etc. | 1 | — | >1–5 | — |
| Blushers (all types) | 12 | 2 | >1–5 | — |

*(Continued on next page)*

**TABLE 23**
Historic and current use of Propylene Glycol Stearate and Propylene Glycol Stearate SE *(Continued)*

| Product type | 1976 uses (Elder 1983) | 2001 uses (FDA 2001) | 1976 use concentrations (Elder 1983) (%) | 2002 uses concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| Face powder | — | 1 | — | — |
| Foundations | 2 | 29 | >1–5 | — |
| Lipstick | — | 1 | — | — |
| Makeup bases | 76 | 2 | >1–5 | — |
| Makeup fixatives | — | 2 | — | — |
| Makeup (other) | 5 | 1 | >1–5 | — |
| Shaving cream | 1 | — | >1–5 | — |
| Skin-cleansing creams, lotions, liquids, and pads | 1 | — | ≤0.1 | — |
| Face and neck skin care preparations | | 2 | | — |
| Body and hand skin care preparations | 6* | 2 | >0.1–25* | — |
| Moisturizers | 7 | 6 | >0.1–5 | — |
| Night skin care preparations | — | 4 | — | — |
| Paste masks/mud packs | — | 1 | — | — |
| Skin freshener | — | 1 | — | — |
| Skin lighteners | 3 | N/A** | >1–5 | N/A** |
| Skin care preparation (other) | 1 | — | >1–5 | — |
| Suntan gels, creams, and liquids | 1 | 1 | >1–5 | — |
| **Total uses/ranges for Propylene Glycol Stearate SE** | **131** | **60** | **>0.1–5** | **—** |

*This category was combined when the original safety assessment was performed and is now two separate categories.
**No longer considered a cosmetic product category.

exposure, and site of deposition within the respiratory system. Particle size is the most important factor affecting the location of deposition (Jensen and O'Brien 1993). The mean aerodynamic diameter of pump hair spray particles is $\geq 80\ \mu$, and the diameter of anhydrous hair spray particles is 60 to 80 $\mu$. Typically less than 1% are below 10 $\mu$ which is the upper limit for respirable particles (Bower 1999). Based on the particle size, these ingredients would not be respirable in formulation.

## REFERENCES


Archuleta, M. M. 1995. *Aqueous foam toxicology evaluation and hazard review*. Albuquerque, NM: Sandia National Labs.

Bahl, M. K. 1985. ESCA studies on the skin lipid removal by solvents and surfactants. *J. Soc. Cosmet. Chem.* 36:287–296.

Bernhofer, L. P., M. Seiberg, and K. M. Martin. 1999. The influence of the response of skin equivalent systems to topically applied consumer products by epithelial-mesenchymal interactions. *Toxicol In Vitro* 13:219–229.

Bower, D. 1999. Unpublished information on hair spray particle size provided at the September 9, 1999, CIR Expert Panel meeting.[25]

Charbonnier, V., B. M. Morrison, Jr., M. Paye, and H. I. Maibach. 2000. An open assay model to induce subclinical non-erythematous irritation. *Contact Dermatitis.* 42:207–211.

Charbonnier, V., B. M. Morrison, Jr., Paye, M., and Maibach, H. I. 2001. Subclinical, non-erythematous irritation with an open assay model (washing): sodium lauryl sulfate (SLS) versus sodium laureth sulfate (SLES) *Food Chem. Toxicol.* 39:279–286.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2002. Ingredient use data. Unpublished data submitted by CTFA.[25]

Dillarstone, A., and M. Paye. 1993. Antagonism in concentrated surfactant system. *Contact Dermatitis* 28:198.

Elder, R. L. ed. 1982. Final Report on the Safety Assessment Sodium Laureth Sulfate and Ammonium Laureth Sulfate. *J. Am. Col. Toxicol*. 2:1–34.

Food and Drug Administration (FDA). 2002. Cosmetic product formulation data. *FDA database.* Washington, DC: FDA.

Gettings, S. D., R. A. Lordo, P. I. Feder, and K. L. Hintze. 1998. A comparison of Low Volume, Draize and *in vitro* eye irritation data. III. Surfactant-based formulations. *Food Chem. Toxicol.* 36:209–231.

Jensen, P. A., and D. O'Brien. 1993. Industrial Hygiene. In ed. Willeke K. and P. A. Baron, 538–540. *Aerosol measurement. Principles techniques and applications*, New York: John Wiley and Sons.

Koyama, K., Y. Kasuya, K. Koyama, and Goto, K. 1997. Nitric oxide-mediated vasorelaxation induced by sodium polyoxyethylene laurylether sulfate. *Toxicol. Appl. Pharm.* 145:294–300.

Osgood, T. B., J. L. Ubels, G. A. Smith, and C. E. Dick. 1990. Evaluation of ocular irritancy of hair care products. *J. Toxicol. Cutan. Ocul. Toxicol.* 9:37–51.

Stern, M., M. Klausner, R. Alvarado, K. Renskers, and M. Dickens. 1998. Evaluation of the EpiOcular™ Tissue Model as an alternative to the Draize eye irritation test. *Toxicol. In Vitro* 12:455–461.

Tachon, P., K. Cotovio, K. G. Dossou, and M. Prunieras. 1989. Assessment of surfactant cytotoxicity: Comparison with Draize eye test. *Int. J. Cosmet. Sci.* 11:233–243.


[25]Available from the Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

**TABLE 24**
Historic and current use of Sodium Laureth Sulfate and Ammonium Laureth Sulfate

| Product type | 1976 uses (Elder 1982) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1982) (%) | 2002 uses concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| *Ammonium Laureth Sulfate* | | | | |
| Baby shampoo | 1 | 1 | >5–10 | — |
| Baby products (other) | — | 1 | — | — |
| Bath oils, tablets, and salts | — | 1 | — | 10 |
| Bubble baths | 6 | 45 | >0.1–50 | — |
| Hair conditioners | — | 2 | — | — |
| Permanent waves | — | 1 | — | — |
| Rinses (noncoloring) | 1 | 4 | >0.1–1 | — |
| Shampoos (noncoloring) | 23 | 149 | >0.1–>50 | 7–36 |
| Hair tonics, dressings, etc. | — | 1 | — | — |
| Hair preparations (other) | — | 6 | — | — |
| Hair dyes and colors | 31 | — | >5–25 | 5 |
| Makeup bases | — | 2 | — | — |
| Bath soaps and detergents | 1 | 16 | >10–25 | 1–20 |
| Skin-cleansing creams, lotions, liquids and pads | — | 9 | — | 1–30 |
| Face and neck skin care preparations | —* | 2 | —* | |
| Body and hand skin care preparations | | 2 | | 8 |
| Paste masks (mud packs) | — | 2 | — | — |
| **Total uses/ranges for Ammonium Laureth Sulfate** | **63** | **244** | **>0.1–50** | **1–36** |
| *Sodium Laureth Sulfate* | | | | |
| Baby shampoo | — | 9 | — | 10 |
| Baby products (other) | 2 | 6 | >5–10 | 5–25 |
| Bath oils, tablets, and salts | 11 | 7 | >25–>50 | 14 |
| Bubble baths | 59 | 82 | >5–>50 | 6–24 |
| Bath capsules | — | 1 | — | — |
| Bath preparations (other) | 78 | 68 | >1–>50 | 6–19 |
| Eyeliner | — | 2 | — | — |
| Eye makeup remover | 1 | 14 | >1–5 | 0.1 |
| Mascara | — | 8 | — | 0.1–0.3 |
| Eye makeup (other) | — | 1 | — | — |
| Powders | — | — | — | 0.6 |
| Fragrance preparations (other) | — | 6 | — | 18 |
| Hair conditioners | — | 2 | — | 0.7 |
| Permanent waves | 13 | 2 | >0.1–25 | 0.6 |
| Rinses (noncoloring) | 1 | 1 | >1–5 | — |
| Shampoos (noncoloring) | 89 | 378 | >1–>50 | 11–50 |
| Hair tonics, dressings, etc. | — | 4 | — | — |
| Hair preparations (other noncoloring) | — | 4 | — | — |
| Hair dyes and colors | 2 | 40 | >5–10 | 3–10 |
| Hair bleaches | 1 | — | >5–10 | — |
| Shampoos (coloring) | — | 9 | — | — |
| Hair-coloring preparations (other) | — | 1 | — | 14 |
| Foundations | — | 1 | — | — |
| Makeup bases | — | 1 | — | — |
| Makeup (other) | — | — | — | 15 |
| Nail polish and enamel removers | — | 1 | — | 0.6 |

*(Continued on next page)*

**TABLE 24**
Historic and current use of Sodium Laureth Sulfate and Ammonium Laureth Sulfate *(Continued)*

| Product type | 1976 uses (Elder 1982) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1982) (%) | 2002 uses concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| Bath soaps and detergents | 4 | 102 | >10–25 | 2–47 |
| Feminine hygiene deodorant | — | — | — | 7 |
| Personal cleanliness products (other) | 2 | 62 | >1–5 | 13–16 |
| Aftershave lotion | — | 2 | — | — |
| Shaving cream | — | 2 | — | 1–5 |
| Skin-cleansing creams, lotions, liquids and pads | 19 | 95 | >1–50 | 0.6–25 |
| Face and neck skin care preparations | —* | 8 | —* | — |
| Body and hand skin care preparations | | 6 | | 11–17 |
| Depilatories | 9 | — | ≤0.1–10 | — |
| Foot and powder and sprays | — | 3 | — | 11 |
| Moisturizers | — | 4 | — | 0.5 |
| Paste masks (mud packs) | — | 4 | — | — |
| Skin fresheners | 1 | 1 | >0.1–1 | — |
| Skin care preparations (other) | — | 12 | — | 0.4–11 |
| Suntan gels, creams, and liquids | — | 1 | — | — |
| **Total uses/ranges for Sodium Laureth Sulfate** | **282** | **952** | **≤0.1–>50** | **0.1–50** |

*This category was combined when the original safety assessment was performed and is now two separate categories.

Tani, N., S. Kinoshita, Y. Okamoto, M. Kotani, H. Itagaki, N. Murakami, S. Sugiura, M. Usami, K. Kato, H. Kojima, T. Ohno, K. Saijo, M. Kato, M. Hayashi, and Y. Ohno. 1999. Interlaboratory validation of the *in vitro* eye irritation tests for cosmetic ingredients (8) evaluation of cytotoxicity tests on SIRC cells. *Toxicol. In Vitro* 13:175–187.

Tavss, E. A., E. Eigen, and A. M. Klingman. 1985. Anionic surfactants. *J. Soc. Cosmet.* 36:251–254.

Waldman, B. A. 1982. Analysis of 1,4-dioxane in ethoxylated compounds by gas chromatography/mass spectrometry using selected ion monitoring. *J. Soc. Cosmet. Chem.* 33:19–25.

Wenninger, J. A., and G. N. McEwen, Jr., eds. 2002. *International Cosmetic Ingredient Dictionary and Handbook*, 9th ed., vol. 1–4, 101, 1569. Washington, DC: CTFA.

## SODIUM LAURYL SULFATE AND AMMONIUM LAURYL SULFATE

A safety assessment of Sodium Lauryl Sulfate (SLS) and Ammonium Lauryl Sulfate was published in 1983 (Elder 1983) with the conclusion that "Sodium Lauryl Sulfate and Ammonium Lauryl Sulfate appear to be safe in formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin. In products intended for prolonged contact with skin, concentrations should not exceed 1%."

Over 250 scientific research studies conducted since the original safety assessment was published are listed at the end of this review. These new studies, along with the updated information below regarding types and concentrations of use, were considered by the CIR Expert Panel. In addition, the Panel acknowledged the Internet rumor that these ingredients are carcinogenic. After this review, however, the Panel determined to not reopen this safety assessment.

SLS was used in 703 cosmetic products in 1981, with the highest usage in the noncoloring shampoo category at a maximum concentration of >50%. SLS currently is used in 1018 cosmetic products, with the single largest use in hair dyes and colors, at concentrations from 0.2% to 20%. The maximum current concentration of SLS is 50%, in noncoloring shampoos. Table 25 presents the available use information for SLS.

Ammonium Lauryl Sulfate was used in 164 cosmetic products in 1981, with the highest concentration range from >0.1% to 50% in noncoloring shampoos. Ammonium Lauryl Sulfate currently is used in 306 cosmetic products, with the single largest use in non-coloring shampoos at a maximum concentration of 55%. Table 25 also includes the available use information for Ammonium Lauryl Sulfate.

The CIR Expert Panel discussion focused on the skin irritation, penetration enhancement, and potential carcinogenic activity of these ingredients. New studies confirmed the irritant properties of these ingredients and reinforced concentration limit of 1% for leave-on uses established by the Panel. Moreover, the Panel noted that SLS and Ammonium Lauryl Sulfate may increase the penetration of other cosmetic ingredients, and suggested that this information should be considered during formulation.

The available studies that looked for carcinogenesis failed to find any evidence that Ammonium Lauryl Sulfate are

**TABLE 25**
Historical and current use of Sodium Lauryl Sulfate and Ammonium Lauryl Sulfate

| Product type | 1981 uses (Elder 1983) | 2002 uses (FDA 2002) | 1981 use concentrations (Elder 1983) (%) | 2002 uses concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| | *Sodium Lauryl Sulfate* | | | |
| Baby shampoos | 2 | — | >1–5 | 3 |
| Bath oils, tablets, and salts | 7 | 8 | >1–>50 | — |
| Bubble baths | 73 | 48 | >0.1–50 | 10–14 |
| Bath capsules | 2 | 1 | >5–10 | — |
| Bath preparations (other) | 24 | 24 | >0.1–50 | 2–20 |
| Eyebrow pencils | 2 | — | >1–5 | 0.2 |
| Eyeliners | — | 3 | — | 0.08–0.2 |
| Eye shadow | — | — | — | 0.05 |
| Eye makeup remover | 2 | — | >1–5 | 0.2 |
| Mascara | 9 | 13 | ≤0.1–1 | 0.06–0.2 |
| Eye makeup (other) | – | 9 | — | 0.3 |
| Sachets | 20 | — | >0.1–1 | 0.3 |
| Fragrance preparations (other) | 3 | 2 | ≤0.1–10 | — |
| Hair conditioners | 6 | 9 | >0.1–25 | 0.1 |
| Hair straighteners | 9 | 12 | >0.1–5 | — |
| Permanent waves | 9 | 1 | ≤0.1–10 | 0.1 |
| Rinses (noncoloring) | 1 | — | >0.1–1 | — |
| Shampoos (noncoloring) | 226 | 181 | ≤0.1–>50 | 5–50 |
| Hair tonics, dressings, etc. | 2 | — | >0.1–50 | 0.2 |
| Wave sets | — | 1 | — | — |
| Hair preparations (other noncoloring) | 6 | 5 | ≤0.1–5 | — |
| Hair dyes and colors | 61 | 349 | ≤0.1–5 | 0.2–20 |
| Hair tints | 1 | — | >1–5 | 0.02–0.2 |
| Hair rinses (coloring) | — | — | — | 0.4 |
| Shampoos (coloring) | 9 | 2 | >1–50 | — |
| Hair lighteners with color | — | 1 | — | — |
| Hair bleaches | 21 | 18 | ≤0.1–25 | 0.4–2 |
| Hair-coloring preparations (other) | 5 | 5 | ≤0.1–10 | 3 |
| Blushers (all types) | 1 | — | >0.1–1 | — |
| Foundations | 14 | 11 | ≤0.1–1 | 0.2–1.4 |
| Makeup bases | 8 | 10 | ≤0.1–1 | 0.8 |
| Rouges | 1 | — | >0.1–1 | — |
| Makeup (other) | — | 1 | — | 2 |
| Cuticle softeners | 1 | — | >0.1–1 | — |
| Nail creams and lotions | — | 1 | — | — |
| Nail polish and enamel | — | — | — | 0.01 |
| Manicuring preparations (other) | 1 | 2 | >0.1–1 | 0.01 |
| Dentifrices | 28 | 34 | >0.1–10 | 1–8 |
| Mouthwashes and breath fresheners | 4 | 5 | >0.1–1 | — |
| Oral hygiene products (other) | 2 | 1 | >0.1–5 | — |
| Bath soaps and detergents | 11 | 53 | ≤0.1–50 | 0.01–11 |
| Underarm deodorants | 6 | 4 | >0.1–1 | 1 |
| Douches | 1 | — | >1–5 | — |

*(Continued on next page)*

**TABLE 25**
Historical and current use of Sodium Lauryl Sulfate and Ammonium Lauryl Sulfate *(Continued)*

| Product type | 1981 uses (Elder 1983) | 2002 uses (FDA 2002) | 1981 use concentrations (Elder 1983) (%) | 2002 uses concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| Personal cleanliness products (other) | 7 | 20 | >0.1–>50 | 10–11 |
| Aftershave lotions | 2 | 1 | >0.1–1 | — |
| Preshave lotions | — | — | — | 3 |
| Shaving cream | 5 | 36 | >0.1–5 | 0.9–5* |
| Shaving preparations (other) | — | — | — | — |
| Skin-cleansing creams, lotions, liquids, and pads | 28 | 45 | ≤0.1–50 | 3–10 |
| Depilatories | 8 | 5 | ≤0.1–10 | 0.02 |
| Face and neck skin care preparations | 27** | 4 | ≤0.1–5** | 0.3 |
| Body and hand skin care preparations | | 35 | | 0.06–0.3 |
| Foot powders and sprays | — | 2 | — | 0.3 |
| Moisturizers | 23 | 25 | ≤0.1–1 | 0.2 |
| Night skin care preparations | 4 | 1 | ≤0.1–5 | — |
| Paste masks/mud packs | 9 | 4 | ≤0.1–5 | 2 |
| Skin fresheners | 1 | 1 | >0.1–1 | — |
| Skin care preparations (other) | 6 | 19 | ≤0.1–5 | 0.01–5 |
| Suntan gels, creams, and liquids | 4 | 2 | ≤0.1–1 | — |
| Indoor tanning preparations | — | 1 | — | — |
| Suntan preparations (other) | 2 | 3 | ≤0.1–1 | — |
| **Total uses/ranges for Sodium Lauryl Sulfate** | **703** | **1018** | **≤0.1–>50** | **0.01–50** |
| | *Ammonium Lauryl Sulfate* | | | |
| Baby shampoos | 2 | — | >10–25 | — |
| Bath oils, tablets, and salts | 1 | — | >25–50 | — |
| Bubble baths | 19 | 5 | >5–50 | 10–12 |
| Bath preparations (other) | - | 4 | — | 10–45 |
| Fragrance preparations (other) | — | — | — | 12* |
| Hair conditioners | — | 2 | — | — |
| Rinses (noncoloring) | — | 3 | — | — |
| Shampoos (noncoloring) | 131 | 242 | >0.1–50 | 8–55 |
| Hair tonics, dressings, etc. | — | 1 | — | — |
| Hair preparations (other) | — | 8 | — | — |
| Hair dyes and colors | — | 1 | — | — |
| Hair rinses (coloring) | — | 14 | — | — |
| Hair shampoos (coloring) | 2 | 1 | >10–25 | — |
| Bath soaps and detergents | 4 | 14 | >10–50 | 5–47 |
| Personal cleanliness products (other) | — | 2 | — | 3–12 |
| Skin-cleansing creams, lotions, liquids, and pads | 4 | 8 | >1–50 | 10 |
| Skin care preparations (other) | 1 | 1 | >0.1–1 | — |
| **Total uses/ranges for Ammonium Lauryl Sulfate** | **164** | **306** | **>0.1–50** | **3–55** |

*Specified as a rinse-off product.
**These categories were combined when the original safety assessment was performed and are now two separate categories.

carcinogenic. None of the available data suggested any possibility that SLS or Ammonium Lauryl Sulfate could be carcinogenic. Despite assertions to the contrary on the Internet, the carcinogenicity of these ingredients is only a rumor.

## REFERENCES


Abdul-Hussain, S., and D. Acosta. 1994. In vitro model to evaluate the cytotoxicity of two groups of surfactant mixtures with rat keratinocyte cultures. *Toxic. Subs. J.* 13:1–14.

Abidi T. F., C. A. Faaland, D. D. Scala, L. D. Rhein, and J. D. Laskin. 1989. Ethoxylated alcohol (Neodol-12) and other surfactants in the assay of protein kinase C. *Biochim. Biophys. Acta* 992:362–368.

Aiba, S., A. Terunuma, H. Manome, and H. Tagami. 1997. Dendritic cells differently respond to haptens and irritants by their production of cytokines and expression of co-stimulatory molecules. *Eur. J. Immunol.* 27:3031–3038.

Agner, T. 1990. Susceptibility of atopic dermatitis patients to irritant dermatitis cause by sodium lauryl sulphate. *Acta Derm. Venerol.* 71:296–300.

Agner, T., and J. Serup. 1988. Contact thermography for assessment of skin damage due to experimental irritants. *Acta Derm. Venerol.* 68:192–195.

Agner, T., and J. Serup. 1989. Skin reactions to irritants assessed by non-invasive bioengineering methods. *Contact Dermatitis* 20:352–359.

Agner, T., and J. Serup. 1990. Sodium lauryl sulphate for irritant patch testing-A dose-response study using bioengineering methods for determination of skin irritation. *J. Invest. Dermatol.* 95:543–547.

Agner, T., and J. Serup. 1993. Time course of occlusive effects on skin evaluated by measurement of transepidermal water loss (TEWL): Including patch tests with sodium lauryl sulphate and water. *Contact Dermatitis* 28:6–9.

Agner, T., J. Serup, V. Handlos, and W. Batsberg. 1989. Different skin irritation abilities of different qualities of sodium lauryl sulphate. *Contact Dermatitis* 21:184–188.

Ahlfors, E. E., and A. Larsson. 1988. Chemically induced inflammation in ratoral mucosa. *Scand. J. Dent. Res.* 96:428–434.

Aiba, S., and S. I. Katz. 1990. Phenotypic and functional characteristics of in vivoactivated Langerhans cells. *J. Immunol.* 145:2791–2796.

Allen, M. H., S. H. Wakeline, D. Holloway, S. Lisby, I. Baadsgaard, J. N. Barker, and J. P. McFadden. 2000. Association of TFNA gene polymorphism at position-308 with susceptibility to irritant contact dermatitis. *Immunogenesis* 51: 201–205.

Allenby, C. F., D. A. Basketter, A. Dickens, E. G. Barnes, and H. C. Brough. 1993. An arm immersion model of compromised skin: (I). Influence on irritation reactions. *Contact Dermatitis* 28:84–88.

American Cancer Society (ACS). 1998a. Debunking the myth. Article dated 09/23/1998.

ACS. 1998b. Bubble, bubble, toil and trouble. Article dated 09/23/1998. http://www.cancer.org/eprise/main/docroot/NWS/content/NWS_2_1x_Bubble_Bubble_Toil_and_Trouble

Anavkar, A. S., and C. V. Natraj. 1989. An in vitro method for evaluation of the irritancy of anionic surfactants. *J. Am. Oil. Chem. Soc.* 66:1386–1389.

Anderberg, E. K., and P. Artursson. 1993. Epithelial transport of drugs in cell culture. VIII: Effect of sodium dodecyl sulfate on cell membranes and tight junction permeability in human intestinal epithelial (Caco-2) cells. *J. Pharm. Sci.* 82:392–398.

Anderson, C., C. Svensson, F. Sjögren, T. Andersson, and K. Wårdell. 1995. Human in vivo microdialysis technique can be used to measure cytokines in contact reactions. *Curr. Probl. Dermatol.* 23:121–130.

Anderson, C., K. Sundberg, and O. Froth. 1986. Animal model for assessment of skin irritancy. *Contact Dermatitiss* 15:143–151.

Anonymous. 2002. Poisonous Shampoo?: Shampoo containing "SLS" is a cancer hazard—Fiction! http://www.truthorfiction.com/rumors/shampoo.htm

Arechabala, B., C. Coiffard, P. Rivalland, L. J. M. Coiffard, and Y. de Roeck-Holtzhauer. 1999. Comparison of cytotoxicity of various surfactants tested on normal human fibroblast cultures using the neutralred test, MTT assay and LDH release. *J. Appl. Toxicol.* 19:163–165.

Ariyoshi, T., H. Hasegawa, Y. Nanri, and K. Arizono. 1990. Profile of hemoproteins and heme-metabolizing enzymes in rats treated with surfactants. *Bull. Environ. Contam. Toxicol.* 44:369–376.

Baert, J. H., R. J. Veys, and K. Ampe. 1996. The effect of sodium lauryl sulfate on the expression of cytokeratin mRNA in hamster cheek pouch epithelium. *J. Oral. Pathol. Med.* 25:497–501.

Baert, J. H., R. J. Veys, K. Ampe, and J. A. De Boever, 1996. The effect of sodium lauryl sulphate and triclosan in hamster cheek pouch mucosa. *Int. J. Exp. Pathol.* 77:73–78.

Bangha, E., U. Hinnen, and P. Elsner, 1996. Irritancy testing in occupational dermatology: Comparison between two quick tests and the acute irritation induced by sodium lauryl sulphate. *Acta Dermato-Venerol.* 76:450–452.

Bárány, E., M. Lindberg, and M. Lodén. 1999. Biophysical characterization of skin damage and recovery after exposure to different surfactants. *Contact Dermatitis* 40:98–103.

Basketter, D., L. Blaikie, and F. Reynolds. 1996. The impact of atopic status on a predictive human test of skin irritation potential. *Contact Dermatitis* 35:33–39.

Basketter, D. A., M. Chamberlain, H. A. Griffiths, M. Rowson, E. Whittle, and M. York. 1997. The classification of skin irritants by human patch test. *Food Chem. Toxicol.* 35:845–852.

Basketter, D. A., and H. A. Griffiths. 1993. A study of the relationship between susceptibility to skin stinging and skin irritation. *Contact Dermatitis* 29:185–188.

Basketter, D. A., J. A. Miettinen, and A. Lahti. 1998. Acute irritant reactivity to sodium lauryl sulfate in atopics and non-atopics. *Contact Dermatitis* 38:253–257.

Basketter, D. A., E. W. Scholes, and I. Kimber. 1994. The performance of the local lymph node assay with chemicals identified as contact allergens in the human maximization test. *Food Chem. Toxicol.* 32:543–547.

Basketter, D. A., E. Whittle, H. A. Griffiths, and M. York. 1994. The identification and classification of skin irritation hazard by a human patch test. *Food Chem. Toxicol.* 32:769–775.

Begoan, P. 2001. Myth busting. http://www.cosmeticscop.com/skinfacts/mythbusting.htm#sodium.

Benoit, J., M. Cormier, and J. Wepierre. 1988. Comparative effects of four surfactants on growth, contraction, and adhesion of cultured human fibroblasts. *Cell. Biol. Toxicol.* 4:111–122.

Berardesca, E., G. P. Vignoli, F. Distante, P. Brizzi, and G. Rabbiosi. 1995. Effects of water temperature on surfactant-induced skin irritation. *Contact. Dermatitis* 32:83–87.

Berardesca, E., D. Fideli, P. Gabba, M. Cespa, G. Rabbiosi, and H. I. Maibach. 1990. Ranking of surfactant skin irritancy in vivo in man using the plastic occlusion stress test (POST). *Contact Dermatitis* 23:1–5.

Bergtresser, P. R., and W. H. Eaglestein. 1973. Irritation by hydrophillic ointment under occlusion. *Arch. Dermatol.* 108:218–219.

Berry, M., and D. L. Easty. 1993. Isolated human and rabbit eye: Models of corneal toxicity. *Toxicol. In Vitro* 7:461–464.

Biochemical Research Lab. 2000. Toxicological properties of several commercially available surfa ctants, with cover letter dated 04/10/00 (sanitized). NTIS Report No. OTS0574051.

Blakemore, W. M., J. E. Rule, and M. C. Bowman. 1979. Trace analysis of two detergents in blood from guinea pigs after immersion in aqueous baths. *Toxicol. Lett. (Amsterdam)* 3:127–136.

Blanken, R., M. J. T. van Vilsteren, R. A. Tupker, and P. J. Coenraads. 1989. Effect of mineral oil and linoleic-acid-containing emulsions on the skin vapour loss of sodium-lauryl-sulphate-induced irritant skin reactions. *Contact Dermatits* 20:93–97.

Bloom, E., M. Sznitowska, J. R. Polansky, and H. I. Maibach. 1993. In vitro tests for irritants: Qualitative differences in biological properties. *In Vitro Toxicol.* 6:171–185.

Booman, K. A., T. M. Cascieri, J. Demetrulias, A. Driedger, J. F. Griffith, G. T. Grochoski, B. Kong, W. C. Mc Cormick, H. North-Root, M. G. Rozen, and R. I. Sedlak. 1988. In vitro methods for estimating eyeirritancy

of cleaning products phase I: Preliminary assessment. *J. Toxicol.* 7:173–185.

Brand, C. U., and L. R. Braathen. 1996. Investigation of skin-derived lymph: An approach to get insight into the skin immune system. *Dermatology* 193:283–288.

Brand, C. U., Hunziker, T., and L. R. Braathen. 1992. Studies on human skin lymph containing Langerhans cells from sodium lauryl sulphate contact dermatitis. *J. Invest. Dermatol.* 99:109S–110S.

Brasch, J., D. Becker, and I. Effendy. 1999. Reproducibility of irritant patch test reactions to sodiuml auryl sulfate in a double-blind placebo-controlled randomized study using clinical scoring. *Contact Dermatitis* 41:150–155.

Butler, N. J., G. R. Langley, and J. Winwood. 1992. A cell suspension agar diffusion test using Neutral Red release to assess the relative irritancy potential of cosmetic ingredients and formulations. *Int. J. Cosmet. Sci.* 15:33–42.

Chung, J. H., H. C. Eun, S. Y. Jung, and K. H. Cho. 1993. A comparative study of cytotoxicity of skin irritants between cultured human, oral and skin keratinocytes. *J. Invest. Dermatol.* 101:430.

Cohen, C., G. Dossou, A. Rougier, and R. Rouget. 1990. Measurement of inflammatory mediators produced by human keratinocytes in-vitro a predictive assessment of cutaneous irritation. *Toxicol. In Vitro* 5:407–410.

Conrads, A., and H. Zahn. 1987. A study of the interaction of sodium dodecyl sulphate with the proteins of human heel stratum corneum. *Int. J. Cosmet. Sci.* 9:29–46.

Cooper, A., J. Fentem, and M. Balls. 1994. Inhibition of intercellular communication: An in vitro assay for detecting potential tumour promoters. *Toxicol. In Vitro* 8:535–537.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2002. Concentration of Use-Sodium Lauryl Sulfate and Ammonium Lauryl Sulfate. Unpublished data. 3 pages.[26]

Cruchley, A. T., A. O'Regan, and D. M. Williams. 1992. Sodium lauryl sulphate increased human mucosal permeability. *J. Dent. Res.* 71:693. Abstract.

Cua, A. B., K.-P. Wilhelm, and H. I. Maibach. 1990. Cutaneous sodium lauryl sulfate irritation potential: Age and regional variability. *Brit. J. Dermatol.* 123:607–613.

Cumberbatch, M., R. J. Dearman, and I. Kimber. 1998. Interleukin 1$\alpha$ required for Langerhans cell migration provoked in mice by the skin irritant sodium lauryl sulphate. *Hum. Exp. Toxicol.* 17:497.

Cumberbatch, M., R. C. Scott, D. A. Basketter, E. W. Scholes, J. Hilton, R. J. Dearman, and I. Kimber. 1993. Influence of sodium lauryl sulphate on 2,4-dinitrochlorobenzene-induced lymph node activation. *Toxicol*. 77:181–191.

Dahl, M. V., and M. J. Roering. 1984. Sodium lauryl sulfate irritant patch tests. III. Evaporation of aqueous vehicle influences inflammatory response. *J. Am. Acad Dermatol.* 11:477–479.

Dahl, M. V., F. Pass, and R. J. Trancik. 1984. Sodium lauryl sulfate irritant patch tests. II. Variations of test responses among subjects and comparison to variations of allergic responses elicited by *Toxicodendron* extract. *J. Am. Acad Dermatol.* 11:474–477.

de Brugerolle de Fraissinette, A., V. Picarles, S. Chibout, M. Kolopp, J. Medina, P. Burtin, M. E. Ebelin, S. Osborne, F. K. Myer, A. Spake, M. Rosdy, B. De Wever, E. A. Ettlin, and A. Cordier. 1999. Predictivity of an in vitro model for acute and chronic skin irritation (SkinEthic) applied to the testing of topical vehicles. *Cell Biol. Toxicol.* 15:121–135.

DeLeo, V. A., D. Hanson, S. Scheide, B. J. Kong, and S. DeSalva. 1989. The effect of surfactants on metabolism of chloine phospholipids in human epidermal keratinocytes in culture. *J. Toxicol. Cutan. Ocul. Toxicol.* 8:227–240.

de Vries, I. J. M., E. G. Langeveld-Wildschut, F. C. van Reijsen, I. C. Bihari, C. A. Bruijnzeel-Koomen, and T. Thepen. 1997. Nonspecific T-cell homing during inflammation in atopic dermatitis: Expression of cutaneous lymphocyte-associated antigen and integrin $\alpha$E$\beta$7 skin-infiltrating T cells. *J. Allergy Clin. Immunol.* 100:694–701.

[26]Available from Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

Dickson, F. M., J. N. Lawrence, and D. J. Benford. 1993. Surfactant-induced cytotoxicity in cultures of human keratinocytes and a commercially available cell line (3T3). *Toxicol. In Vitro* 7:381-384.

Dickson, F. M., J. N. Lawrence, and D. J. Benford. 1994. Cytotoxicity of 12 chemicals of known human and animal skin irritation potential in human keratinocyte cultures. *Toxicol. In Vitro* 8:661–663.

Dierickx, P. J. 1989. Cytotoxicity testing of 114 compounds by the determination of the protein content in HEP G2 cell cultures. *Toxicol. In Vitro* 3:189–193.

Dihoom, M., G. S. Mahmoud, and O. H. Sudani. 1996. An outbreak of hand dermatitis among workers using sodium lauryl sulfate for skin cleansing. *Contact. Dermatitis* 34:366–367.

Di Nardo, A., K. Sugino, P. Wertz, J. Ademola, and H. I. Maibach. 1996. Sodium lauryl sulfate (SLS) induced irritant contact dermatitis: A correlation study between ceramides and in vivo parameters of irritation. *Contact Dermatitic* 35:86–91.

Effendy, I. 1995. Are irritants clinically useful? *Cosmet. Toiletries* 110:39–40.

Effendy, I., and H. I. Maibach. 1995. Surfactants and experimental irritant contact dermatitis. *Contact. Dermatitis* 33:217–225.

Eichhorn, U., R. Klöcking, H. Schweizer, and H.-P. Klöcking. 1987. Cell membrane toxicity detected with the chromium-51 release test. *Mech. Models Toxicol.* 11:334–337.

Elder, R. L., ed. 1983. Final report on the safety assessment of sodium lauryl sulfate and ammonium lauryl sulfate. *J. Am. Col. Toxicol.* 2:127–181.

Elsner, P., and G. Burg. 1993. Irritant reactivity is a better risk marker for nickel sensitivity than atopy. *Acta. Dermato-Venerol.* 73:214–216.

Elsner, P., D. Wilhelm, and H. I. Maibach. 1990. Multiple parameter assessment of vulvar irritant contact dermatitis. *Contact Dermatitis* 23:20–26.

P. Elsner, D. Wilhelm, and H. I. Maibach. 1991. Effect of low-concentration sodium lauryl sulfate on human vulvar and forearm skin: Age-related differences. *J. Reprod. Med.* 36:77–81.

Emilson, A., M. Lindberg, and B. Forslind. 1993. The temperature effect on in vitro penetration of sodium lauryl sulfate and nickel chloride through human skin. *Acta Derm. Venerol.* 73:203–207.

Emilson, A., M. Lindberg, and A. Scheynius. 1998. Differential epidermal expression of the invariant chain in allergic and irritant contact dermatitis. *Acta Derm. Venerol.* 78:402–407.

Etter, J.-C. L., and A. Wildhaber. 1985. Biopharmaceutical test of ocular irritation in the mouse. *Food Chem. Toxicol.* 23:321–324.

Eun, H. C., J. H. Chung, S. Y. Jung, K. H. Cho, and K. H. Kim. 1994. A comparative study of the cytotoxicity of skin irritants on cultured human oral and skin keratinocytes. *Br. J. Dermatol.* 130:24–28.

Färm, G. 1998. Repeated open application tests (ROAT) in patients allergic to colophony evaluated visually and with bioengineering techniques. *Acta Derm. Venerol.* 78:130–135.

Ferguson, T. M., and C. Prottey. 1976. Effect of surfactants upon mammalian cells in vitro. *Food Cosmet. Toxiol.* 14:431–434.

Fisher, G. J., J. Esmann, C. E. Griffiths, H. S. Talwar, E. A. Duell, C. Hammerberg, J. T. Elder, L. J. Finkel, G. D. Karabin, B. J. Nickoloff, K. D. Cooper, and J. J. Voorhees. 1991. Cellular, immunologic and biochemical characterization of topical retinoic acid-treated human skin. *J. Invest. Dermatol.* 96:699–707.

Fisher, G. J., A. Tavakkol, C. E. Griffiths, J. T. Elder, Q. Y. Zhang, L. Finkel, D. Danielpour, A. B. Glick, H. Higley, and L. Ellingsworth. 1992. Differential modulation of transforming growth factor-beta 1 expression and mucindeposition by retinoic acid and sodium lauryl sulfate in human skin. *J. Invest. Dermatol.* 98:102–108.

Fitzpatrick, M. J., I. K. Berezesky, and B. F. Trump. 1991. Evaluation of toxicity of model xenobiotics in-vitro utilizing JB6 cells. *J. Cell. Biol.* 115:21A.

Flanagan, S. A., M. H. Smolensky, R. Harrist, R. L. Brown, V. K. Menon, and J. P. McGovern. 1984. Scapular reactivity to contact irritants: Application-time and area variations. *Chronobiologia* 11:93–108.

Flower, C., B. J. Phillips, and D. Anderson. 1987. Investigation of surface-activity as a possible mechanism of clastogenic action of mono-2-ethylhexylphtalate. *Mutagenesis* 2:304. Abstract.

FDA. 1981. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

FDA. 2001. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

Food and Drug Research Labs (FDRL). 1979a. Initial submission: Primary skin irritation study with ammonium lauryl sulfate in rabbits with cover letter dated 051592. NTIS Report No. OTS0539899.

FDRL. 1979b. Initial submission: Eye irritation test with ammonium lauryl sulfate in rabbits with cover letter dated 051592. NTIS Report No.OTS0539909.

FDRL. 1985a. Initial submission: Primary dermal irritation study of 15% active solution of sodium lauryl sulfate in New Zealand White rabbits (final report) with attachments and letter dated 11/22/91. NTIS Report No.OTS0534770.

FDRL. 1985b. Initial submission: Primary dermal irritation study of 15% active solution of ammonium lauryl sulfate in New Zealand White rabbits (final report; with attachments and letter dated 03/13/92). NTIS Report No. OTS0536168.

Forsey, R. J., H. Shahidulluh, C. Sands, E. McVittie, R. D. Aldridge, J. A. A. Hunter, and S. E. M. Howie. 1998. Epidermal Langerhans cell apoptosis is induced in vivo by nonanoic acid but not by sodium lauryl substrate. *Br. J. Dermatol.* 139:453–461.

Freeman, S., and H. Maibach. 1988. Study of irritant contact dermatitis by repeat patch test with sodium lauryl sulfate and assessed by visual methods, transepidermal water loss, and laser Doppler velocimetry. *J. Am. Acad. Dermatol.* 19:496–502.

Fröndin, T., and C. Anderson. 1987. Multiple parameter assessment of skin irritancy. *Contact. Dermatitis* 17:92–99.

Frosch, P. J., and B. M. Czarnetzki. 1987. Surfactants cause in-vitro chemotaxis and chemokinesis of human neutrophils. *J. Invest. Dermatol.* 88:52S–55S.

Frosch, P. J., A. Schulze-Dirks, M. Hoffman, I. Axthelm, and A. Kurte. 1993a. Efficacy of skin barrier creams. (I). The repetitive irritation test (RIT) in the guinea pig. *Contact Dermatits* 28:94–100.

Frosch, P. J., A. Schulze-Dirks, M. Hoffman, and I. Axthelm. 1993b. Efficacy of skin barrier creams. (II). Ineffectiveness of a popular "skin protector" against various irritants in the repetitive irritation test in the guinea pig. *Contact. Dermatitis* 29:74–77.

Frosch, P. J., and C. Wissing. 1982. Cutaneous sensitivity to ultraviolet light and chemical irritants. *Arch. Dermatol. Res.* 272:269–278.

Fuchs, J., and L. Packer. 1999. Antioxidant protection from solar-simulated radiation-induced suppression of contact hypersensitivity to the recall antigen nickel sulfate in human skin. *Free Radic. Biol. Med.* 27:422–427.

Fullerton, A., U. Broby-Johansen, and T. Agner. 1994. Sodium lauryl sulphate in an in vitro model using human skin. *Contact. Dermatitis* 30:222–225.

Fulmer, A. W., and G. J. Kramer. 1986. Stratum corneum lipid abnormalities in surfactant-induced dry scaly skin. *J. Invest. Dermatol.* 86:598–602.

Gatto, H., J. Viac, M. Charveron, and D. Schmitt. 1992. Study of immune-associated antigens (IL-1 and ICAM-1) in normal keratin ocytes treated by sodium lauryl sulphate. *Arch. Dermatol. Res.* 284:186–188.

Gehring, W. 1990. Effects of irritants in atopic dermatitis. *Contact Dermatitis* 22:292–293.

Gibson, W. T., and M. E. Teall. 1983. Interactions of C12 surfactants with the skin: Changes in enzymes and visible and histological features of rat skin treated with sodium lauryl sulphate. *Food Chem. Toxicol.* 21:587–594.

Goh, C. L. 1988. A comparison of the effect of UVB and sodium lauryl sulphate on the skin water vapour loss. *Ann. Acad. Med. Singapore* 17:495–497.

Gollhausen, R., and A. M. Kligman. 1985. Effects of pressure on contact dermatitis. *Am. J. Ind. Med.* 8:323–328.

Grant, R. L., and D. Acosta. 1996. Prolonged adverse effects of benzalkonium chloride and sodium dodecyl sulfate in a primary culture system of rabbit corneal epithelial cells. *Fundam. Appl. Toxicol.* 33:71–82.

Grant, R. L., C. Yao, D. Gabaldon, and D. Acosta. 1992. Evaluation of surfactant cytotoxicity potential by primary cultures of ocular tissues: I. Characterization of rabbit corneal epithelial cells and initial injury and delayed toxicity studies. *Toxicology* 76:153–176.

Green, K., R. E. Johnson, J. K. Chapman, E. Nelson, and L. Cheeks. 1989. Preservative effects on the healing rate of rabbit corneal epithelium. *Lens. Eye Toxic. Res.* 6:37–41.

Gräsjo, A., A. Leijon-Kuligowski, H. Törma, G. M. Roomans, and M. Lindberg. 1996. Different pathways in irritant contact eczema? Early differences in the epidermal elemental content and expression of cytokines after application of 2 different irritants. *Contact. Dermatitis* 35:355–360.

Griffith, J. F., G. A. Nixon, R. D. Bruce, P. J. Reer, and E. A. Bannan. 1980. Dose-response studies in the albino rabbit eye as a basis for selecting optimum testing conditions for predicting hazard to the human eye. *Toxicol. Appl. Pharmacol.* 55:501–513.

Griffiths, H. A., K.-P. Wilhelm, M. K. Robinson, X. M. Wang, J. M. McFadden, M. Work, and D. A. Basketter. 1997. Interlaboratory evaluation of a human patch test for the identification of skin irritation potential/hazard. *Food Chem. Toxicol.* 35:255–260.

Grunewald, A. M., M. Gloor, W. Gehring, and P. Kleesz. 1995. Damage to the skin by repetitive washing. *Contact. Dermatitis* 32:225–232.

Guironnet, G., C. Dalbiez-Gauthier, F. Rousset, D. Schmitt, and J. Peguet-Navarro. 2000. In vitro human T cell sensitization to haptens by monocyte-derived dendritic cells. *Toxicol. In Vitro* 14:517–522.

Gülden, M. 1993. In vitro toxicity screening using cultured rat skeletal muscle cells: I. Surfactants and mitochondrial poisons. *Toxicol. In Vitro* 7:25–34.

Gupta, B. N., C. Agarwal, and A. Singh. 1987. Effect of sodium lauryl sulfate on rat and liver kidney enzymes an in-vitro study. *Bull. Environ. Contam. Toxicol.* 39:425–433.

Hall-Manning, T. J., G. H. Holland, G. Rennie, P. Revell, J. Hines, M. D. Barratt, and D. A. Basketter. 1998. Skin irritation potential of mixed surfactant systems. *Food Chem. Toxicol.* 36:233–238.

Hasegawa, Y., T. Irkura, and D.-I. Mizuno. 1970. Screening test for the prevention of metastases produced by Ehrlich carcinoma cells. *Chem. Pharm. Bull.* 18:810–814.

Haskell Laboratories. 1984. Initial submission: Approximate lethal concentrations by inhalation of sodium lauryl sulfate and sodium dodecylbenzene sulfonate with cover letter dated 090292. NTIS Report No. OTS0546357.

Held, E., and T. Agner. 1999. Comparison between 2 test models in evaluation the effect of a moisturizer on irritated human skin. *Contact Dermatitis* 40:261–268.

Herlofson, B. B., and P. Barkvoll. 1996. Oral mucosal desquamation caused by two toothpaste detergents in an experimental model. *Eur. J. Oral Sci.* 104:21–26.

Hinnen, U., P. Elsner, and G. Burg. 1995. Assessment of skin irritancy by 2 short tests compared to acute irritation induced by sodium lauryl sulfate. *Contact Dermatitis* 33:236–239.

Hoefakker, S., M. Caubo, E. H. van't Erve, M. J. Roggeveen, W. J. A. Boersma, T. van Joost, W. R. F. Notten, and E. Claassen. 1995. In vivo cytokine profiles in allergic and irritant contact dermatitis. *Contact. Dermatitis* 33:258–266.

Hoh, A., K. Maier, and R. M. Dreher. 1987. Multilayered keratinocyte culture used for in vitro toxicology. *Mol. Toxicol.* 1:537–546.

Howett, M. K., E. B. Neely, N. D. Christensen, B. Wigdahl, F. C. Krebs, D. Malamud, S. D. Patrick, M. D. Pickel, P. A. Welsh, C. A. Reed, M. G. Ward, L. R. Budgeon, and J. W. Kreider. 1999. A broad-spectrum microbiocide with virucidal activity against sexually transmitted viruses. *Antimicrob. Agents Chemother.* 43:314–321.

Hunziker, T., C. U. Brand, A. Kapp, E. R. Waelti, and L. R. Braathen. 1992. Increased levels of inflammatory cytokines in human skin lymph derived from sodium lauryl sulphate-induced contact dermatitis. *Br. J. Dermatol.* 127:254–257.

Hunziker T., C. U. Brand, A. Limat, and L. R. Braathen. 1993. Alloactivating and antigen-presenting capacities of human skin lymph cells derived from sodium lauryl sulfate-induced contact dermatitis. *Eur. J. Dermatol.* 3:137–140.

Igarashi, H. 1986. With which component of the bovine isolated cornea does sodium lauryl sulfate react to produce opacity? *Toxicol. Lett.* 32:249–254.

Ikarashi, Y., Y. Tsukamoto, T. Tsuchiya, and A. Nakamura. 1993. Influence of irritants on lymph node cell proliferation and the detection of contact sensitivity to metal salts in the murine local lymph node assay. *Contact. Dermatitis* 29:128–132.

Ikarashi, Y., T. Tsuchiya, and A. Nakamura. 1993. A sensitive mouse lymph node assay with two application phases for detection of contact allergens. *Arch. Toxicol.* 67:629–636.

Ingram, A. J., and P. Grasso. 1975. Patch testing in the rabbit using a modified human patch test method: Application of histological and visual assessment. *Br. J. Dermatol.* 92:131–142.

Jain, P. T., M. J. Fitzpatrick, P. C. Phelps, I. K. Berezesky, and B. F. Trump. 1992. Studies of skin toxicity in vitro: Dose-response studies on JB6 cells. *Toxicol. Pathol.* 20:394–404.

Janik, F., and H. U. Wolf. 1992. The $Ca^{+2}$-transport-ATPase of human erythrocytes as an in vitro toxicity test system-acute effects of some chlorinated compounds. *J. Appl. Toxicol.* 12:351–358.

Johnson, O. H., S. Casey, M. K. Doletz, K. E. McCaleb, A. M. Miller, P. A. Papa, L. B. Swett, M. A. Valentini, and C. T. Helmes. 1984. A study of biocides for the selection of candidates for carcinogen bioassay. *J. Environ. Sci. Health* 19:1–25.

Judge, M. R., H. A. Griffiths, D. A. Basketter, I. R. White, R. J. G. Rycroft, and J. P. McFadden. 1996. Variation in response of human skin to irritant challenge. *Contact Dermatitis* 34:115–117.

Junghans, V., C. Gutgesell, T. Jung, and C. Neumann. 1998. Epidermal cytokines IL-1beta, TNF-alpha, and IL-12 in patients with atopic dermatitis: Response to application of house dust mite antigens. *J. Invest. Dermatol.* 111:1184–1188.

Kacani, L., M. Ferencik, F. Devinsky, J. Most, and M. P. Dierrich. 1994. Immunomodulatory effect of sodium dodecyl sulfate on human neutrophils and the human promyelocytic HL-60 line. *Eur. J. Pharmacol.* 270:285–289.

Kawachi, T., T. Komatsu, T. Kada, M. Ishidate, M. Sasaki, T. Sugiyama, and Y. Tazima. 1980. Results of recent studies on the relevance of various short-term screening tests in Japan. In: The predictive value of short-term screening tests in carcinogenicity evaluation. *Appl. Methods Oncol.* 3:253–267.

Kawai, K., M. Nakagawa, J. Kawai, and K. Kawai. 1992. Evaluation of ski irritancy of sodium lauryl sulphate: A comparative study between the replica method and visual evaluation. *Contact Dermatitis* 27:174–181.

Kemp, R. B., R. W. J. Meredith, and S. H. Gamble. 1985. Toxicity of commercial products on cells in suspension culture a possible screen for the Draize eye irritation test. *Food Chem. Toxicol.* 23:267–270.

Kennah, H. E., S. Hignet, P. E. Laux, J. D. Dorko, and C. S. Barrow. 1989. An objective procedure for quantitating eye irritation based upon changes of corneal thickness. *Fundam. Appl. Toxicol.* 12:258–268.

Kligman, A. M., and L. H. Kligman. 1998. A hairless mouse model for assessing the chronic toxicity of topically applied chemicals. *Food Chem. Toxicol.* 36:867–878.

Kobiler, D., S. Lustig, Y. Gozes, D. Ben-Nathan, and Y. Akov. 1989. Sodium doedecylsulphate induces a breach in the blood-brain barrier and enables a West Nile Virus to penetrate into mouse brain. *Brain Res.* 496:314–316.

Kojima, H., A. Hanamura, S. Miyamoto, A. Sato, H. Konishi, and I. Yoshimura. 1995. Evaluation of seven alternative assays on the main ingredients in cosmetics as predictors of Draize eye irritation scores. *Toxicol. In Vitro* 9:333–340.

Kolde, G., and J. Knop. 1987. Different cellular reaction patterns of epidermal Langerhans cells after application of contact sensitizing, toxic, and tolerogenic compounds. A comparative ultrastructural and morphometric time-course analysis. *J. Invest. Dermatol.* 89:19–23.

Kondo, S., S. Pastore, G. M. Shivji, R. C. McKenzie, and D. N. Sauder. 1994. Characterization of epidermal cytokine profiles in sensitization and elicitation phases of allergic contact dermatitis as well as irritant contact dermatitis in mouse skin. *Lymphokine Cytokine Res.* 13:367–375.

Korting, H. C., T. Herzinger, A. Haringer, M. Kerscher, T. Angerpointer, and H. I. Maibach. 1994. Discrimination of the irritancy potential of surfactants in vitro by two cytotoxicity assays using normal human keratinocytes, HaCaT cells, and 3T3 mouse fibroblasts: Correlation with in vivo data from a soap chamber assay. *J. Dermatol. Sci.* 7:119–129.

Krasteva, M., J. Peguet-Navarro, C. Moulon, P. Courtellemont, G. Redziniak, and D. Schmitt. 1996. In vitro primary sensitization of hapten-specific T cells by cultured human epidermal Langerhans cells—a screening predictive assay for contact sensitizers. *Clin. Exp. Allergy* 26:563–570.

Krebs, F. C., S. R. Miller, D. Malamud, M. K. Howett, and B. Wigdahl. 1999. Inactivation of human immunodeficiency virus type 1 by nonoxynol-9, C31G, or an alkyl sulfate, sodium dodecyl sulfate. *Antiviral Res.* 43:157–173.

Lammintausta, K., H. I. Maibach, and D. Wilson. 1988. Susceptibility to cumulative and acute irritant dermatitis an experimental approach in human volunteers. *Contact. Dermatitis* 19:84–90.

Larsen, C. G., T. Ternowitz, F. G. Larsen, C. Zachariae, and K. Thestrup-Pedersen. 1989. ETAF-interleukin-1 and epidermal lymphocyte chemotactic factor in epidermis overlying an irritant patch test. *Contact. Dermatitis* 20:335–340.

Lawrence, J. N., and D. J. Benford. 1995. Comparison of tumour promoter-induced prostaglandin E2 release in human and rat keratinocytes. *Carinogenesis* 16:1247–1251.

Lawrence J. N., F. M. Dickson, and D. J. Benford. 1997. Skin irritant-induced cytotoxicity and prostaglandin E12 release in human skin keratinocyte cultures. *Toxicol. In Vitro* 11:627–631.

Lawrence, J. N., S. Starkey, F. M. Dickson, and D. J. Benford. 1996. Use of human and rat keratinocyte cultures to assess skin irritation potential. *Toxicol. In Vitro* 10:331–340.

Lawrence, R. S., M. H. Groom, D. M. Ackroyd, and W. E. Parish. 1985. The chorioallantoic membrane in irritation testing. *Food Chem. Toxicol.* 24:497–502.

Le, M., S. Cals, J. Schalkwijk, and P. van der Valk. 1996. An immunohistochemical study on mild skin irritation by a single application of a low-molarity sodium dodecyl sulfate solution: Keys to prevention of irritant contact dermatitis. *Curr. Probl. Dermatol.* 25:67–77.

Le, M., J. Schalkwijk, G. Sigenthaler, P. C. M. van de Kerkhof, J. H. Veerkamp, and P. G. M. vander Valk. 1996. Changes in keratin ocyte differentiation following mild irritation by sodium dodecyl sulphate. *Arch. Dermatol. Res.* 288:684–690.

Lee, C. H., Y. Kawasaki, and H. I. Maibach. 1994. Effect of surfactant mixtures on irritant contact dermatitis potential in man: Sodium lauroyl glutamate and sodium lauryl sulfate. *Contact. Dermatitis* 30:205–209.

Lee, C. H., and H. I. Maibach. 1995. The sodium lauryl sulfate model: An overview. *Contact. Dermatitis* 33:1–7.

Lee, C. H., and H. I. Maibach. 1994. Study of cumulative irritant contact dermatitis in man utilizing open application on subclinically irritated skin. *Contact. Dermatitis* 30:271–275.

Lee, J. Y., I. Effendy, and H. I. Maibach. 1997. Acute irritant contact dermatitis: Recovery time in man. *Contact. Dermatitis* 36:285–290.

Li, L.-F., V. C. Fiedler, and R. Kumar. 1997a. Protein kinase C isoform levels in normal and sodium dodecyl sulphate-irritated mouse skin. *Br. J. Dermatol.* 139:11–15.

Li, L.-F., V. C. Fiedler, and R. Kumar. 1997b. Mouse skin protein kinase C isoforms in irritant and allergic contact dermatitis. *J. Invest. Dermatol.* 108:621. Abstract.

Li, L.-F., V. C. Fiedler, and R. Kumar. 1998. Down-regulation of protein kinase C isoforms in irritant contact dermatitis. *Contact. Dermatitis* 38:319–324.

Lindberg, M., G. Färm, and A. Scheynius. 1991. Differential effects of sodium lauryl sulphate and non-anoic acid on the expression of CD1a and ICAM-1 in human epidermis. *Acta Derm. Venereol.* 71:384–388.

Lindberg, M., and T. G. Grundin. 1987. Elemental changes in guinea-pig epidermis in the hyperplastic response to irritant stimuli. *Br. J. Dermatol.* 116:477–484.

Lisby, S., O. Baadsgaard, K. D. Cooper, and G. L. Vejlsgaard. 1989. Decreased number and function of antigen-presenting cells in the skin following application of irritant agents: Relevance for skin cancer? *J. Invest. Dermatol.* 92:842–847.

Lisby, S., K. M. Müller, C. V. Jongeneel, J.-H. Saurat, and C. Hauser. 1995. Nickel and skin irritants up-regulate tumor necrosis factor-$\alpha$ mRNA in keratinocytes by different by potentially synergistic mechanisms. *Int. Immunol.* 7:343–352.

Lodén, M. 1990. The simultaneous penetration of water and sodium lauryl sulfate through isolated human skin. *J. Soc. Cosmet. Chem.* 41:227–233.

Löffler, H., and I. Effendy. 1997. Crescendo reactions to sodium lauryl sulfate and retinoic acid in irritant patch tests. *Contact. Dermatitis* 37:47–48. Abstract.

Loveless, S. E., G. S. Ladics, G. F. Gerberick, C. A. Ryan, D. A. Basketter, E. W. Scholes, R. V. House, J. Hilton, R. J. Dearman, and I. Kimber. 1996. Further evaluation of the local lymph mode assay in the final phase of an international collaborative trial. *Toxicology* 108:141–152.

Luster, M. I., J. L. Wilmer, D. R. Germolec, J. Spalding, T. Yosihda, K. Gaido, P. P. Simenova, F. G. Burleson, and A. Bruccoleri. 1995. Role of keratinocyte-derived cytokines in chemical toxicology. *Toxicol. Lett.* 82/83:471–476.

Machida, M., K. Sano, M. Arakawa, M. Hayashi, and S. Awazu. 1994. Effects of surfactants and protease inhibitors on nasal absorption of recombinant human granulocyte colony-stimulating factor (rhG-CSF) in rats. *Biol. Pharm. Bull.* 17:1375–1378.

Manetz, T. S., D. A. Pettit, and B. J. Meade. 2001. The determination of draining lymph node cell cytokine mRNA levels in BALA/c mice following dermal sodium lauryl sulfate, dinitrofluorobenzene, and toluene diisocyanate exposure. *Toxicol. Appl. Pharmacol.* 171:174–183.

Marinovich, M., E. Tragni, A. Corsini, and C. L. Galli. 1990. Quantification of in vitro cytotoxicity of surfactants: Correlation with their eye irritation potential. *J. Toxicol. Cutan. Ocul. Toxicol.* 9:169–178.

Marks, R., and T. Kingston. 1985. Acute skin toxicity reactions in man tests and mechanisms. *Food Chem. Toxicol.* 23:155–164.

Mathur, A. K., B. N. Gupta, A. Singh, S. Singh, and R. Shanker. 1993. Renal toxicity of nickel, sodium lauryl sulphate and their combination after dermal application in guinea pigs. *Biomed. Environ. Sci.* 6:231–236.

Mathur, A. K., C. Agarwal, A. Singh, and B. N. Gupta. 1988. Effect of sodium lauryl sulphate and nickel alone and in combination on the skin of guinea pigs. *Toxicol. Lett.* 42:249–256.

Mathur, A. K., B. N. Gupta, A. Singh, S. Singh, S. Narang, and R. Shanker. 1992. Cutaneous toxicity of sodium lauryl sulphate, nickel, and their combination in guinea pigs: Biochemical and histopathological observations. *Bull. Environ. Contam. Toxicol.* 49:871–878.

Mathur, A. K., B. N. Gupta, A. Singh, S. Singh, R. Shanker, and S. Narang. 1991. Hepato-toxicity of nickel, sodium lauryl sulphate and their combination after repeated dermal application in guinea pigs. *J. Environm. Sci. Health A Environ. Eng.* A26:1333–1343.

McFadden, J. P., S. H. Wakelin, and D. A. Basketter. 1998. Acute irritation thresholds in subjects with Type I-Type VI skin. *Contact. Dermatitis* 38:147–149.

McGregor, D. B., A. Brown, P. Cattanach, I. Edwards, D. McBride, and W. J. Caspary. 1986. Results of L-5178Y mouse lymphoma cell mutagenesis experiments with coded compounds. *Toxicol. Lett. (Amsterdam)* 31:213. Abstract.

McGregor, D. B., A. Brown, P. Cattanach, I. Edwards, D. McBride, C. Riach, and W. J. Caspary. 1988. Responses of the L5178Y tk+/tk− mouse lymphoma cell forward mutation assay III. 72 coded chemicals. *Environ. Mol. Mutagen.* 12:85–154.

McLelland, J., S. Shuster, and J. N. S. Matthews. 1991. 'Irritants' increase the response to an allergen in allergic contact dermatitis. *Arch. Dermatol.* 127:1016–1019.

Meeks, R. G., D. Zaharevitz, and R. F. Chen. 1981. Membrane effects of retinoids: Possible correlation with toxicity. *Arch. Biochem. Biophys.* 207:141–147.

Mikulowska, A. 1990. Reactive changes in the Langerhans' cells of human skin cause by occlusion with water and sodium lauryl sulfate. *Acta Derm. Venerol.* 70:468–473.

Mikulowska, A., and A. Andersson. 1996. Sodium lauryl sulfate effect on the density of epidermal Langerhans cells. Evaluation of different test models. *Contact. Dermatitis* 34:397–401.

Miura, Y. 1987. Effects of in-vivo administration of detergents on the hepatic microsomal cytoch rome P-450 system in rat. *J. Appl. Toxicol.* 7:213–217.

Miura, Y., H. Hisaki, B. Fukushima, T. Nagai, and T. Ikeda. 1989. Detergent induced changes in serum lipid composition in rats. *Lipids* 24:915–918.

Mohamadzadeh, M., M. Müller, T. Hultsch, A. Enk, J. Saloga, and J. Knop. 1994. Enhanced expression of IL-8 in normal human keratinocytes and human keratinocyte cell line HaCaT in vitro after stimulation with contact sensitizers, tolerogens and irritants. *Exp. Dermatol.* 3:298–303.

Montserret, R., M. J. McLesih, A. Böckmann, C. Geourjon, and F. Penin. 2000. Involvement of electrostatic interactions in the mechanism of peptide folding induced by sodium dodecyl sulfate binding. *Biochemistry* 39:8362–8373.

Mortelmans, K., S. Haworth, T. Lawlor, W. Speck, B. Tainer, and E. Zeiger. 1986. *Salmonella* mutagenicity testing of 270 chemicals. *Environ. Mutagen.* 8:1–119.

Muir, C. K. 1987. Surfactant-induced opacity of bovine isolated cornea: An epithelial phenomenon. *Toxicol. Lett.* 38:51–54.

Müller-Decker, K., T. Heinzelmann, G. Fürstenberger, A. Kecskes, W.-D. Lehmann, and F. Marks. 1998. Arachidonic acid metabolism in primary irritant dermatitis produced by patch testing of human skin with surfactants. *Toxicol. Appl. Pharmacol.* 153:59–67.

Newby, C. S., R. M. Barr, M. W. Greaves, and A. I. Mallet. 2000. Cytokine release and cytotoxicity in human keratinocytes and fibroblasts induced by phenols and sodium dodecyl sulfate. *J. Invest. Dermatol.* 115:292–298.

Nordlind, K., and J. Thyberg. 1986. In-vitro effects of sodium lauryl sulfate on DNA synthesis and fine structure of human thymocytes. *Int. Arch. Allergy Appl. Immunol.* 81:165–169.

North-Root, H., F. Yackovich, J. Demtrulias, M. Gacula, Jr., and J. E. Heinze. 1985. Prediction of the eye irritation potential of shampoos using the in-vitro SIRC cell toxicity test. *Food Chem. Toxicol.* 23:271–274.

Oba, K., and R. Takei. 1992. Carcinogenic mutagenic-genetic toxicity and teratogenic properties. In *Surfactant science series, vol. 43, Anionic surfactants: Biochemistry, toxicology, dermatology,* 2nd ed., ed. C. Gloxhuber, K. Kuenstler, 331–409. New York: Marcel Dekker, Inc.

Ollmar, S., and L. Emtestam. 1992. Electrical impedence applied to non-invasive detection of irritation in skin. *Contact. Dermatitis* 27:37–42.

Osborne, R., and M. A. Perkins. 1990. In-vitro irritation testing with human skin cell cultures. *Toxicol. In Vitro.* 5:563–568.

Osborne, R., M. A. Perkins, and C. Hudson. 1990a. Evaluation of surfactant-induced toxicity in cultured human skin cells. *Invest. Dermatol.* 94:562. Abstract.

Osborne, R., M. A. Perkins, and C. Hudson. 1990b. Evaluation of surfactant-induced toxicity in cultured human skin cells. *Clin. Res.* 38:616A.

O'Neill, C. A., R. A. Gunther, G. J. Jesmok, and S. N. Giri. 1991. Effects of recombinant human interleukin-2 and excipient infusion on plasma levels of prostaglandins and thromboxane B2 in sheep. *Lymphokine Cytokine Res.* 10:207–212.

Palacio, S., D. Schmitt, and J. Vivac. 1997. Contact allergens and sodium lauryl sulfate upregulate vascular endothelial growth factor in normal keratinocytes. *Br. J. Dermatol* 137:540–544.

Pasche-Koo, F., A. Arechalde, J.-F. Arrighi, and C. Hauser. 1995. Effect of *N*-acetylcysteine, an inhibitor of tumor necrosis factor, in irritant contact dermatitis in the human. *Curr. Probl. Dermatol.* 23:198–206.

Patil, S. M., P. Singh, and H. I. Maibach. 1994. Cumulative irritancy in man to sodium lauryl sulfate: The overlap method phenomenon. *Int. J. Pharmaceut.* 110:147–154.

Patil, S. M., P. Singh, K. Sarasour, and H. I. Maibach. 1995. Quantification of sodium lauryl sulfate penetration into the skin and underlying tissues after topical application—pharmacological and toxicological implications. *J. Pharm. Sci.* 84:1240–1244.

Patterson, S. E., J. V. Williams, and J. G. Marks, Jr. 1999. Prevention of sodium lauryl sulfate irritant contact dermatitis by Pro-Q aerosol foam skin protectant. *J. Am. Acad. Dermatol.* 40:783–785.

Phillips, B. J., D. Anderson, and S. D. Gangolli. 1986. *Environ. Health Perspect.* 65:263–266.

Pichowski, J. S., M. Cumberbatch, Dearman, D. A. Basketter, and I. Kimber. 2000. Investigation of induced ch anges in interleukin 1beta mRNA expression by cultured human dendritic cells as an in vitro approach to skin sensitization testing. *Toxicol. In Vitro* 14:351–360.

Pinnagoda, J., R. A. Tupker, P. J. Coenraads, and J. P. Nater.1989. Prediction of susceptability to an irritant response by transepidermal water loss. *Contact. Dermatitis* 20:341–346.

Ponec, M., and J. Kempenaar. 1995. Use of human skin recombinants as an in vitro model for testing the irritation potential of cutaneous irritants. *Skin. Pharmacol.* 8:49–59.

Potokar, M. S. 1992. Acute subacute and chronic toxicity data on anionics. In *Surfactant science series, vol. 43, Anionic surfactants: Biochemistry, toxicology, dermatology*, 2nd ed., ed. C. Gloxhuber and K. Kuenstler, 81–116. New York: Marcel Dekker, Inc.

Prinsen, M. K., T. Romijn, and Snoeig, N. J. 1997. Skin sensitization testing: The relevance of rechallenge and pretreatment with sodium lauryl sulfate in guinea pig maximization test. *Food Chem. Toxicol.* 35:923–926.

Product Safety Labs. 1980a. Initial submission: Letter from Rhone-Poulenc Inc submitting two skin corrosion studies with sodium lauryl sulfate in rabbits. NTIS Report No. OTS0539861.

Product Safety Labs. 1980b. Initial submission: Modified eye irritation study with sodium lauryl sulfate in rabbits with cover letter dated 051592. NTIS Report No. OTS0539896.

Product Safety Labs. 1980c. Initial submission: Letter from Rhone-Poulenc Inc submitting two corrosion studies with ammonium lauryl sulfate in rabbits. NTIS Report No. OTS0539864.

Product Safety Labs. 1980d. Initial submission: DOT skin corrosion and primary skin irritation studies with sodium lauryl sulfate in rabbits with cover letter dated 051592. NTIS Report No. OTS0539901.

Rees, P., J. Watson, R. H. Cumming, J. Liddell, and P. Turner. 1996. Effects of heat shock on Gram negative bacteria: Use of lysis by sodium dodecyl sulphate as a probe for the integrity of DNA. *Bioseparation* 6:125–132.

Rheins, L. S., M. A. Haren, and E. V. Buehler. 1993. Alterations in the cutaneous immune response following topical application of sodium lauryl sulfate and Kathon CG. *J. Toxicol. Cutan. Ocul. Toxicol.* 12:249–259.

Rheins, L. D., F. A. Simion, R. L. Hill, R. H. Cagan, J. Mattai, and H. I. Maibach. 1990. Human cutaneous response to a mixed surfactant system: Role of solution phenomena in controlling surfactant irritation. *Dermatologica* 180:18–23.

Rivalland, P., L. Coiffard, and Y. De Roeck-Holtzhauer. 1994. Determination of the cytotoxicity of sodium lauryl sulfate on reconstituted skin. *Cell. Biol. Toxicol.* 10:436.

Robinson, M. K. 1999. Population differences in skin structure and physiology and the susceptibility to irritant and allergic dermatitis: Implication for skin safety testing and risk assessment. *Contact. Dermatitis* 41:65–79.

Robinson, M. K., M. A. Perkins, and D. A. Basketter. 1998. Application of a 4-h human patch test method for comparative and investigative assessment of skin irritation. *Contact. Dermatitis* 38:194–202.

Roguet, R., K. G. Dossou, and A. Rougier. 1992. Use of in vitro skin recombinants to evaluate cutaneous toxicity: A preliminary study. *J. Toxicol.* 11:305–315.

Rougier, A. 1995. Examples of the use of cell cultures in skin irritancy assessment. *Curr. Probl. Dermatol.* 22:214–230.

Rougier, A., M. Cottin, O. De Silva, P. Catroux, R. Rouget, and K. G. Doosou. 1994. The use of in vitro methods in the ocular irritation a ssessment of cosmetic products. *Toxicol. In Vitro* 8:893–905.

Rowe, T. C., D. Grabowski, and R. Ganapathi. 2001. Isolation of covalent enzyme-DNA complexes. *Methods Mol. Biol.* 95:129–135.

Ryan, C. A., and G. F. Gerberick. 1999. Cytokine mRNA expression in human epidermis after patch treatment with rhus and sodium lauryl sulfate. *Am. J. Contact. Dermatitis* 10:127–135.

Santa Maria, A., J. M. Pozuelo, A. Lopez, and F. Sanz. 1996. Toxicity of potential irritants in mammalian cells in vitro. *Ecotoxicol. Environ. Safety* 34:56–58.

Scaife, M. C. 1985. An in-vitro cytotoxicity test to predict the ocular irritation potential of detergents and detergent products. *Food Chem. Toxicol.* 23:253–258.

Schneider, A. I., K. Maier-Reif, and T. Graeve. 1997. The use of an in vitro cornea for predicting molecular and cellular toxicity. *In Vitro Toxicol.* 10:309–318.

Seidenarsi, S. 1994. Echographic evaluation with image analysis of irritant reactions induced by nonanoic acid and hydrochloric acid. *Contact. Dermatitis* 31:146–150.

Seidenari, S., and B. Belletti. 1994. Instrumental evaluation of subclinical irritation induced by sodium lauryl sulfate. *Contact. Dermatitis* 30:175.

Seidenari, S., B. Belletti, and M. E. Schiavi. 1996. Skin reactivity to sodium lauryl sulfate in patients with respiratory atopy. *J. Am. Acad. Dermatol.* 35:47–52.

Seidenarsi, S., and A. Di Nardo. 1992. B scanning evaluation of irritant reactions with binary transformation and image analysis. *Acta Derm. Venerol. Suppl.* 175:9–13.

Serup, J., and B. Staberg. 1987. Ultrasound for assessment of allergic and irritant patch test reactions. *Contact. Dermatitis* 17:80–84.

Shadduck, J. A., J. Everitt, and P. Bay. 1985. Use of in-vitro cytotoxicity to rank ocular irritation of six surfactants. In *Alternative methods in toxicology*, *vol. 3, In vitro toxicology*, ed. A. M. Goldberg, 641–650.

Shopis, C., and B. Eng. 1985. Rapid cytotoxicity testing using a semi-automated protein determination on cultured cells. *Toxicol. Lett.* 26:1–8.

Sladowski, D. T., S. J. Steer, L. Moore, A. Willshaw, R. H. Clothier, and M. Balls. 1994. The complement activation assay: The test for immediate phototoxicity. *Toxicol. In Vitro* 8:513–515.

Spoo, J. W., R. A. Rogers, and N. A. Monteiro-Riviere. 1992. Effects of formaldehyde, DMSO, benzoyl peroxide, and sodium lauryl sulfate on isolated perfused porcine skin. *In Vitro Toxicol.* 5:251–260.

Stephens, T. J., and P. R. Bergstresser. 1985. Fundamental concepts in photoimmunology and photoallergy. *J. Toxicol. Cutan. Ocul. Toxicol.* 4:193–218.

Steven, F. S., M. M. Griffin, M. Anees, and E. W. Benbow. 1992. Observations on the conformational changes in the structure of a cell surface protease, followed by its ability to be recognized by competitive and noncompetitive inhibitors. *J. Enzyme Inhib.* 6:251–258.

Stolz, R., U. Hinnen, and P. Elsner. 1997. An evaluation of the relationship between 'atopic skin' and skin irritability in metalworker trainees. *Contact. Dermatitis* 36:281–284. New York: Mary Ann Liebert, Inc.

Stringer, C. P., R. Hicks, and P. A. Botham. 1991. The expression of MHC Class II (Ia) antigens on mouse keratinocytes following epicutaneous application of contact sensitizers and irritants. *Br. J. Dermatol.* 125:521–528.

Tachon, P., J. Cotovio, K. G. Dossou, and M. Prunieras. 1989. Assessment of surfactant cytotoxicity: Comparison with the Draize eye test. *Int. J. Cosmet. Sci.* 11:233–243.

Tausch, I., Bielfeldt, A. Hildebrand, and J. Gassmüller. 1996. Validation of a modified Duhring Chamber Test (DCT) as a repeated patch test for the assessment of the irritant potential of topical preparations. *Parfume Kosmet.* 77:28–31

Tavss, E. A., E. Eigen, and A. M. Kligman. 1988. Anionic detergent-induced skin irritation and anionic detergent-induced pH rise of bovine serum albumin. *J. Soc. Cosmet. Chem.* 39:267–272.

Thyrum, P. T., and B. Jirgensons. 1980. Interactions between tumor-promoting agents and histones studied by circular dichromism. *Cancer. Biochem. Biophys.* 5:7–13.

Treffel, P., and B. Gabard. 1996. Measurement of sodium lauryl sulfate-induced skin irritation. *Acta Derm. Venereol.* 76:341–343.

Tupker, R. A., E. E. Bunte, V. Fidler, J. W. Wiechers, and P. J. Coenraads. 1999. Irritancy ranking of anionic detergents using one-time occlusive, repeated occlusive and repeated open tests. *Contact. Dermatitis* 40:316–322.

Tupker, R. A., P.-J. Coenraads, J. Pinnagoda, and J. P. Nater. 1989. Baseline transepidermal waterloss (TEWL) as a prediction of susceptability to sodium lauryl sulphate. *Contact. Dermatitis* 20:265–269.

Tupker, R. A., J. Pinnagoda, P.-J. Coenraads, and J. P. Nater. 1989. The influence of repeated exposure to surfactants on the human skin as determined by

transepidermal water loss and visual scoring. *Contact. Dermatitis* 20:108–114.

Tupker, R. A., J. Pinnagoda, and J. P. Nater. 1990. The transient effect of sodium lauryl sulfate on the epidermal barrier assessed by transepidermal water loss: Inter-individual variation. *Acta Derm. Venerol.* 70:1–5.

Tuschl, H., R. Kovac, and E. Weber. 2001. The expression of surface markers on dendritic cells as indicators for the sensitizing potential of chemicals. *Toxicol. In Vitro* 14:541–549.

Ulfgren, A. K., L. Klareskog, and M. Lindberg. 2000. An immunohistochemical analysis of cytokine expression in allergic and irritant contact dermatitis. *Acta Derm. Venerol.* 80:167–170.

Van Der Valk, P. G. M., and H. I. Maibach. 1989. Post-application occlusion substantially increases the irritant response of the skin to repeated short-term sodium lauryl sulfate (SLS) exposure. *Contact. Dermatitis* 21:335–338.

van de Sandt, J. J. M., T. T. Bos, and A. A. J. J. L. Rutten. 1995. Epidermal cell proliferation and terminal differentiation in skin organ culture after topical exposure to sodium dodecyl sulphate. *In Vitro Cell. Dev. Biol. Anim.* 31:761–766.

Van Duijnhoven-Avontuur, W. M. G., J. A. C. Alkemade, J. Schalkwijk, P. D. Mier, and P. G. M. Van der Valk. 1994. The inflammatory and proliferative response of normal skin in a model for acute chemical injury: Ornithine decarboxylase induction as a common feature in various models for acute skin injury. *Br. J. Dermatol.* 130:725–730.

Van Neste, D. 1990. In vivo evaluation of unbound water accumulation in stratum corneum: The influence of acute skin irritation induced by sodium lauryl sulfate. *Dermatologica* 181:197–201.

Van Neste, D., and B. De Brouwer. 1992. Monitoring of skin response to sodium lauryl sulphate: Clinical scores versus bioengineering methods. *Contact. Dermatitis* 27:151–156.

Van Neste, D., G. Mahmoud, and M. Masmoudi. 1987. Experimental induction of rough dermatitic skin in humans. *Contact. Dermatitis* 16:27–33.

Villeponteau, B. 1989. Characterization of a topoisomerase-like activity at specific hypersensitive sites in the *Drosophila* histone gene cluster. *Biochem. Biophys. Res. Commun.* 162:232–237.

Vinardell, M. P., and M. Macián. 1994. Comparative study of the HET-CAM test and the Draize eye test for assessment of irritancy potential. *Toxicol. In Vitro* 8:467–470.

von den Driesch, P., M. Fartasch, A. Hüner, and M. Ponec. 1995. Expression of integrin receptors and ICAM-1 on keratinocytes in vivo and in an in vitro reconstructed epidermis: Effect of sodium dodecyl sulphate. *Arch. Dermatol. Res.* 287:249–253.

Wahlberg, J. E., and H. I. Maibach. 1981. Sterile cutaneous pustles: A manifestation of primary irritancy?: Identification of contact pustologens. *J. Invest. Dermatol.* 76:381–383.

Wahlberg, J. E., K. Wrangsjö, and A. Hietasalo. 1985. Skin irritancy from nonanoic acid. *Contact. Dermatitis* 13:266–269.

Walker, A. P. 1985. A more realistic animal technique for predicting human eye response. *Food Chem. Toxicol.* 23:175–178.

Ward, R. K., A. W. Hubbard, H. Sulley, M. J. Garle, and R. H. Clotheir. 1998. Human keratinocyte cultures in an in vitro approach for the assessment of surfactant-induced irritation. *Toxicol. In Vitro.*12:163–173.

Watson, R. E. B., N. M. Craven, S. Kang, C. J. P. Jones, C. M. Kielty, and C. E. M. Griffiths. 2001. A short-term screening protocol, using fibrillin -1 as a reporter molecule, for photoaging repair agents. *J. Invest. Dermatol.* 116:672–678.

Welzel, J., C. Metker, H. H. Wolff, and K.-P. Wilhelm. 1998. SLS-irritated human skin shows no correlation between degree of proliferation and TEWL increase. *Arch. Dermatol. Res.* 290:615–620.

Wilhelm, K.-P., G. Freitag, and H. H. Wolff. 1994. Surfactant-induced skin irritation and skin repair. Evaluation of the acute human irritation model by noninvasive techniques. *J. Am. Acad. Dermatol.* 30:944–949.

Wilhelm, K.-P., and H. I. Maibach. 1990. Susceptibility to irritant contact dermatitis induced by sodium lauryl sulfate. *J. Am. Acad. Dermatol* 23:122–124.

Wilhelm, K.-P., J. C. Saunders, H. I. Maibach. 1990. Increased stratum corneum turnover induced by subclinical irritant dermatitis. *Br. J. Dermatol.* 122:793–798.

Willis, C. M., C. J. M. Stephens, and J. D. Wilkinson. 1988a. Experimentally-in duced irritant contact dermatitis: Determination of optimum irritant concentrations. *Contact. Dermatitis* 18:20–24.

Willis, C. M., C. J. M. Stephens, and J. D. Wilkinson. 1988b. Assessment of erythema in irritant contact dermatitis. *Contact. Dermatitis* 18:138–142.

Willis, C. M., C. J. M. Stephens, and J. D. Wilkinson. 1989. Epidermal damage induced by irritants in man: A light and electron microscopic study. *J. Invest. Dermatol.* 93:695–699.

Willis, C. M., C. J. M. Stephens, J. D. Wilkinson. 1990a. Differential effects of structurally unrelated chemical irritants on the density and morphology of epidermal CD1+ cells. *J. of Invest. Dermatol.* 95:711–716.

Willis, C. M., C. J. M. Stephens, J. D. Wilkinson. 1990b. Differential patterns of epidermal leukocyte infiltration in patch test reactions to structurally unrelated chemical irritants. *J. Invest. Dermatol.* 101:364–370.

Willis, C. M., C. J. M. Stephens, and J. D. Wilkinson. 1992. Differential effects of structurally unrelated chemical irritants on the density of proliferating keratinocytes in 48 h patch test reactions. *J. Invest. Dermatol.* 99:449–453.

Willshaw, A., L. J. Moore, and M. Balls. 1994. In vitro alternatives for the detection of photoirritant chemicals: The EEC trial. *Toxicol. In Vitro* 8:723–735.

Wilmer, J. L., F. G. Burleson, F. Kayama, J. Kanno, and M. I. Luster. 1994. Cytokine induction in human epidermal keratinocytes exposed to contact irritants and its relation to chemical-induced inflammation in mouse skin. *J. Invest. Dermatol.* 102:915–922.

Wollina, U., V. Fuenfstueck, C. Hipler, and B. Knopf. 1988. Alterations of epidermal lectin binding sites in acute contact dermatitis. *Contact. Dermatitis* 19:109–115.

Xu, G., H. M. Leibich, R. Lehmann, and S. Müller-Hagedorn. 2001. Capillary electrophoresis of urinary normal and modified nucleosides of cancer patients. *Methods Mol. Biol.* 162:459–474.

Yang, E. K., H. H. Yoon, D. H. Lee, and J. K. Park. 2000. Assessment of toxic potential of industrial chemicals using a cultured human bioartificial skin model: Production of interleukin 1$\alpha$ and hydroxyeicosatetraenoic acids. *Skin Pharmacol. Appl. Skin Physiol.* 13:246–257.

York, M., D. A. Basketter, J. A. Cuthbert, and L. Neilson. 1995. Skin irritation testing in man for hazard assessment—evaluation of four patch systems. *Hum. Exp. Toxciol.* 14:729–734.

Younger Laboratories. 1974. Initial submission: Dermal toxicity study of dodecyl sodium sulfate in rabbits with cover letter dated 08 /13/ 92. NTIS Report No. OTS0555175.

Zehnder, S., R. Mark, S. Manning, A. Sakr, J. L. Lichtin, and K. L. Gabriel. 1992. Human in vivo method for assessing reduction of the irritation potential of sodium lauryl sulfate by mild surfactants: Validation with an ether carboxylate with two different degrees of ethoxylation. *J. Soc. Cosmet. Chem.* 43:313–330.

Zhitkovich, A., and M. Costa. 1992. A simple, sensitive assay to detect DNA-protein crosslinks in intact cells and in vivo. *Carcinogenesis* 13:1485–1489.

Zhou, J., R. Mark, T. Stoudemayer, A. Sakr, J. L. Lichthin, and K. L. Gabriel. 1991. The value of multiple instrumental and clinical methods, repeated patch applications, and daily evaluations for assessing stratum corneum changes induced by surfactants. *J. Soc. Cosmet. Chem.* 42:105–128.

## SWEET ALMOND OIL AND ALMOND MEAL

The CIR Expert Panel published the Final Report on the Safety Assessment of Sweet Almond Oil and Almond Meal in 1983 (Elder 1983), with the conclusion that these ingredients are safe for topical application to humans in the present practices of use and concentration.

Since that time, the naming convention for plant-derived cosmetic ingredients has been changed, and Sweet Almond Oil and Almond Meal have been renamed Prunus Amygdalus Dulcis Oil and Prunus Amygdalus Dulcis Seed Meal (Pepe et al. 2002). New studies since the original safety assessment are listed at the end of this review. These new studies, along with the updated information regarding types and concentrations of use, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

The number of cosmetic formulations using Prunus Amygdalus Dulcis Oil reported to the FDA increased from 280 in 1976 to 375 in 2002. Concentration of use has not changed appreciably, although there was a reported use of sweet almond oil at 76% in a manicuring product. In addition, the Panel noted new uses in baby products, hair sprays, and eye preparations. The number of cosmetic formulations using Prunus Amygdalus Dulcis Seed Meal reported to the FDA decreased from 16 in 1976 to 15 in 2002, with not significant change in use concentration. Table 26 provides the historic and current product uses and concentrations for Prunus Amygdalus Dulcis Oil and Prunus Amygdalus Dulcis Seed Meal.

Regarding use in hair sprays, the Panel noted that inhalation toxicity data are not included in the original report. A new study in which almond oil, in a nasal spray, was administered to female subjects, without evident toxicity to the lungs, indicates that Sweet Almond Oil and Sweet Almond Seed Meal could be used safely in a hair spray.

The effects of inhaled aerosols depends on the specific chemical species, the concentration, the duration of exposure, and site of deposition within the respiratory system. Particle size is the most important factor affecting the location of deposition (Jensen and O'Brien 1993). The mean aerodynamic diameter of pump hair spray particles is $\leq 80\ \mu$ and the diameter of anhydrous spray particles is 60 to 80 $\mu$. Typically, less than 1% are below 10 $\mu$ which is the upper limit for respirable particles (Bower 1999). Based on the particle size, Sweet Almond Oil and Sweet Almond Seed Meal in aerosol formulations would not be respirable in formulation.

As with the use of all plant-derived cosmetic ingredients, the Panel also reminded manufacturers that cosmetic products should be formulated to limit the presence of heavy metal/pesticide residues as follows: lead $\leq 0.1$ ppm; arsenic $\leq 3$ ppm; mercury $\leq 1$ ppm; and total PCB/pesticide contamination $\leq 40$ ppm, with $\leq 10$ ppm for any specific residue.

## REFERENCES


Beisson, F., N. Ferte, S. Bruley, R. Voultoury, R. Verger, and V. Arrondel. 2001. Oil-bodies as substrates for lipolytic enzymes. *Biochim. Biophys. Acta* 1531:47–58.

Bonhomme, L., G. Fredj, J. L. Grossiord, A. M. Szekely, C. Jasmin, et al. 1993. Formulation of all-trans-retinoic acid gel for topical treatment of epidemic Kaposi sarcoma lesions. *J. Pharm. Clin.* 12:77–80.

Brosig, J., and S. Clemens. 1997. [Echographic diagnosis of efferent lacrimal ducts with contrast media.] *Klin. Monatsbl. Augenheilkd.* 210:27–32.

Cicinelli, E., F. Savino, I. Cagnazzo, P. Scorcia, and P. Galantino. 1992. Progesterone administration by nasal spray in menopausal women: Comparison between two different spray formulations. *Gynecol. Endocrinol.* 6:247–251.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2002. Ingredient Use Data—Prunus Amygdalus Dulcis (Sweet Almond) Oil and Prunus Amygdalus Dulcis (Sweet Almond) Seed Meal. Unpublished data submitted by CTFA dated September 13, 2002. 2 pages.[27]

Davis, P. A., and C. K. Iwahashi. 2001. Whole almonds and almond fractions reduce aberrant crypt foci in a rat model of colon carcinogenesis. *Cancer. Lett.* 165:27–33.

Elder, R. L. ed. 1983. Final report on the safety assessment of sweet almond oil and almond meal. *J. Am. Col. Toxicol.* 2:85–99.

Guillet, G., and M. H. Guillet. 2000 [Percutaneous sensitization to almond oil in infancy and study of ointments in 27 children with food allergy.] *Allergy Immunol. (Paris)* 32:309–311.

Guillot, J. P., J. Y. Giauffret, and M. C. Martini. 1979. A study of skin and eye irritation in the rabbit eye due to different sources of some cosmetic raw materials. Pat II. *Int. J. Cosmet. Sci.* 1:27–57.

Hammer, K. A., C. F. Carson, and T. V. Riley. 1999. Antimicrobial activity of essential oils and other plant extracts. *J. Appl. Microbiol.* 86:985–990.

Hyson, D. A., B. O. Schneeman, and P. A. Davis. 2002. Almonds and almond oil have similar effects on plasma lipids and LDL oxidation in healthy men and women. *J. Nutr.* 132:703–707.

Ishidate, M., Y. Takizawa, Y. Sakabe, M. Ishizaki, D. Watanabe, M. Tate, and K. Takemoto. 1988. Results of mutagenicity screening of food additives (part 9). *Tokishikoroji Foramu (Toxicol. Forum)* 11:663–669.

Iskander, F. Y. 1993. Determination of seventeen elements in edible oils and margarine by instrumental neutron activation analysis. *J. Am. Oil. Chem. Soc.* 70:803–805.

Jumma, M., and B. W. Muller. 1998. Effect of oil components and homogeniziation conditions on the physiochemical properties and stability of parenteral fat emulsions. *Int. J. Pharmacol.* 163:81–89.

Marti-Mestres, G., H. Mailols, V. Van Sam, B. Guillot, et al. 1994. Study of the hydration and occlusive power in vivo and in vitro of lipophillic excipients and of their oil-phase emulsions. *Int. J. Cosmet. Sci.* 16:161–170.

Messiha, F. S. 1990. Effect of almond and anis oils on mouse liver alcohol dehydrogenase, aldehyde dehydrogenase and heart liver lactate dehydrogenase isoenzymes. *Toxicol. Lett.* 54:183–188.

Niinimaki, A., K. Reijula, T. Pirila, A-M. Koistinen. 1993. Papain-induced allergic rhinoconjunctivitis in a cosmetologist. *J. Allerg. Clin. Immunol.* 92:492–493.

Opdyke, D. L. J. 1979. Monographs on fragrance raw materials. Almond Oil Sweet. *Food Cosmet. Toxicol.* 17:709.

Patkar, K. L., C. M. Usha, H. S. Shetty, N. Paster, and J. Lacey. 1993. Effect of spice essential oils on growth and aflatoxin B1 production by Aspergillus flavus. *Lett. Appl. Microbiol.* 17:49–51.

Ruiz Del Castillo, M. L., M. Herraiz, and G. P. Blanch. 2000. Determination of the enantiomeric of gamma-lactones in edible oils by on-line coupled high performance liquid chromatography and gas chromatography. *J. Agric. Food Chem.* 48:1186–1190.

Sanchez, A., D. A. Rubano, G. W. Shavilk, P. Fagenstrom, U. D. Register, and R. W. Hubbard. 1988. Separate effects of dietary protein and fat on serum cholesterol levels: Another view of amino acid content of proteins. *Arch. Latinoam Nutr.* 38:239–250.

Spiller, G. A., D. J. Jenkins, L. N. Cragen, J. E. Gates, O. Bosello, K. Berra, C. Rudd, M. Stevenson, and R. Superko. 1992. Effect of diet high in monounsaturated fat from almonds on plasma and cholesterol and lipoproteins. *J. Am. Col. Nutr.* 11:126–130.

Thomas, P., A. Boussuges, M. Gainnier, V. Quenee, S. Donati, M. L. Ayem, A. Barthelemy, and J. M. Sainty. 1998. [Fat embolism after intrapenile injection of sweet almond oil.] *Rev. Mal. Respir.* 15:307–308.


[27] Available from Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

**TABLE 26**
Historical and current product formulation data for Prunus Amygdalus Dulcis Oil and Prunus Amygdalus Dulcis Seed Meal

| Product type | 1976 uses (Elder 1983) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1983) (%) | 2002 use concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| *Prunus Amygdalus Dulcis Oil (formerly Sweet Almond Oil)* | | | | |
| Baby shampoos | — | 1 | — | — |
| Baby lotions, oils, powders, and creams | — | 4 | — | — |
| Baby products (other) | — | 2 | — | — |
| Bath oils, tablets, and salts | 1 | 5 | >0.1–1 | 0.1 |
| Bubble bath | — | 1 | — | 0.01 |
| Bath preparations (other) | — | 4 | — | 0.05–0.1 |
| Eye lotion | — | 1 | — | — |
| Eye makeup remover | — | 2 | — | — |
| Eye makeup (other) | — | 3 | — | 0.4 |
| Powders | — | 5 | — | 2 |
| Fragrance preparations (other) | 3 | 4 | >1–5 | 1 |
| Hair conditioners | — | 19 | — | 2 |
| Hair sprays (aerosol fixatives) | — | 3 | — | — |
| Shampoos (noncoloring) | 1 | 5 | ≤0.1 | 0.3 |
| Hair tonics, dressings, etc. | — | 16 | — | 1–3 |
| Hair preparations (other noncoloring) | — | 2 | — | — |
| Hair lighteners with color | — | — | — | 0.1 |
| Hair bleaches | — | 2 | — | — |
| Blushers | 3 | — | >5–10 | — |
| Face powders | 1 | — | ≤0.1 | — |
| Foundations | 2 | 1 | >0.1–10 | — |
| Lipstick | 184 | 3 | ≤0.1–25 | 0.5 |
| Makeup bases | 5 | 1 | >0.1–5 | — |
| Makeup (other) | — | — | — | 0.4 |
| Cuticle softeners | — | 2 | — | — |
| Nail creams and lotions | — | 1 | — | — |
| Nail polish and enamel removers | 1 | 1 | ≤0.1 | — |
| Manicuring preparations (other) | — | — | — | 1–76 |
| Bath soaps and detergents | — | 16 | — | 0.5 |
| Deodorants (underarm) | — | — | — | 0.004 |
| Personal cleanliness products (other) | — | 3 | — | — |
| Aftershave lotions | — | — | — | 0.1 |
| Shaving cream | 1 | 2 | >1–5 | — |
| Skin-cleansing creams, lotions, liquids, and pads | 12 | 32 | ≤0.1–50 | 0.1 |
| Depilatories | — | 2 | — | — |
| Face and neck skin care preparations | 9* | 19 | >1–5* | — |
| Body and hand skin care preparations | | 60 | | 0.08–8 |
| Foot powders and sprays | — | — | — | 3 |
| Moisturizers | 21 | 60 | ≤0.1–25 | 0.2–11 |
| Night skin care preparations | 17 | 16 | >1–50 | 0.4–3 |
| Paste masks/mud packs | 3 | 12 | >1–5 | 0.5 |
| Skin fresheners | — | 1 | — | — |
| Skin care preparations (other) | 6 | 43 | >0.1–25 | 3–5 |
| Suntan gels, creams, and liquids | 10 | 17 | >0.1–25 | 0.01–2 |

*(Continued on next page)*

**TABLE 26**
Historical and current product formulation data for Prunus Amygdalus Dulcis Oil and Prunus Amygdalus Dulcis Seed Meal *(Continued)*

| Product type | 1976 uses (Elder 1983) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1983) (%) | 2002 use concentrations (CTFA 2002) (%) |
|---|---|---|---|---|
| Indoor tanning preparations | — | 2 | — | 0.5 |
| Suntan preparations (other) | — | 2 | — | — |
| **Total uses/ranges for Prunus Amygdalus Dulcis Oil** | **280** | **375** | **≤0.1–50** | **0.004–76** |
| *Prunus Amygdalus Dulcis Seed Meal (formerly Sweet Almond Meal)* | | | | |
| Powders | — | — | — | 27 |
| Cuticle softeners | — | 1 | — | — |
| Bath soaps and detergents | — | 2 | — | 0.5–2 |
| Personal cleanliness products (other) | — | 1 | — | — |
| Skin-cleansing creams, lotions, liquids, and pads | 6 | 2 | >1–25 | — |
| Body and hand skin care preparations | — | 1 | — | 0.5 |
| Paste masks | 6 | 7 | >0.1–5 | 2 |
| Skin care preparations (other) | 4 | 1 | >0.1–5 | — |
| **Total uses/ranges for Prunus Amygdalus Seed Meal** | **16** | **15** | **>0.1–25** | **0.5–27** |

*These categories were combined when the original safety assessment was performed and are now two separate categories.

Van Hoogmoed, L. M., D. W. Agnew, M. Whitcomb, D. W. Hyde, M. H. MacDonald, and J. R. Snyder. 2002. Ultrasonographic and histologic evaluation of medial and middle patellar ligaments in exercised horses following injections with ethanolamine oleate and 2% iodine in almond oil. *Am. J. Vet. Res.* 63:738–743.

Weber, L. F. 1937. External causes of dermatitis. A list of irritants. *Arch. Dermatol. Syphilo.* 35:129–179.

## VINYL ACETATE/CROTONIC ACID COPOLYMER

A safety assessment of the Vinyl Acetate/Crotonic Acid Copolymer was published in 1983 with the conclusion that this ingredient is "considered safe as a cosmetic ingredient under present practices of product and concentration use" (Elder 1983). New studies (listed at the end of this section), along with updated information regarding types and concentrations of use, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

The name of Vinyl Acetate/Crotonic Acid Copolymer as listed in the *International Cosmetic Ingredient Dictionary and Handbook*, 9th edition, has been changed to VA/Crotonates Copolymer (Pepe et al. 2002).

VA/Crotonates Copolymer was used in 55 cosmetic products in 1976, with the largest use occurring in hair sprays at concentrations of >0.01% to 25%. In 2002, VA/Crotonates Copolymer was used in 38 cosmetic products (FDA 2002), at a maximum use concentration of 11% in hair sprays (CTFA 2002b). Table 27 presents the available use information for VA/Crotonates Copolymer.

The CIR Expert Panel acknowledged the use of Vinyl Acetate/Crotonic Acid Copolymer in aerosol hair sprays. The effects of inhaled aerosols depend on the specific chemical species, the concentration, the duration of exposure, and site of deposition within the respiratory system. Particle size is the most important factor affecting the location of deposition (Jensen and O'Brien 1993). The mean aerodynamic diameter of pump hair spray particles is $\geq 80\ \mu$, and the diameter of anhydrous hair spray particles is 60 to 80 $\mu$. Typically less than 1% are below 10 $\mu$, which is the upper limit for respirable particles (Bower 1999). Based on the particle size, Vinyl Acetate/Crotonic Acid Copolymer would not be respirable in formulation.

Although there were reports associating vinyl acetate with nasopharyngeal carcinoma in rat inhalation studies, studies show that the reported carcinogenicity of vinyl acetate in rats is through a nongenotoxic mechanism, and the amount of residual vinyl acetate monomer in VA/Crotonates Copolymer was below the no-observed-effect level. Confirming this, occupational studies in which workers were exposed to vinyl acetate ranging from 5 to 10 ppm, with intermittent exposures near 50 ppm and acute exposures to 300 ppm, showed no long-term chronic effects.

## REFERENCES

Bogdanffy, M. S., and M. L. Taylor. 1993. Kinetics of nasal carboxylesterase-mediated metabolism of vinyl acetate. *Drug Metab. Dispos.* 21:1107–1111.

Bogdanffy, M. S., H. C. Dreef-Van Der Meulen, R. B. Beems, V. J. Feron, T. C. Tascieri, T. R. Taylor, M. B. Vinegar, and R. W. Rickard. 1994a. Chronic

**TABLE 27**
Historical and current product formulation data for VA/Crotonates Copolymer (formerly Vinyl Acetate/Crotonates Copolymer)

| Product category | 1976 use (Elder 1983) | 2002 use (FDA 2002) | 1976 use concentrations (Elder 1983) (%) | 2002 use concentrations (CTFA 2002b) (%) |
|---|---|---|---|---|
| Bath capsules | — | — | — | 9 |
| Eye makeup remover | — | — | — | 9 |
| Mascara | — | 5 | — | — |
| Hair conditioners | 4 | 1 | >1–10 | — |
| Hair sprays (aerosol fixatives) | 30 | 9 | >0.01–25 | 2–11 |
| Hair straighteners | — | 1 | — | — |
| Hair tonics, dressings, etc. | 2 | 10 | >1–5 | 0.05–4 |
| Wave sets | 9 | 3 | >1–5 | 2 |
| Hair preparations (other noncoloring) | 10 | 9 | >1–10 | 2–3 |
| Hair dyes and colors | — | — | — | 5 |
| Moisturizers | — | — | — | 2 |
| **Totals uses/ranges for VA/Crotonates Copolymer** | **55** | **38** | **>0.01–25** | **0.05–11** |

toxicity and oncogenicity inhalation study with vinyl acetate in the rat and mouse. *Fundam. Appl. Toxicol*. 23:215–229.

Bogdanffy, M. S., T. R. Tyler, M. B. Vinegar, R. W. Rickard, F. M. Carpanini, and T. Cascieri. 1994b. Chronic toxicity and oncogenicity study with vinyl acetate in the rat: In utero exposure in drinking water. *Fundam. Appl. Toxicol*. 23:206–214.

Bower, D. 1999. Unpublished information on hair spray particle size provided at the September 9, 1999, CIR Expert Panel meeting.[28]

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2002a. Information regarding VA/Crotonates Copolymer. Unpublished data submitted by CTFA October 31, 2002. 1 page.[28]

CTFA. 2002b. Concentrations of use VA/Crotonates Copolymer. Unpublished data submitted by CTFA November 1, 2002. 1 page.[28]

Deese, D. E., and R. E. Joyner. 1969. Vinyl acetate: A study of chronic human exposure. *American Industrial Hygiene Assoc. Journal*. 30:449–457.

Elder, R. L. 1983. Final report on the safety assessment of vinyl acetate/crotonic acid copolymer. *J. Am. Col. Toxicol*. 2:125–140.

Food and Drug Administration (FDA). 2002. Frequency of use of cosmetic ingredients. *FDA database*. Washington:FDA.

Fromming, K. H., K. P. Krahl, and F. Fischer. 1983. Enteric coated film tablets from an aqueous solution of a copolymer of vinyl acetate and crotonic acid. Part 3. Roentgenographical experiments. *Pharm. Ind*. 45:199–202.

Hurtt, M. E., M. B. Vinegar, R. W. Rickard, T. C. Cascieri, and T. R. Tyler. 1995. Developmental toxicity of oral and inhaled vinyl acetate in the rat.*Fundam. Appl. Toxicol*. 24:198–205.

International Agency on Risk of Cancer (IARC). 1995. Vinyl acetate. *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*. 63:443–466.

Jensen PA, O'Brien D. 1993. Industrial Hygiene. In: Willeke K, Baron PA eds. *Aerosol Measurement. Principles Techniques and Applications*. New York: John Wiley and Sons, Inc., 538–540.

Krahl, K. P., and K. H. Fromming. 1982. Enteric coated film tablets from an aqueous of a copolymer of vinylacetate and crotonic acid. Part 2. In vivo drug release from enteric coated tablets with methylene blue. *Pharm. Ind*. 44:1084–1087.

Kuykendall, J. R., and M. S. Bogdanffy. 1992. Reaction kinetics of DNA-histone crosslinking by vinyl acetate and acetaldehyde. *Carcinogenesis*. 13:2095–2100.

Lahdetie, J. 1988. Effects of vinyl acetate and acetaldehyde on sperm morphology and meiotic micronuclei in mice. *Mutat. Res*. 202:171–178.

Lijinsky, W., and M. D. Reuber. 1983. Chronic toxicity studies of vinyl acetate in Fischer rats. *Toxicol. Appl. Pharm*. 68:43–53.

Maki-Paakkanen, J., and H. Norppa. 1987. Induction of Micronuclei by Vinyl Acetate in Mouse Bone Marrow Cells and Cultured Human Lymphocytes. *Mutat. Res*. 190:41–45.

Maltoni, C., A. Ciliberti, G. Lefemine, and M. Soffritti. 1997. Results of a long-term experimental study on the carcinogenicity of vinyl acetate monomer in mice. *Ann. NY Accad. Sci*. 837:209–238.

Mebus, C. A., F. M. Carpanini, R. W. Rickard, T. C. Cascieri, T. R. Tyler, and M. B. Vinegar. 1995. A two-generation reproduction study in rats receiving drinking water containing vinyl acetate. *Fundam. Appl. Toxicol*. 24:206–216.

Minardi, F., F. Belpoggi, M. Soffritti, A. Ciliberti, M. Lauriola, E. Cattin, and C. Maltoni. 2002. Results of long-term carcinogenicity bioassay on vinyl acetate monomer in Sprague-Dawley rats. *Ann. N.Y. Acad. Sci*. 982:106–122.

Norppa, H., F. Tursi, P. Pfaffli, J. Maki-Paakkanen, and H. Jarventaus.1985. Chromosome damage induced by vinyl acetate through formation of acetaldehyde in human lymphocytes and Chinese ovary cells. *Cancer Res*. 45:4816–4821.

Pepe, R. C., J. A. Wenninger, and G. N. McEwen. 2002. International Cosmetic Ingredient Dictionary and Handbook. 9th ed. Washington, D.C.: CTFA.

Simon, P., J. G. Filser, and H. M. Bolt. 1985. Metabolism and pharmacokinetics of vinyl acetate. *Arch. Toxicol*. 57:191–195.

Sipi, P., H. Jarventaus and H. Norppa. 1992. Sister-chromatid exchanges induced by vinyl esters and respective carboxylic acids in cultured human lymphocytes. *Mutat Res*. 279:75–82.

[28]Available from Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.