*International Journal of Toxicology*, 25(Suppl. 2):1–89, 2006

ISSN: 1091-5818 print / 1092-874X online
DOI: 10.1080/10915810600964618

# Annual Review of Cosmetic Ingredient Safety Assessments—2004/2005[1]

The Cosmetic Ingredient Review (CIR) program Expert Panel has assessed the safety of almost 1300 cosmetic ingredients since its inception in 1976. These safety assessments were published in the *Journal of Environmental Pathology and Toxicology* in 1980, the *Journal of the American College of Toxicology*, from 1982 to 1996, and since then in the *International Journal of Toxicology*.

Because information relevant to the safety of ingredients may have become available since 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 the CIR Expert Panel decides to not reopen a safety assessment, this finding is summarized and announced publicly. To assure that the scientific community is aware of any new information and the decision to not reopen, this *Annual Review of Cosmetic Ingredient Safety Assessments* is prepared.

A reference list is provided that updates the available published literature and includes any unpublished data made available since the original safety assessment.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 2004/2005, and decided not to reopen are:

Benzethonium Chloride and Methylbenzethonium Chloride
2-Bromo-2-Nitropropane-1,3-Diol
Butylated Hydroxyanisole (BHA)
Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol
Cetearyl Octanoate (Ceteraryl Ethylhexanoate)
Cholesterol
Chloroxylenol
Diisopropanolamine, Isopropanolamine, Triisopropanolamine, and Mixed Isopropanolamines
Dioctyl Adipate and Diisopropyl Adipate
Formaldehyde
Hydrolyzed Collagen
*p*-Hydroxyanisole
Isostearyl Neopentanoate
2-Nitro-*p*-Phenylenediamine and 4-Nitro-*o*-Phenylenediamine
Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, Stearic Acid
Panthenol and Pantothenic Acid
*p*-Phenylenediamine
Phenyl Trimethicone
Propylene Carbonate
Propyl Gallate
Polyvinylpyrrolidone/Vinyl Acetate Copolymer
Safflower Oil
Sodium Borate and Boric Acid
Sodium Dehydroacetate and Dehydroacetic Acid
Sodium Lauryl Sulfoacetate
Sodium Sesquicarbonate, Sodium Bicarbonate, and Sodium Carbonate
Stearyl Alcohol, Oleyl Alcohol, and Octyl Dodecanol
Toluene
Toluenesulfonamide/Formaldehyde Resin
Tragacanth Gum
Vinyl Acetate/Crotonic Acid Copolymer
Zinc Phenolsulfonate

Received 2 May 2006; accepted 14 August 2006.
[1]Reviewed by the Cosmetic Ingredient Review Expert Panel. Address correspondence to Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036, USA.

## BENZETHONIUM CHLORIDE AND METHYLBENZETHONIUM CHLORIDE

A safety assessment of Benzethonium Chloride and Methylbenzethonium Chloride was published in 1985 with the conclusion that these ingredients are safe at concentrations of 0.5% in cosmetics applied to the skin, and up to 0.02% for cosmetics used in the eye area (Elder 1985). New studies, along with the updated information below regarding types and concentrations of use, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

**Benzethonium Chloride** is a quaternary ammonium salt used as an antimicrobial agent, cosmetic biocide, deodorant

**TABLE 1**
Historical and current cosmetic product uses and concentrations for Benzethonium Chloride and historical uses of Methylbenzethonium Chloride

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| | | *Benzethonium Chloride* | | |
| **Baby care*** | 1 | — | >0.1–1 | — |
| **Bath*** | 1 | — | ≤0.1 | — |
| **Eye makeup** | | | | |
| Eyeliners | 2 | — | >0.1–1 | — |
| **Fragrances** | | | | |
| Colognes and toilet waters | 6 | — | >0.1–1 | — |
| Perfumes | 3 | — | >0.1–1 | — |
| Powders | 1 | — | >0.1–1 | — |
| **Noncoloring hair care** | | | | |
| Conditioners | 2 | — | >0.1–1 | — |
| Sprays/aerosol fixatives | 1 | — | ≤ 0.1 | — |
| Rinses | 3 | — | ≤0.1 | — |
| Shampoos | 1 | — | >0.1–1 | — |
| Tonics, dressings, etc. | 1 | 2 | ≤0.1 | — |
| Wave sets | 1 | — | ≤0.1 | — |
| Other noncoloring hair care | 2 | 3 | ≤0.1 | — |
| **Makeup** | | | | |
| Other makeup | — | — | — | 0.03 |
| **Personal hygiene** | | | | |
| Underarm deodorants | 11 | 6 | ≤0.1 | 0.05 |
| Douches | 7 | 1 | >0.1–5 | — |
| Feminine deodorants | 3 | 1 | ≤0.1 | — |
| Other personal hygiene | 7 | 5 | ≤1 | 0.1–0.3 |
| **Shaving** | | | | |
| Aftershave lotions | 2 | 3 | ≤0.1 | — |
| Mens talcum | 2 | — | ≤1 | 0.1 |
| Preshave lotions | 1 | — | >0.1–1 | — |
| Other | — | 1 | — | — |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 5 | 2 | ≤1 | 0.2% |
| Face and neck skin care | 7** | 1 | ≤1** | — |
| Body and hand skin care | | 5 | | — |
| Foot powders and sprays | — | 2 | — | 0.1 |
| Moisturizers | 2 | 1 | ≤0.1 | ≤0.1 |
| Paste masks/mud packs | 2 | — | ≤0.1 | — |
| Skin fresheners | 13 | — | ≤1 | — |
| Other skin care | 3 | 4 | ≤0.1 | — |
| **Suntan products** | | | | |
| Suntan gels, creams, liquids and sprays | 2 | 2 | ≤0.1 | — |
| Indoor tanning preparations | 1 | — | ≤0.1 | — |
| **Total uses/ranges for Benzethonium Chloride** | **93** | **39** | **≤5** | **0.03–0.3** |
| | | *Methylbenzethonium Chloride* | | |
| **Baby Care** | | | | |
| Lotions, oils, powders, and creams | 2 | — | ≤1 | — |

**TABLE 1**
Historical and current cosmetic product uses and concentrations for Benzethonium Chloride and historical uses of Methylbenzethonium Chloride *(Continued)*

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| **Fragrances** | | | | |
| Colognes and toilet waters | 1 | — | ≤0.1 | — |
| **Noncoloring hair care** | | | | |
| Conditioners | 1 | — | ≤0.1 | — |
| Sprays/aerosol fixatives | 6 | — | ≤0.1 | — |
| **Personal hygiene** | | | | |
| Underarm deodorants | 5 | — | ≤1 | — |
| Douches | 1 | — | >0.1–1 | — |
| Feminine deodorants | 2 | — | ≤0.1 | — |
| Other personal hygiene | 1 | — | ≤0.1 | — |
| **Shaving** | | | | |
| Aftershave lotions | 4 | — | ≤1 | — |
| Other shaving | 1 | — | ≤0.1 | — |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 1 | — | ≤0.1 | — |
| Face and neck creams, lotions, powder and sprays | 1 | — | ≤0.1 | — |
| Moisturizers | 1 | — | ≤0.1 | — |
| Skin fresheners | 3 | — | ≤0.1 | — |
| **Suntan** | | | | |
| Suntan gels, creams, liquids and sprays | 2 | — | ≤0.1 | — |
| Other suntan | 1 | — | ≤0.1 | — |
| **Total uses/ranges for Methylbenzethonium Chloride** | **33** | — | **≤1.0** | — |

*No details were provided describing specific product categories.
**These categories were combined and have since been separated.

agent, or surfactant—suspending agent in cosmetics. In voluntary reports provided by industry to the Food and Drug Administration (FDA) in 1981, Benzethonium Chloride was used in 93 cosmetic products, with a maximum concentration up to 5% (Elder 1985). In 2002, information provided by industry to FDA indicated that Benzethonium Chloride was used in 39 cosmetic products (FDA 2002). A survey conducted by the Cosmetic, Toiletry, and Fragrance Association (CTFA) found that the maximum use concentration for Benzethonium Chloride was 5% in douches (CTFA 2003). The current and historical data on use as a function of product category are given in Table 1. The most recent information now constitutes the present use of this ingredient.

Newly available unpublished toxicology data were considered supportive of the original conclusion. The CIR Expert Panel did consider an analysis by Blumenthal et al. (1995), in which a margin of safety was calculated for Benzethonium Chloride as an antibacterial agent in consumer handsoaps as follows:

- Soap usage of 15 g/day (90th percentile of human use $= 10 \times 1.5$ g).
- Maximum use concentration of 5%
- 1% of soap remaining on human skin after washing
- human dermal absorption of Benzethonium Chloride from hand soap formulations = 50%
- Average body weight 40 kg
- No observable effect level (NOEL) of 12.5 mg/kg $day^{-1}$ for systemic toxicity from an NTP 13-week dermal study

Exposure calculation:

$$1.5 \text{ g/day} \times 5\% \times 1\% \times 50\% = 3.75 \text{ mg/day}$$

$$3.75 \text{ mg/day}/40 \text{ kg} = 0.09375 \text{ mg/kgday}^{-1} \text{ maximum possible exposure}$$

The NOEL value divided by the maximum possible exposure yielded a margin of safety of 113 for Benzethonium Chloride.

**Methylbenzethonium Chloride** is also a quaternary ammonium salt with functions in cosmetics that include antimicrobial agent, antistatic agent, cosmetic biocide, and deodorant agent. In the earlier safety assessment, Methylbenzethonium Chloride was used in 33 cosmetic products, at a maximum concentration up to 1% in baby lotions, oils, powders, and creams, and

in underarm deodorants, douches, and aftershave lotions (Elder 1985). Industry reported no uses to the FDA in 2002 (FDA 2002) and CTFA found no uses in its survey (CTFA 2003).

The historical data on use of Methylbenzethonium Chloride as a function of product category are given in Table 1. Were this ingredient to be used in the future, the CIR Expert Panel expects that it would be used at concentrations and in product types similar to those in the original safety assessment.

## REFERENCES


Arana, B. A., C. E. Mendoza, N. R. Rizzo, and A. Kroeger. 2001. Randomized, controlled, double-blind trial of topical treatment of cutaneous leishmaniasis with paromoycin plus methylbenzethonium chloride ointment in Guatemala. *Am. J. Med. Hyg*. 65:466–470.

Arechabala, B., C. Coiffard, P. Rivalland, L. J. M. Ciffard, and Y. de Roeck-Holtzhauer. 1999. Comparison of various surfactants tested on normal human fibroblast cultures using the neutral red test, MTT assay and LDH release. *J. Appl. Toxicol*. 19:163–165.

Blumenthal, H., J. F. Borzelleca, and G. P. Schoenig. 1995. Expert Panel Review of Benzethonium Chloride. Volume I: Panel commentary. Unpublished data submitted by Toxicology/ Regulatory Services, Inc., November 14, 2003. (16 pages.)[2]

Coates, K. M., and P. Flood. 2001. Ketamine and its preservative, benzethonium chloride, both inhibit human recombinant $\alpha 7$ and $\alpha 4\beta 2$ neuronal nicotinic acetylcholine receptors in Xenopus oocytes. *Br. J. Pharmacol*. 134:871–879.

Cosmetic Toiletry and Fragrance Association (CTFA). 2003. Concentration of use. Benzethonium Chloride and methylbenzethonium chloride. Unpublished data submitted by CTFA September 3, 2003. (1 page.)[2]

De Flora, S., A. Camoirano, P. Zanacchi, and C. Bennicelli. Mutagenicity testing with TA97 and TA102 of 30 DNA-damaging compounds, negative with other Salmonella strains. *Mutat. Res*. 134:159–165.

Dirieux, M. E., and G. W. Nietgen. 1997. Synergistic inhibition of muscarinic signaling by ketamine stereoisomers and the preservative benzethonium chloride. *Anesthesiology* 86:1326–1333.

Elder, R. 1985. Final report on the safety assessment of benzethonium chloride and methylbenzethonium chloride. *J. Am. Coll. Toxicol*. 4:65–106.

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

Fräki, J. E., K. Kalimo, P. Touhimaa, and E. Aantaa. 1985. Contact allergy to various components of topical preparations for treatment of external otitis. *Acta Otolarungol*. 100:414–418.

Ikarashi, Y., T. Tsuchiya, and A. Nakamura. 1993. Comparison of three in vitro assays to determine the ocular toxicity of detergent, oil, and organic solvents. *J. Toxicol. Cutan. Ocul. Toxicol*. 12:15–24.

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. *Toxic. In Vitro* 9(3):333–340.

Krause, G., and A. Kroeger. 1994. Topical treatment of American cutaneous leishmaniasis with paramomycin and methylbenzethonium chloride: A clinical study under field conditions in Ecuador. *Trans. R. Soc. Trop. Med. Hyg.* 88:92–94.

Krause, G., and A. Kroeger. 1999. Topical paromomycin/ methylbenzethonium chloride plus parenteral melglumine antimonate as treatment of American cutaneous leishmaniasis: Controlled study. *Clin. Infect. Dis*. 29:466–467.

Lonza, Inc. 1988. Sub-acute (28-day) oral toxicity study with benzethonium chloride in rats. Unpublished data submitted by Toxicology/Regulatory Services, Inc., January 8, 2004. (46 pages.)[2]

Lonza, Inc. 1995a. Acute eye irritation test in the rabbit. SPL project number 102/213. Unpublished data submitted by Toxicology/Regulatory Services, Inc., January 8, 2004. (19 pages.)[2]

Lonza, Inc. 1995b. Magnusson & Kligman maximisation study in the guinea pig. SPL project number 102/213. Unpublished data submitted by Toxicology/Regulatory Services, Inc., January 8, 2004. (36 pages.)[2]

Lonza, Inc. 1995c. Developmental toxicity study of Hyamine 1622 in rats. Unpublished data submitted by Toxicology/Regulatory Services, Inc., January 8, 2004. (223 pages.)[2]

Lonza, Inc. 1996a. Magnusson-Kligman guinea pig maximization study with Hyamine 1622. Unpublished data submitted by Toxicology/Regulatory Services, Inc., January 8, 2004. (39 pages.)[2]

Lonza, Inc. 1996b. Acute oral toxicity median lethal dosage determination with Hyamine 1622 in rats. Unpublished data submitted by Toxicology/Regulatory Services, Inc., January 8, 2004. (63 pages.)[2]

Lonza, Inc. 1996c. One week human skin irritation study. Unpublished data submitted by Toxicology/Regulatory Services, Inc., January 8, 2004. (16 pages.)[2]

Lonza, Inc. 1996d. Exclusive repeated insult patch test. Unpublished data submitted by Toxicology/Regulatory Services, Inc., January 8, 2004. (32 pages.)[2]

Lonza, Inc. 2000a. Dermal irritation of benzethonium chloride in rats. Unpublished data submitted by Toxicology/Regulatory Services, Inc., January 8, 2004. (7 pages.)[2]

Lonza, Inc. 2000b. Preliminary pharmacokinetics study of dermally applied $^{14}$C-benzethonium chloride. Unpublished data submitted by Toxicology/Regulatory Services, Inc., January 8, 2004. (22 pages.)[2]

Lonza, Inc. 2000c. The in vitro percutaneous absorption of [$^{14}$C]-benzethonium chloride through human and rat skin. Unpublished data submitted by Toxicology/Regulatory Services, Inc., January 8, 2004. (58 pages.)[2]

Lonza, Inc. 2002a. The in vitro percutaneous absorption of [$^{14}$C]-benzethonium chloride through human skin at an incorporation rate 0.1% (w/v) in GMS cream and ethanol. Unpublished data submitted by Toxicology/Regulatory Services, Inc., January 8, 2004. (40 pages.)[2]

Lonza, Inc. 2002b. The in vitro percutaneous absorption of [$^{14}$C]-benzethonium chloride through human skin as a 1.0% (*w/v*) solution in ethanol. Unpublished data submitted by Toxicology/Regulatory Services, Inc., January 8, 2004. (33 pages.)[2]

Maibach, H. I., and C. T. Mathias. 1985. Vulvar dermatitis and fissures—irritant dermatitis from methyl benzethonium chloride. *Contact. Dermatitis* 13(5):340.

Marinovich, M., E. Tragina, A. Corsini, and C. Galli. 1990. Quantification of in vitro cytotoxicity of surfactants: correlation with their eye irritant potential. *J. Toxicol. Cutan. Ocul. Toxicol*. 9:169–178.

Morrissey, R. E., B. A. Schwetz, J. C. Lamb IV, M. D. Ross, J. L. Teague, and R. W. Morris. 1988. Evaluation of rodent sperm, vaginal cytology, and reproductive organ weight data from National Toxicology Program 13-week studies. *Fundam. Appl. Toxicol*. 11:343–358.

Nagasawa, M., H. Hayashi, and T. Nakayoshi. 2002. In vitro evaluation of skin sensitivity of povidone-iodine and other antiseptics using a three-dimensional human skin model. *Dermatology* 204(Suppl 1):109–113.

National Toxicology Program (NTP). 1995. Toxicology and carcinogenesis studies of benzethonium chloride (CAS No. 121-54-0) in F344/N rats and B6C3F$_1$ mice. Available from NTP, P.O. Box 12233, Research Triangle Park, NC 27709. NTP Report No. 438.

Nisikawa, M., M. Tatsuno, S. Suzuki, and H. Tsuchihashi. 1991. The analysis of quaternary ammonium compounds in human urine by direct inlet electron impact ionization mass spectrometry. *Forensic Sci. J*. 51:131–138.

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

Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP). 2002. Opinion of the SCCNFP concerning benzethonium chloride. Available on the Internet at http://europa.eu.int/comm/food/fs/sc/sccp/out158_en.pdf Accessed September 11, 2003. 16 pages.

SCCNFP. 2003. Opinion of the SCCNFP concerning benzethonium chloride. Available on the Internet at: http://europa.eu.int/comm/health/ph_risk/


[2]Available for review: Director, Cosmetic Ingredient Review (CIR), 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

committees/sccp/documents/out250_en.pdf Accessed January 22, 2004. 10 pages.

Soto, J., P. Fuya, R. Herrera, and J. Berman. 1998. Topical paromomycin/methylbenzethonium chloride plus parenteral meglumine antimonate as treatment for American cutaneous leishmaniasis: controlled study. *Clin. Infect. Dis*. 26:56–58.

Sykes, E., M. Gibson, and C. Dmuchowski. 1996. Homogentisic acid interference in the measurement of urinary protein using benzethonium chloride. *Ann. Clin. Biochem*. 33:86–88.

Takeoka, G., L. Dao, R. Y. Wong, R. Lundin, and N. Mahoney. 2001. Identification of benzethonium chloride in commercial grapefruit seed extracts. *J. Agric. Food Chem*. 49:3316–3320.

Tennant, R. W., J. Spalding, and J. E. French. 1996. Evaluation of transgenic mouse bioassays for identifying carcinogens and noncarcinogens. 365:119–127.

Watanabe, M., K. Watanabe, K. Suzuki, O. Nikaido, I. Ishi, H. Konishi, N. Tanaka, and T. Sugahara. 1989. Use of primary rabbit cornea cells to replace the Draize rabbit eye irritancy test. *Toxicol. In Vitro* 3:329–334.

Zaman, Z., E. Speeleveld, L. Sneyers, and K. Desmet. 1997. Inhibition of acetylcholine esterase and choline esterase by benzethonium chloride and avoidance of the benzethonium chloride carry-over inhibitory effect. *Eur. J. Clin. Chem. Clin. Biochem*. 35:603–607.

## 2-BROMO-2-NITROPROPANE-1,3-DIOL (BRONOPOL)

A safety assessment of 2-Bromo-2-Nitropropane-1,3-Diol was published in 1980 with the conclusion that this preservative is safe as a cosmetic ingredient at concentrations up to and including 0.1% except under circumstances where its action with amines or amides can result in the formation of nitrosamines or nitrosamides (Elder 1980).

In 1984, a report addendum considered newly available data that use concentrations were reported at levels up to 1%. In addition, the action of 2-Bromo-2-Nitropropane-1,3-Diol as a nitrosating agent was emphasized and data provided demonstrating that it was present in formulations with amines such as Triethanolamine. The CIR Expert Panel reaffirmed the concentration limitation at 0.1% and the need to avoid use where nitrosamines or nitrosamides could be formed (Elder 1984).

Studies available since the addendum 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.

2-Bromo-2-Nitropropane-1,3-Diol was used in 323 products in 1976 (Elder 1980), with the largest single use in makeup fixatives at concentrations of $\leq$0.1%. Frequency of use data provided by industry to FDA in 2002 indicated that 2-Bromo-2-Nitropropane-1,3-Diol was used in only one noncoloring hair preparation (FDA 2002). Use concentration data provided from an industry survey in 2003 indicated use in several other product categories (CTFA 2003). The current maximum use concentration was 0.1%. Complete information is included in Table 2.

## REFERENCES

Adams, R. M., and H. I. Maibach. 1985. A five-year study of cosmetic reactions. *J. Am. Acad. Dermatol.* 13:1062–1069.

Berne, B., A. Bostrom, A. F. Grahnen, and M. Tammela. 1996. Adverse effects of cosmetics and toiletries reported to the Swedish Medical Products Agency. 1989–1994. *Contact Dermatitis* 34:359–362.

BIBRA International Ltd. 1995. Toxicity profile. 2-bromo-2-nitro-1,3-propanediol. Surrey:BIBRA International Ltd. 9 pages.[3]

Boots Co., Ltd. 1986. Myacide S-1: Response to EPA letter dated March 13, 1986: Product chemistry hydrolysis. Unpublished compilation submitted to EPA. 63 pages.[3]

Camarasa, J.G. 1986. Contact dermatitis due to bronopol. *Contact Dermatitis* 14:191–192.

Campiglio, R., G. Brambilla, V.G. Briatico, P. De Micheli, and C. Nava. 1984. Aspects of allergic disease in the cosmetics industry. *Medicina del Lavoro* 75:407–411.

Carrara, M., L. Cima, R. Cerini, and M.D. Carbonare. 1993. An in vitro method for assessing potential toxicity of cosmetic products. *J. Toxicol. Cutan. Ocul. Toxicol*. 12:3–13.

Challis, B. C., and T. I. Yousaf. 1991. The reaction of geminal bromonitroalkanes with nucleophiles. Part 1. The decomposition of 2-bromo-2-nitropropane-1,3-diol ('Bronopol') in aqueous base. *J. Chem. Soc. Perkin. Trans.* 2:283–286.

Choudry, K., M. H. Beck, and H. L. Muston. 2002. Allergic contact dermatitis from 2-bromo-nitropropane-1,3-diol in Metrogel. *Contact Dermatitis* 46:60–61.

Collins, C. 1986. Bronopol Boots: Acute inhalation toxicity study—rats: 4 hour exposure: Lab Project Number: 4920-316/14:316/14. Unpublished data from Hazleton Labs Europe, Ltd. submitted to EPA. 51 pages.[3]

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2003. Use concentration data on 2-bromo-2-nitropropane-1,3-diol from industry survey. Unpublished data submitted by CTFA, July 24, 2003 (1 page).[3]

Crampton, E. 1986. Bronopol—hydrolysis study. Unpublished data from The Boots Co. PLC submitted to EPA. 33 pages.[3]

De Groot, A. C., J. W. Weyland, J. D. Bos, and B. A. Jagtman. 1986. Contact allergy to preservatives. I. *Contact Dermatitis* 14:120–122.

Elder, R. L., ed. 1980. Final report on the safety assessment of 2-bromo-2-nitropropane-1,3-diol. *J. Environ. Pathol. Toxicol.* 4:47–61.

Elder, R. L., ed. 1984. Addendum to the final report on the safety assessment of 2-bromo-2-nitropropane-1,3-diol. *J. Am. Coll. Toxocol.* 4:139–155.

Emmons, W. W., and J. G. Marks, Jr. 1985. Immediate and delayed reactions to cosmetic ingredients. *Contact Dermatitis* 13:258–265.

Environmental Protection Agency (EPA). 1995. Reregistration eligibility decision (RED): Bronopol. (Includes RED facts: bronopol fact sheet). NTIS Report No. PB96188461.

EPA. 2002. Bronopol; Notice of filing a pesticide petition to establish a tolerance for a certain pesticide chemical in or on food. *Federal Register* 67:78459–78467.

EPA. 2003. Notice of filing a pesticide petition. Personal communication with Ms. Kathryn Boyle. July 7, 2003.[3]

European Commission. 2003. The rules governing cosmetic products in the European Union. Volume 1. Cosmetics legislation—Cosmetic products. http://dg3.eudra.org/F3/home.html. Internet site accessed June 30, 2003.

Everest, R., and M. O'Donovan. 1986. Bronopol-Boots: In vitro mammalian cell mutation assay: Proj. ID TX 86043. Unpublished data from the Boots Company PLC submitted to EPA. 24 pages.[3]

Everest, R., and C. Williams. 1986a. Bronopol-Boots: In vitro bacterial mutagenicity testing: Proj. ID TX 86004. Unpublished data from the Boots Company PLC submitted to EPA. 15 pages.[3]

Everest, R., and C. Williams. 1986b. Bronopol-Boots: In vitro human lymphocyte clastogenicity testing: Proj. ID TX 86049. Unpublished data from the Boots Company PLC submitted to EPA. 19 pages.[3]

Everest, R., and C. Williams. 1986c. Bronopol-Boots: Micronucleus assay in mice: Proj. ID TX 86001. Unpublished data from the Boots Company PLC submitted to EPA. 21 pages.[3]

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

[3]Available for review: Director, Cosmetic Ingredient Review (CIR), 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

**TABLE 2**
Historical and current cosmetic product uses and concentrations for 2-Bromo-2-Nitropropane-1,3-Diol

| Product category | 1976 use (Elder 1980) | 2002 use (FDA 2002) | 1976 concentrations (Elder 1980) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| **Bath** | | | | |
| Bath oils, tablets, and salts | 1 | — | ≤0.1 | — |
| Bubble baths | 4 | — | ≤0.1 | — |
| Bath soaps and detergents | 1 | — | ≤0.1 | — |
| Other bath | 5 | — | ≤0.1 | — |
| **Eye makeup** | | | | |
| Eyebrow pencil | 14 | — | ≤0.1 | — |
| Eyeliner | 11 | — | ≤0.1 | — |
| Eye shadow | 3 | — | ≤0.1 | 0.1 |
| Eye makeup remover | — | — | — | 0.05 |
| Mascara | 6 | — | ≤0.1 | — |
| Other eye makeup | 2 | — | ≤0.1 | — |
| **Fragrances** | | | | |
| Colognes and toilet waters | — | — | — | 0.03 |
| Perfumes | — | — | — | 0.1 |
| Other fragrances | 2 | — | >0.1–1 | — |
| **Noncoloring hair care** | | | | |
| Hair conditioners | 22 | — | ≤0.1–1 | — |
| Rinses | 6 | — | ≤0.1–1 | — |
| Shampoos | 9 | — | ≤0.1 | — |
| Hair tonics, dressings, etc. | 3 | — | ≤0.1–1 | — |
| Wave sets | 1 | — | ≤0.1 | — |
| Other noncoloring hair care | 1 | 1 | ≤0.1 | — |
| **Hair coloring** | | | | |
| Hair dyes and colors | 3 | — | >0.1–1 | — |
| Shampoos | 6 | — | ≤0.1 | — |
| **Makeup** | | | | |
| Blushers | 20 | — | ≤0.1 | 0.1 |
| Foundations | 6 | — | ≤0.1 | — |
| Leg and body paints | 2 | — | ≤0.1 | — |
| Lipstick | — | — | — | 0.1 |
| Makeup bases | 3 | — | ≤0.1 | — |
| Makeup fixatives | 134 | — | ≤0.1 | — |
| Other makeup | 1 | — | ≤0.1 | — |
| **Personal hygiene** | | | | |
| Underarm deodorants | 2 | — | ≤0.1 | — |
| **Shaving** | | | | |
| Aftershave lotion | 1 | — | ≤0.1 | 0.03 |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 17 | — | ≤0.1 | 0.02 |
| **Depilatories** | | | | |
| Face and neck skin care preparations | 3* | — | >0.1–1* | — |
| Body and hand skin care preparations | | — | | — |
| Moisturizers | 9 | — | ≤0.1 | — |
| Night skin care preparations | 3 | — | ≤0.1 | — |
| Paste masks/mud packs | 8 | — | ≤0.1 | — |
| Skin fresheners | 3 | — | ≤0.1 | 0.01 |
| Other skin care | 6 | — | ≤0.1 | 0.009 |
| **Suntan preparations** | | | | |
| Suntan gels, creams, and liquids | 3 | — | ≤0.1–1 | 0.05 |
| Indoor tanning preparations | 1 | — | ≤0.1 | — |
| Other suntan | 1 | — | ≤0.1 | — |
| **Total uses/ranges for 2-Bromo-2-Nitropropane-1,3-Diol** | **323** | **1** | **≤0.1–1** | **≤0.1** |

*These categories were originally combined, but are now separate.

FDA. 2003. Prohibited ingredients and related safety issues. http://www.csfan.fda.gov. Internet site accessed June, 2003.

Ford, G. P., and M. H. Beck. 1986. Reactions to quaternium 15, bronopol, and germall 115 in a standard series. *Contact Dermatitis* 14:271–274.

Fransway, A. F., and N. A. Schmitz. 1991. The problem of preservation in the 1990s: II. Formaldehyde and formaldehyde-releasing biocides: Incidences of cross-reactivity and the significance of the positive response to formaldehyde. *Am. J. Contact Dermatitis* 2:78–88.

Frosch, P. J., I. R. White, R. J. G. Rycroft, et al. 1990. Contact allergy to bronopol. *Contact Dermatitis* 22:24–26.

Glass, R., and S. Hewertson. 1993. Study of the excretion, distribution, and metabolism of bronopol in the rat: Lab Project Number: DT93077: RD/RCG.SJH/763474: BHR/006. Unpublished data from Boots Pharmaceuticals submitted to EPA. 252 pages.[3]

Goossens, A., M. H. Beck, E. Haneke, J. P. McFadden, S. Nolting, G. Durupt, and G. Ries. 1999. Adverse cutaneous reactions to cosmetic allergens. *Contact Dermatitis* 40:112–113.

Grattan, C. E., R. R. Harman, and R. S. Tan. 1986. Milk recorder dermatitis. *Contact Dermatitis* 14:217–220.

Herzog, J., J. Dunne, R. Aber, M. Claver, and J. G. Marks, Jr. 1988. Milk tester's dermatitis. *J. Am. Acad. Dermatol.* 32:1693–1698.

Hindmarsh, M. 1990. Mortality in calves associated with the feeding of milk containing bronopol. *Aust. Vet. J.* 67:309–310.

Irwine, L. 1992a. Bronopol: Oral (gavage). Rabbit developmental toxicity (teratogenicity) study: Lab Project Number: BON/3/R. Unpublished data from Toxicol Laboratories, Ltd. submitted to EPA. 198 pages.[3]

Irwine, L. 1992b. Bronopol: Oral (gavage). Rabbit developmental toxicity (teratogenicity) study: Lab Project Number: BON/3/R. Unpublished data from Toxicol Laboratories, Ltd. submitted to EPA. 200 pages.[3]

Jacobs, M. C., I. R. White, R. J. Rycroft, and N. Taub. 1995. Patch testing with peservatives at St John's from 1982 to 1993. *Contact Dermatitis* 33:247–254.

Jackson, R., B. Hall, and D. Self. 1992. Bronopol—Environmental fate phase 4 response: Photodegradation—Water. Unpublished data from Inveresk Research International Ltd. 28 pages.[3]

Jantova, S., J. Hojerova, B. Hanusova, and M. Mikulasova. 2001. Cytotoxic and genotoxic activity of certain preservatives in cosmetics. *Ceska Slov. Farm.* 50:238–242.

Kränke, B., C. Szolar-Platzer, and W. Aberer. 1996. Reactions to formaldehyde and formaldehyde releasers in a standard series. *Contact Dermatitis* 35:192–193.

Liggett, M., and B. Parcell 1984. Irritant effects on the rabbit eye of bronules: 8422D/BTS 186/SE. Unpublished data from Huntingdon Research Center plc submitted to EPA. 17 pages.[3]

Marks, J. G. Jr., D. V. Belsito, V. A. DeLeo, et al. 1995. North American Contact Dermatitis Group standard tray patch test results (1992 to 1994). *Am. J. Contact Dermatitis* 6:160–165.

Marks, J. G. Jr., D. V. Belsito, V. A. DeLeo, et al. 1998. North American Contact Dermatitis Group patch test results for the detection of delayed-type hypersensitivity to topical allergens. *J. Am. Acad. Dermatol*. 38:911–918.

Marks, J. G. Jr., D.V. Belsito, V.A. Deleo, et al. 2000. North American Contact Dermatitis Group standard tray patch test results, 1996 to 1998. *Arch. Dermatol*. 136:272–273.

Marks, J. G. Jr., D. V. Belsito, V. A. Deleo, et al. 2003. North American Contact Dermatitis Group patch-test results, 1998 to 2000. *Am. J. Contact Dermatitis* 14:59–62.

Palmer, K. 1995. Bronopol: Oral (gavage) rat developmental toxicity study. Final report: Lab project numbers: BON/9/R: TXO95007. Unpublished data from Toxicol Labs Ltd submitted to EPA. 165 pages.[3]

Pepe, R. C., J. A. Wenninger, and G. N. McEwen, Jr., eds. 2002. *International Cosmetic Ingredient Dictionary and Handbook*, 9th ed., 201–202, Washington, DC: CTFA.

Perrenoud, D., A. Bircher, T. Hunziker, et al. 1994. Frequency of sensitization to 13 common preservatives in Switzerland. Swiss Contact Dermatitis Research Group. *Contact Dermatitis* 30:276–279.

Podmore, P. 2000. Occupational allergic contact dermatitis from both 2-bromo-nitropropane-1,3-diol and methylchloroisothiazolinone plus methylisothiazolinone in spin finish. *Contact Dermatitis* 43:45.

Rudzki, E., P. Rebandel, and Z. Grzywa. 1993. Occupational dermatitis from cosmetic creams. *Contact Dermatitis* 29:210.

Sanyal, A. K., M. Basu, and A. B. Banerjee. 1996. Rapid ultraviolet spectrophotometric determination of bronopol: application to raw material analysis and kinetic studies of bronopol degradation. *J. Pharmaceut. Biomed. Anal.* 14:1447–1453.

Scalia S., S. Simeoni, and E. Bousquet. 2001. Determination of bronopol in cosmetic products by HPLC with electrochemical detection. *Pharmazie* 56:318–320.

Schnuch, A., J. Geier, W. Uter, and P. J. Frosch. 1998. Patch testing with preservatives, antimicrobials, and industrial biocides. Results from a multicentre study. *Br. J. Dermatol.* 138:467–476.

Shaw, S. 1997. Patch testing bronopol. *Cosmet. Toiletries* 112:67–68, 71–73.

Shehade, S. A., M. H. Beck, and V. F. Hillier. 1991. Epidemiological survey of standard series patch test results and observations on day 2 and day 4 readings. *Contact Dermatitis* 24:119.

Smithson, A. 1984. Bronopol: Data on individual animals in toxicity studies: Report No. TXA 83082. Unpublished data from Boots Co. LTD (Nottingham, England; CDL:252631-A) submitted to EPA, March 7, 1984.[3]

Steele, C. 1994. Bronopol: Oral (gavage) rat developmental toxicity dose ranging study. Lab Project Number: TX94032: BON/8/93. Unpublished data from Boots Pharmaceuticals submitted to EPA. 106 pages.[3]

Storrs, F. J., L. E. Rosenthal, R. M. Adams, et al.1989. Prevalence and relevance of allergic reactions in patients patch tested in North America 1984 to 1985. *J. Am. Acad. Dermatol*. 20:1038–1045.

Torresani, C., I. Periti, and L. Beski. 1996. Contact urticaria syndrome from formaldenyde with multiple physical urticarias. *Contact Dermatitis* 35:174–175.

Wang, H., G. J. Provan, and K. Helliwell. 2002. Determination of bronopol and its degradation products by HPLC. *J. Pharmaceut. Biomed. Anal*. 29:387–392.

Wilson, C. L., and S. M. Powell. 1990. An unusual case of allergic contact dermatitis in a veterinary surgeon. *Contact Dermatitis* 23:42–43.

## BUTYLATED HYDROXYANISOLE (BHA)

A safety assessment of Butylated Hydroxyanisole was published in 1984 with the conclusion that this ingredient is safe as a cosmetic ingredient in the practices of use (Elder 1984). 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.

The name of Butylated Hydroxyanisole as listed in the *International Cosmetic Ingredient Dictionary and Handbook* has been changed to BHA (Pepe et al. 2002).

BHA functions in cosmetics include antioxidant and fragrance ingredient. It was used in 3217 cosmetic products in 1981, with the largest use occurring in lipstick at concentrations of $\leq$10% (Elder 1984). In 2002, BHA was used in 1224 cosmetic products (FDA 2002), at a maximum use concentration of 0.2% in colognes, toilet waters, and perfumes (CTFA 2003). Table 3 presents the available use information for BHA. The most recent information now constitutes the present use of this ingredient.

## REFERENCES

Buetler, T. M., E. P. Gallagher, C. Wang, D. Stahl, J. D. Hayes, and D. L. Eaton. 1995. Induction of phase I and phase II drug-metabolizing enzyme mRNA, protein, and activity by BHA, ethoxyquin, and oltipraz. *Toxicol. Appl. Pharmacol*. 135:45–57.

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

| Product category | 1981 uses (Elder 1984) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1984) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| **Baby care** | | | | |
| Lotions, oils, powders, and creams | 1 | 1 | >0.1–1 | 0.0001 |
| **Bath** | | | | |
| Oils, tablets, and salts | 20 | 4 | ≤0.1 | 0.0004 |
| Bubble baths | 7 | — | ≤0.1 | 0.00001 |
| Bath soaps and detergents | 2 | 5 | ≤0.1 | 0.000004 |
| Other bath | 10 | 3 | ≤1 | 0.0001 |
| **Eye makeup** | | | | |
| Eyebrow pencil | 33 | 51 | ≤1 | 0.0001 |
| Eyeliner | 75 | 399 | ≤1 | 0.1 |
| Eye shadow | 410 | 38 | ≤5 | 0.002 |
| Eye lotion | 2 | 2 | ≤0.1 | — |
| Eye makeup remover | 11 | 6 | ≤0.1 | 0.02 |
| Mascara | 65 | 18 | ≤1 | 0.1 |
| Other eye makeup | 39 | 10 | ≤1 | 0.001 |
| **Fragrances** | | | | |
| Colognes and toilet waters | 97 | 18 | ≤1 | 0.2 |
| Perfumes | 62 | 6 | ≤1 | 0.2 |
| Powders | 12 | 2 | ≤0.1 | 0.0002 |
| Sachets | 21 | — | ≤0.1 | — |
| Other fragrances | 24 | 10 | ≤1 | 0.004 |
| **Noncoloring hair care** | | | | |
| Conditioners | 8 | 5 | ≤0.1 | 0.0002 |
| Sprays | 1 | — | — | 0.0001 |
| Shampoos | 6 | — | ≤0.1 | 0.0005 |
| Tonics, dressings, etc. | 10 | 8 | ≤1 | 0.02 |
| Wave sets | 1 | — | — | — |
| Other noncoloring hair care | — | — | — | 0.05 |
| **Hair coloring** | | | | |
| Other hair coloring | 5 | 1 | ≤0.1 | — |
| **Makeup** | | | | |
| Blushers | 176 | 26 | ≤5 | 0.2 |
| Face powders | 98 | 11 | ≤1 | 0.005 |
| Makeup foundations | 119 | 30 | ≤0.1 | 0.05 |
| Lipstick | 1256 | 279 | ≤25 | 0.2 |
| Makeup bases | 64 | 4 | ≤1 | 0.005 |
| Rouges | 48 | 1 | ≤1 | 0.04 |
| Makeup fixatives | 10 | — | ≤0.1 | — |
| Other makeup | 106 | 23 | ≤5 | 0.05 |
| **Nail care** | | | | |
| Basecoats and undercoats | 1 | 3 | ≤0.1 | — |
| Cuticle softeners | 2 | 2 | ≤0.1 | 0.001 |
| Creams and lotions | 4 | 1 | ≤0.1 | — |
| Polish and enamel | — | — | — | 0.06 |
| Polish and enamel remover | 1 | — | ≤0.1 | — |
| Other nail care | 2 | 4 | ≤0.1 | 0.004 |

**TABLE 3**
Historical and current cosmetic product uses and concentrations for BHA *(Continued)*

| Product category | 1981 uses (Elder 1984) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1984) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| **Oral hygiene** | | | | |
| Dentifrices | — | — | — | 0.01 |
| **Personal hygiene** | | | | |
| Underarm deodorants | 1 | 1 | ≤0.1 | 0.002 |
| Other personal hygiene | 2 | 4 | ≤1 | 0.002 |
| **Shaving** | | | | |
| Aftershave lotions | 11 | 2 | ≤1 | 0.006 |
| Preshave lotions | 3 | — | — | — |
| Shaving cream | 8 | 10 | ≤0.1 | 0.0003 |
| Shaving soap | 1 | — | >0.1–1 | — |
| Other shaving | 3 | — | ≤1 | 0.0003 |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 51 | 23 | ≤1 | 0.05 |
| Face and neck skin care | 77* | 15 | ≤1* | 0.1 |
| Body and hand skin care | | 72 | | 0.1 |
| Hormone skin care** | 1 | ** | — | ** |
| Foot powders and sprays | — | 1 | — | 0.004 |
| Moisturizers | 111 | 51 | ≤1 | 0.06 |
| Night skin care | 30 | 26 | ≤1 | 0.04 |
| Paste masks/mud packs | 6 | 3 | ≤1 | 0.004 |
| Skin lighteners** | 11 | ** | ≤0.1 | ** |
| Skin fresheners | 6 | 2 | ≤0.1 | — |
| Wrinkle smoothers** | 6 | ** | ≤0.1 | ** |
| Other skin care | 42 | 30 | ≤1 | 0.03 |
| **Suntan** | | | | |
| Suntan gels, creams, and liquids | 27 | 7 | ≤1 | 0.1 |
| Indoor tanning | 2 | 1 | ≤0.1 | — |
| Other suntan | 9 | 5 | ≤0.1 | — |
| **Total uses/ranges for BHA** | **3217** | **1224** | **≤0.1–25** | **0.000004-0.2** |

*These categories were combined, but now are listed separately.

**No longer listed as product categories.


Castelli, M. G., E. Benfenati, R. Pastorelli, M. Salmona, and R. Fanelli. 1984. Kinetics of 3-tert-butyl-4-nydroxyanisole (BHA) in man. *Food Chem. Toxicol*. 22:901–904.

Chang, S., G. Chen, C. Yeh, C. Hung, S. Lin, and J. Chung. 2001. Effects of butylated hydroxyanisole and butylated hydroxytoluene on the DNA adduct formation and arylamines N-acetyltransferase activity in human colon tumor cells. *Anticancer Res.* 21:1087–1094.

Clayson, D. B., F. Iverson, E. A. Nera, and E. Lok. 1993. The impotance of cellular proliferation induced by BHA and BHT. *Toxicol. Ind. Health*. 9:231–342.

Conning, D. M., and J. C. Phillips. 1986. Comparative metabolism of BHA, BHT and other phenolic antioxidants and its toxicological relevance. *Food Chem. Toxicol.* 24:1145–1148.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2003. Concentrations of use—mineral waxes. Unpublished data submitted by CTFA on April 21, 2003. (4 pages.)[4]

[4]Available for review: Director, Cosmetic Ingredient Review (CIR), 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

David, M., G. Horvath, I. Schimke, M. M. Mueller, and I. Nagy. 1993. Effects of the antioxidant butylated hydroxyanisole on cytosolic free calcium concentration. *Toxicology* 77:115–121.

Della-Corte, L., and G. Sgaragli. 1984. 2-t-Butyl-4-methoxyphenol (BHA) acute toxicity in rodents: Influence of the administration route. *Pharmcol. Res. Communi.* 16:1041–1047.

Elder, R. L. 1984. Final report on the safety assessment of butylated hydroxyanisole. *J. Am. Coll. Toxicol*. 3:83–146.

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

Grice, H. C. 1988. Safety evaluation of butylated hydroxyanisole from the perspective of effects on forestomach and oesophageal squamous epithelium. *Food Chem. Toxicol*. 26:17–724.

Hageman, G. J., H. Verhagen, and J. C. S. Kleinjans. 1988. Butylated hydroxyanisole, butylated hydroxytoluene and tert-butylhydroquinone are not mutagenic in the Salmonella/microsome assay using new tester strains. *Mutat. Res*. 208:207–211.

Hazelton, G. A., J. J. Hjelle, and C. D. Klaassen. 1986. Effects of butylated hydroxyanisole on acetaminophen hepatotoxicity and glucuronidation in vivo. *Toxicol. Appl. Pharmacol*. 83:474–485.

Hirose, M., A. Hagiwara, T. Masui, K. Inoue, and N. Ito. 1986. Combined effects of butylated hydroxyanisole and other antioxidants in induction of forestomach lesions in rats. *Cancer Lett*. 30:169–174.

Hirose, M., A. Hagiwara, K. Inoue, T. Sakata, N. Ito, H. Kaneoko, A. Yoshitake, and J. Miyamoto. 1987. Metabolism of 2- and 3-tert-butyl-4-hydroxyanisole (2- and 3-BHA) in the rat (I): excretion of BHA in urine, feces, and expired air and distribution of BHA in the main organs. *Toxicology*. 43:139–147.

Hirose, M.A. Masuda, Y. Kurata, E. Ikawa, Y. Mera, and N. Ito. 1986. Histological and autoradiographic studies on the forestomach of hamsters treated with 2-tert-butylated hydroxyanisole, 3-tert-butylated hydroxyanisole, crude butylated hydroxyanisole, or butylated hydroxytoluene. *J. Natl. Cancer Inst*. 76:143–150.

Hocman. 1988. Chemoprevention of cancer: phenolic antioxidants (BHT, BHA). *Int. J. Biochem*. 29:639–651.

International Agency for Research on Cancer (IARC). 1986. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Some naturally occurring and synthetic food components, furocoumarins and ultraviolet radiation*, Vol 40. Lyon, France: IARC.

Ishii, T., K. Itoh, J. Akasaka, T. Yanagawa, S. Takahashi, H. Yoshida, S. Bannai, and M. Yamamoto. 2000. Induction of murine intestinal and hepatic peroxiredoxin MSP23 by dietary butylated hydroxyanisole. *Carcinogenesis* 21:1013–1016.

Ito, N. 1985. Carcinogenicity and modification of the carcinogenic response by BHA, BHT, and other antioxidants. *Crit. Rev. Toxicol*. 15:109–150.

Iverson, F., J. Truelove, E. Nera, E. Lok, D. B. Clayson, and J. Wong. 1986. A 12-week study of BHA in the cynomolgus monkey. *Food Chem. Toxicol*. 24:1197–1200.

Jayalakshmi, C. P., and J. D. Sharma. 1986. Effect of butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) on rat erythrocytes. *Environ. Res*. 41:235–238.

Kanazawa, K., and M. Mizuno. 1992. Butylated hydroxyanisole produces both mutagenic and desmutagenic derivatives under gastric conditions. *Int. J. Tissue Reac*. 14:211–218.

Masui, T., M. Hirose, K. Imaida, S. Fukushima, S. Tamano, and N. Ito. 1986. Sequential changes of the forestomach of F344 rats, Syrian golden hamsters, and B6C3F1 mice treated with butylated hydroxyanisole. *Jpn. J. Cancer Res*. 77:1083–1090.

Matsuoka, A., M. Matsui, N. Miyata, T. Sofuni, and M. Ishidate, Jr. 1990. Mutagenicity of 3-tert-butyl-4-hydroxyanisole (BHA) and its metabolites in short-term tests in vitro. *Mutat. Res.* 241:125–132.

Moch, R. W. 1986. Pathology of BHA- and BHT-induced lesions. *Food Chem. Toxicol.* 24:1167–1169.

National Toxicology Program. 2002. Report on Carcinogens, Tenth Edition. U.S. Department of Health and Human Services, Public Health Service. (5 pages.)

Orton, D. L., and S. Shaw. 2001. Allergic contact dermatitis from pharmaceutical grade CHA in Timodine®, with no patch test reaction to analytical grade BHA. *Contact Dermatitis* 44:191–192.

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

Poulsen, E. 1991. Safety evaluation of substances consumed as technical ingredients (food additives). *Food Addit. Contam*. 8:125–134.

Richer, N., M. Marion, and F. Denizeau. 1989. Inhibition of binding of 2-acetylaminofluorene to DNA by butylatedhydroxytoluene and butylated hydroxyanisole in vitro. *Cancer Lett.* 47:211–216.

Romero, F. J., J. Romá, F. Bosch-Morell, B. Romero, J. Segura-Aguilar, A. Lombart-Bosch, and L. Ernster. 2000. Reduction of brain antioxidant defense upon treatment with butylated hydroxyanisole (BHA) and Sudan III in Syrian golden hamsters. *Neurochem. Res.* 25(3):389–393.

Sakai, A., N. Miyata, and A. Takahashi. 1997. Promoting activity of 3-tert-4-hydroxyanisole (BHA) in BALB/3T3 cell transformation. *Cancer Lett*. 115:213–220.

Schilderman, P. A. E. L., E. Rhijnsburger, I. Zwingmann, and J. C. S. Kleinjans. 1995. Induction of oxidative DNA damage and enhancement of cell proliferation in human lymphocytes in vitro by butylated hydroxyanisole. *Carcinogenesis* 16:507–512.

Schumann, R. 1991. In vitro absorption of butylated hydroxyanisole through human skin. *J. Soc. Cosmet. Chem*. 42:335–340.

Slameňová, D., E. Horvánthová, S. Robichová, L. Hrušovská, A. Gábelová, K. Kleibl, J. Jakubiková, and J. Sedlák. 2003. Molecular and cellular influences of butylated hydroxyanisole on Chinese hamster V79 cells treated with N-methyl-N′-nitro-N-nitrosoguanidine: Antimutagenicity of butylated hydroxyanisole. *Environ. Mol. Mutagen*. 41:28–36.

Sun, B., and M. Fukuhara. 1997. Effects of co-administration of butylated hydroxytoluene, butylated hydroxyanisole and flavinoids on the activation of mutagens and drug-metabolizing enzymes in mice. *Toxicology* 122:61–72.

Tosti, A., F. Bardazzi, F. Valeri, and R. Russo. 1987. Contact dermatitis from butylated hydroxyanisole. *Contact Dermatitis* 17:257–258.

Waters, M. D., A. L. Brady, H. F. Stack, and H. E. Brockman. 1990. Antimutagenicity profiles for some model compounds. *Mutat. Res*. 238:57–85.

White, I. R., C. R. Lovell, and E. Cronin. 1984. Antioxidants in cosmetics. *Contact Dermatitis* 11:265–267.

Whysner, J., and G. M. Williams. 1996. Butylated hydroxyanisole mechanistic data and risk assessment: Conditional species-specific cytotoxicity, enhance cell proliferation, and tumor promotion. *Pharmacol. Therapeut.* 71:137–151.

Williams, G. M., M. J. Iatropoulos, and J. Whysner. 1999. Safety assessment of butylated hydroxyanisole and butylated hydroxytoluene as antioxidant food additives. *Food Chem. Toxicol*. 37:1027–1038.

Williams, G. M., C. A. McQueen, and C. Tong. 1990.Toxicity studies of butylated hydroxyanisole and butylated hydroxytoluene. I. Genetic and cellular effects. *Food Chem. Toxicol.* 28:793–798.

Williams, G. M., C. X. Wang, and M. J. Iatropoulos. 1990. Toxicity studies of butylated hydroxyanisole and butylated hydroxytoluene. II. Chronic feeding studies. *Food Chem. Toxicol*. 28:799–806.

Witschi, H. R., and D. G. Doherty. 1984. Butylated hydroxyanisole and lung tumor development in A/J mice. *Fundam. Appl. Toxicol*. 4:795–801.

World Health Organization (WHO). 1999. Safety evaluation of certain food additives. Evaluation of national assesments of intake of BHA. *WHO Food Addit. Ser.* 42:415–428.

Würtzen, G., and P. Olsen. 1986. BHA study in pigs. *Food Chem. Toxicol*. 24:1229–1233.

Wurtzen, G. 1993. Scientific evaluation of the safety factor for the acceptable daily intake (ADI). Case study: Butylated hydroxyanisole. *Food Addit. Contam*. 10:307–314.

Yeh, C., J. Chung, H. Wu, Y. Li, Y. Lee, and C. Hung. 2000. Effects of butylated hydroxyanisole and butylated hydroxytoluene on DNA adduct formation and arylamines *N*-acetyltransferase activity in PC-3 cells (human prostate tumor) in vitro. *Food Chem. Toxicol*. 38:977–983.

## BUTYLENE GLYCOL, HEXYLENE GLYCOL, ETHOXYDIGLYCOL, AND DIPROPYLENE GLYCOL

A safety assessment was published in 1985 with the conclusion that these ingredients are safe as presently used in cosmetics (Elder 1985). 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.

**Butylene Glycol** was reported to be used in 165 cosmetic preparations in 1981, with the greatest use occurring in mascara, and at concentrations that ranged from less than 0.14% to greater than 50% (Elder 1985). In 2002, industry reports to FDA indicated that Butylene Glycol was used in 813 preparations (FDA 2002). An industry survey of use concentrations in

**TABLE 4**
Historical and current cosmetic product uses and concentrations for Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| | | *Butylene Glycol* | | |
| **Baby care** | | | | |
| Lotions, oils, powders, and creams | — | 2 | — | 13 |
| Other baby care | — | — | — | 3–4 |
| **Bath** | | | | |
| Oils, tablets, and salts | 1 | 3 | 5–10 | 0.08 |
| Soaps and detergents | 1 | 10 | 5–10 | 0.02–1 |
| Other bath | 4 | 20 | 5–>50 | 1 |
| **Eye makeup** | | | | |
| Eyebrow pencils | — | 1 | — | 0.007 |
| Eyeliners | 3 | 12 | 1–5 | 3–12 |
| Eye shadow | 13 | 3 | 5–25 | 2 |
| Eye lotions | — | 5 | — | 3–8 |
| Eye makeup remover | 4 | 16 | 1–5 | 5 |
| Mascara | 34 | 14 | 1–10 | 0.00007–3 |
| Other eye makeup | 1 | 19 | 1–5 | 7 |
| **Fragrances** | | | | |
| Colognes and toilet waters | 3 | 5 | 0.1–25 | 4 |
| Perfumes | 2 | 4 | 1–5 | — |
| Powders | — | 4 | — | — |
| Other fragrances | 1 | 18 | 5–10 | 2 |
| **Noncoloring hair care** | | | | |
| Conditioners | 5 | 10 | ≤1–10 | <1–3 |
| Sprays/aerosol fixatives | — | — | — | 3 |
| Permanent waves | — | 2 | — | 1 |
| Shampoos | 1 | 9 | ≤0.1 | 1–4 |
| Tonics, dressings, etc. | 1 | 11 | 1–5 | 0.02–5 |
| Other noncoloring hair care | — | 12 | — | <1–6 |
| **Makeup** | | | | |
| Blushers | 7 | — | 1–25 | — |
| Face powders | 1 | 2 | 1–5 | 2 |
| Foundations | 19 | 66 | 5–25 | 6–9 |
| Lipsticks | — | 4 | — | 0.2–3 |
| Makeup bases | 1 | 12 | 5–10 | 6 |
| Rouges | 2 | — | 5–>50 | — |
| Makeup fixatives | — | 3 | — | 6 |
| Other makeup | 2 | 15 | 5–25 | 3–4 |
| **Nail care** | | | | |
| Cuticle softeners | 1 | 3 | 5–10 | — |
| Creams and lotions | — | 2 | — | — |
| Nail polishes and enamels | — | 5 | — | — |
| Other nail care | — | 2 | — | — |
| **Oral hygiene** | | | | |
| Other oral hygiene | — | — | — | 0.01 |
| **Personal hygiene** | | | | |
| Underarm deodorants | 1 | 14 | 10–25 | 20–30 |
| Other personal hygiene | 1 | 1 | 1–5 | — |

*(Continued on next page)*

**TABLE 4**
Historical and current cosmetic product uses and concentrations for Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol *(Continued)*

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| **Shaving** | | | | |
| Aftershave lotions | 4 | 8 | 0.1–5 | 0.05–7 |
| Shaving cream | — | 5 | — | 1 |
| Other shaving | — | 5 | — | — |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 13 | 66 | ≤0.1–10 | 0.05–20 |
| Depilatories | — | — | — | 4 |
| Face and neck skin care | 8* | 30 | ≤ 0.1–>50* | 3–7 |
| Body and hand skin care | | 43 | | 0.01–14 |
| Foot powders and sprays | — | 4 | — | |
| Moisturizers | 13 | 171 | ≤0.1–>50 | 0.02–13 |
| Night skin care | 1 | 23 | ≤0.1 | 3–8 |
| Paste masks/mud packs | 3 | 27 | 0.1–10 | 3–12 |
| Skin fresheners | 6 | 16 | ≤0.1–5 | 2–6 |
| Other skin care | 7 | 78 | ≤0.1–10 | 4–89 |
| **Suntan products** | | | | |
| Suntan gels, creams, liquids, and sprays | 1 | 7 | 1–5 | 2–5 |
| Indoor tanning | — | 18 | — | 0.5–20 |
| Other suntan | — | 3 | — | 5 |
| **Total uses/ranges for Butylene Glycol** | **165** | **813** | **≤0.1–>50** | **0.00007–89** |
| | | *Hexylene Glycol* | | |
| **Baby care** | | | | |
| Other baby care | — | — | — | 1 |
| **Bath** | | | | |
| Oils, tablets, and salts | 4 | 1 | 5–25 | — |
| Soaps and detergents | 3 | 3 | 1–5 | — |
| Bubble baths | 3 | 2 | 0.1–5 | — |
| Other bath | — | 2 | — | — |
| **Eye makeup** | | | | |
| Eye lotions | — | 2 | — | 2 |
| Eye makeup remover | 1 | 20 | 0.1–1 | 2 |
| Mascara | — | 1 | — | 0.1 |
| Other eye makeup | — | 3 | — | 0.8 |
| **Fragrances** | | | | |
| Colognes and toilet waters | — | — | — | 0.03 |
| Other | — | 1 | — | — |
| **Noncoloring hair care** | | | | |
| Conditioners | 7 | 3 | 0.1–10 | 4 |
| Permanent waves | 1 | 2 | 10–25 | — |
| Rinses | 1 | — | 10–25 | — |
| Shampoos | 29 | 12 | ≤0.1–10 | — |
| Tonics, dressings, etc. | — | 2 | — | 4 |
| Wave sets | — | 1 | — | — |
| Other noncoloring hair care | — | 2 | — | — |
| **Hair coloring** | | | | |
| Dyes and colors | 20 | 179 | 1–25 | — |

**TABLE 4**
Historical and current cosmetic product uses and concentrations for Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol *(Continued)*

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| Rinses | — | 2 | — | — |
| Bleaches | 1 | 1 | 1–5 | — |
| **Makeup** | | | | |
| Foundations | — | 4 | — | 0.3 |
| Lipsticks | | | | 0.003 |
| Makeup bases | — | 1 | — | |
| Makeup fixatives | — | — | — | 1 |
| **Nail care** | | | | |
| Nail polish and enamel removers | — | 1 | — | — |
| **Personal hygiene** | | | | |
| Underarm deodorants | 2 | — | 0.1–1 | 0.002 |
| Other personal hygiene | — | 1 | — | 0.0009 |
| **Shaving** | | | | |
| Aftershave lotions | — | — | — | 0.1–2 |
| Shaving cream | — | 1 | — | — |
| Other shaving | — | — | — | 2 |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 4 | 22 | 0.1–5 | 0.005–6 |
| Face and neck skin care | 1* | 5 | 1–5* | 0.001–4 |
| Body and hand skin care | | 1 | | 0.0009–1 |
| Moisturizers | 3 | 7 | 0.1–5 | 1 |
| Night skin care | — | 2 | — | 1–4 |
| Paste masks/mud packs | 1 | 6 | 5–10 | 0.3 |
| Skin fresheners | 3 | 2 | 0.1–5 | — |
| Other skin care | 1 | 6 | 1–5 | 3 |
| **Suntan** | | | | |
| Suntan gels, creams, liquids, and sprays | — | 6 | — | 0.01 |
| Other suntan | — | 2 | — | — |
| **Total uses/ranges for Hexylene Glycol** | **85** | **306** | **≤0.1–25** | **0.0009–6** |
| | | *Ethoxydiglycol* | | |
| **Baby care** | | | | |
| Shampoos | — | — | — | <1 |
| Lotions, oils, powders, and creams | — | — | — | <0.5 |
| **Bath** | | | | |
| Oils, tablets, and salts | — | 3 | — | — |
| Soaps and detergents | — | — | — | 0.6 |
| Bubble baths | — | 2 | — | 0.006 |
| **Eye makeup** | | | | |
| Eye lotions | — | — | — | 0.0001–2 |
| Eye makeup remover | — | 1 | — | — |
| Mascara | 1 | 7 | 0.1–1 | — |
| Other eye makeup | — | 1 | — | — |
| **Fragrances** | | | | |
| Colognes and toilet waters | 3 | — | 0.1–10 | 1 |
| Perfumes | — | — | — | 1 |

**TABLE 4**
Historical and current cosmetic product uses and concentrations for Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol *(Continued)*

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| Other fragrances | — | 2 | — | — |
| **Noncoloring hair care** | | | | |
| Conditioners | 4 | 11 | 0.1–5 | 0.04 |
| Sprays/aerosol fixatives | — | 4 | — | 0.00008 |
| Rinses | — | 1 | — | — |
| Shampoos | 1 | 15 | 0.1–1 | 0.02–1 |
| Tonics, dressings, etc. | — | 4 | — | 0.03 |
| Wave sets | 1 | 1 | 1–5 | — |
| Other noncoloring hair care | — | 4 | — | 0.4 |
| **Hair coloring** | | | | |
| Dyes and colors | 14 | 495 | 1–10 | — |
| Tints | 13 | — | 1–5 | — |
| Bleaches | 5 | 6 | 1–5 | — |
| Other hair coloring | 1 | 2 | 1–5 | — |
| **Makeup** | | | | |
| Blushers | — | — | — | 0.0006 |
| Face powders | — | — | — | 0.0008 |
| Foundations | — | 1 | — | 0.005 |
| Lipsticks | — | — | — | 0.00004 |
| Makeup bases | — | — | — | 0.008 |
| Rouges | — | — | — | 0.05 |
| Other | — | — | — | 0.04 |
| **Nail care** | | | | |
| Basecoats and undercoats | — | 1 | — | — |
| Nail polish and enamel removers | 1 | — | 5–10 | — |
| Other nail care | — | — | — | 42 |
| **Personal hygiene** | | | | |
| Underarm deodorants | — | — | — | 0.2 |
| Douches | — | — | — | 0.1 |
| Other personal hygiene | — | — | — | 0.3 |
| **Shaving** | | | | |
| Aftershave lotions | 2 | 2 | 0.1–1 | 0.6 |
| Preshave lotions | — | — | — | 0.0005 |
| Shaving cream | — | 2 | — | 5 |
| Other shaving | — | 2 | — | — |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 14 | 10 | ≤0.1–> 50 | 0.02–80 |
| Depilatories | — | — | — | 2 |
| Face and neck skin care | 3* | 5 | ≤0.1–1* | 0.2–15 |
| Body and hand skin care | | 6 | | 0.1–0.5 |
| Moisturizers | 3 | 3 | 1–10 | 0.04–3 |
| Night skin care | 2 | — | ≤0.1–5 | 0.09–10 |
| Paste masks/mud packs | 3 | 2 | 0.1–25 | 0.002–8 |
| Skin fresheners | 3 | — | 1–5 | 5–8 |
| Other skin care | 5 | 14 | 0.1–10 | 0.05–53 |
| Skin lighteners** | 1 | —* | — | |

**TABLE 4**
Historical and current cosmetic product uses and concentrations for Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol *(Continued)*

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| **Suntan** | | | | |
| Suntan gels, creams, liquids, and sprays | — | 5 | — | — |
| Indoor tanning | — | 10 | — | 1–5 |
| Other suntan | — | — | — | 0.2–9 |
| **Total uses/ranges for Ethoxydiglycol** | **80** | **622** | **≤0.1–> 50** | **0.00004–80** |
| | | *Dipropylene Glycol* | | |
| **Baby care** | | | | |
| Lotions, oils, powders, and creams | — | 1 | — | — |
| **Bath** | | | | |
| Oils, tablets, and salts | 1 | 3 | >50 | — |
| Soaps and detergents | — | 4 | — | 0.8 |
| Bubble baths | — | 1 | — | 0.03 |
| **Eye makeup** | | | | |
| Eye lotions | — | 2 | — | 0.1–4 |
| Eye makeup remover | — | 1 | — | — |
| Mascara | — | 7 | — | — |
| **Fragrances** | | | | |
| Colognes and toilet waters | 2 | — | 5–10 | 7–9 |
| Perfumes | 12 | 4 | 0.1–>50 | 0.01–20 |
| Powders | — | 5 | — | — |
| Sachets | 1 | — | >50 | — |
| Other fragrances | 1 | 5 | >50 | 4 |
| **Noncoloring hair care** | | | | |
| Conditioners | — | 8 | — | 0.2 |
| Sprays/aerosol fixatives | 1 | — | ≤0.1 | 0.6 |
| Rinses | — | — | — | 0.004 |
| Shampoos | 1 | 6 | 5–10 | 0.4 |
| Tonics, dressings, etc. | 1 | 3 | 10–25 | 0.4 |
| Wave sets | 4 | 4 | 5–10 | — |
| **Hair coloring** | | | | |
| Dyes and colors | — | 10 | — | — |
| Other hair coloring | — | 2 | — | — |
| **Makeup** | | | | |
| Blushers | — | 1 | — | 0.08 |
| Foundations | — | 5 | — | 0.2 |
| Lipsticks | 4 | 15 | ≤0.1–10 | 0.03 |
| Makeup bases | 1 | 4 | 1–5 | 0.05 |
| Rouges | — | — | — | 0.08 |
| Other makeup | — | 2 | — | 0.2–7 |
| **Nail care** | | | | |
| Nail polish and enamel removers | — | — | — | 0.004 |
| **Personal hygiene** | | | | |
| Underarm deodorants | 4 | 25 | 1–5 | 8–50 |
| Other personal hygiene | — | 13 | — | 1 |

*(Continued on next page)*

**TABLE 4**
Historical and current cosmetic product uses and concentrations for Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol *(Continued)*

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| **Shaving** | | | | |
| Aftershave lotions | 2 | 2 | 0.1–5 | 3–5 |
| Preshave lotions | — | — | — | 0.6 |
| Shaving cream | — | — | — | 0.07 |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 4 | 38 | ≤0.1 | 0.01–12 |
| Face and neck skin care | 3* | 24 | 1–5* | 2 |
| Body and hand skin care | | 19 | | 0.1–9 |
| Foot powders and sprays | 1 | — | 0.1–1 | — |
| Moisturizers | 4 | 39 | 1–10 | 7 |
| Night creams, lotions, powder, and sprays | — | 4 | — | 2–3 |
| Paste masks/mud packs | — | 14 | — | 0.02–0.03 |
| Skin fresheners | 2 | 3 | 0.1–25 | 2 |
| Other skin care | 1 | 18 | 5–10 | 1–2 |
| **Suntan** | | | | |
| Suntan gels, creams, liquids and sprays | — | 5 | — | — |
| Indoor tanning | — | 4 | — | 1 |
| Other suntan | — | 3 | — | — |
| **Total uses/ranges for Dipropylene Glycol** | **50** | **304** | **≤0.1–>50** | **0.004–50** |

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

2003 found concentrations of use ranging from 0.00007% to 89% (CTFA 2003).

**Hexylene Glycol** was reported to be used in 85 preparations in 1981, with the largest use in shampoos, and at concentrations ranging from less than 0.1% to 25% (Elder 1985). In 2002, Hexylene Glycol was reported to be used in 306 preparations, with the greatest use in hair dyes and colors (FDA 2002). Concentrations of use in 2003 ranged from 0.0005% to 6% (CTFA 2003).

**Ethoxydiglycol** was reported to be used in 80 preparations in 1981, with the largest uses in hair dyes and colors as well as skin cleansing creams, lotions, liquids, and pads. The concentration of use ranged from less than 0.1% to greater than 50% (Elder 1985). In 2002, Ethoxydiglycol was used in 622 preparations (FDA 2002) and at concentrations ranging from 0.0004% to 80% (CTFA 2003).

**Dipropylene Glycol** was reported to be used in 50 preparations in 1981, with the largest single use occurring in perfumes, and at concentrations ranging from less than 0.1% to greater than 50% (Elder 1985). In 2002, Dipropylene Glycol was reported to be used in 304 preparations (FDA 2002) at concentrations ranging from 0.004% to 50% (CTFA 2003).

Table 4 presents the available use and concentration information. The most recent information now constitutes the present practices of use.

## REFERENCES

Alomar, A., L. Conde-Salazar, and C. Romaguera. 1985. Occupational dermatoses from cutting oils. *Contact Dermatitis* 12:129–138.

Bates, H. K., C. J. Price, M. C. Marr, C. B. Myers, and J. J. Heindel. 1992a. Final report on the developmental toxicity of dipropylene glycol (CAS No. 25265-71-8) in Sprague-Dawley rats. Govt reports announcement & Index, issue 18. NTIS/PB92-196179.

Bates, H. K., C. J. Price, M. C. Marr, C. B. Myers, and J. J. Heindel. 1992b. Final report on the developmental toxicity of dipropylene glycol in New Zealand white rabbits. NTIS/PB92-196179.

Biros, M. H., and R. Nordness. 1996. Effects of chemical pretreatment on post-traumatic cortical edema in the rat. *Am. J. Emerg. Med*. 14(1):27–32.

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.

Brooks, T. M., A. L. Meyer, and D. H. Hutson. 1988. The genetic toxicology of some hydrocarbon and oxygenated solvents. *Mutagenesis*. 3:227–232.

Combs, D. J., and L. G. D'Alecy. 1987. Motor performance in rats exposed to severe forebrain ischemia: effect of fasting and 1,3-butanediol. *Stroke*. 18:503–511.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2003. Current concentrations of use for Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol.[5]

[5]Available for review: Director, Cosmetic Ingredient Review (CIR), 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

Cox, S. K., K. E. Ferslew, and L. J. Boelen. 1992. The toxicokinetics of 1,3-butylene glycol versus ethanol in the treatment of ethylene glycol poisoning. *Veterinary Human Toxicol.* 34:36–42.

Demerle-Pallardy, C., D. Duverger, B. Spinnewyn, E. Pirotzky, and P. Braquet. 1991. Peripheral type benzodiazepine binding sites following transient forebrain ischemia in the rat: effect of neuroprotective drugs. *Brain Res.* 565:312–320.

Diegenant, C., L. Constandt, and A. Goossens. 2000. Allergic contact dermatitis due to 1,3-butylene glycol. *Contact Dermatitis* 43:234–235.

Dow Chemical Co. 1994. Determination of the acute oral toxicity of dipropylene glycol in rats with cover letter dated 032894 (sanitized). EPA/OTS Document No. 86940000276S. NTIS/OTS0572379.

Drackley, J. K., Y. K. Kim, B. D. Strang, and J.W. Young. 1989a. Metabolic responses of lactating goats to feed restriction and dietary 1,3-butanediol. *J. Dairy Sci.* 72:3204–3211.

Drackley, J. K., M. J. Richard, D. C. Beitz, and J. W. Young. 1992. Metabolic changes in dairy cows with ketonemia in response to feed restriction and dietary 1,3-butanediol. *J. Dairy Sci.* 75:1622–1634.

Drackley, J. K., J. J. Veenhuizen, M. J. Richard, and J. W. Young. 1991. Metabolic changes in blood and liver of dairy cows during either feed restriction or administration of 1,3-butanediol. *J. Dairy Sci.* 74:4254–4264.

Drackley, J. K., Y. Zhang, D. M. Amaral, and J. W. Young. 1989b. Metabolic effects of intraruminal administration of 1,3-butanediol or tributyrin in lactating goats. *J. Dairy Sci.* 72:1986–1995.

Elder, R. L. 1985. Final report on the Safety Assessment of Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol. *J. Am. Coll. Toxicol.* 4:223–248.

Food and Drug Administration (FDA). 2002. Frequency of use in cosmetics of Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glcyol. *FDA database*. Washington, DC: FDA.

Fujimoto, Y., R. Hayakaawa, M. Suzuki, et al. 1994. A case of contact dermatitis due to 1,3-butylene glcyol. *Environ. Dermatol*. 1:106–110.

Gueldry, S., and J. Bralet. 1994. Effect of 1,3-butanediol on cerebral energy metabolism. Comparison with beta-hydroxybutyrate. *Metab. Brain Dis*. 9:171–181.

Gueldry, S., C. Marie, G. Christofi, G. S. Sarna, and T. P. Obrenovitch. 1994. Change in extracellular and rat brain tissue concentrations of D-beta-hydroxybutyrate after 1,3-butanediol treatment. *J. Neurochem*. 62:223–226.

Gueldry, S., C. Marie, L. Rochette, and J. Bralet. 1990. Beneficial effect of 1,3-butanediol on cerebral energy metabolism and edema following brain embolization in rats. *Stroke* 21:1458–1463.

Hardin, B. D., P. T. Goad, and J. R. Burg. 1984. Developmental toxicity of four glycol ethers applied cutaneously to rats. *Environ. Health Perspect.* 57:69–74.

Hardin, B. D., R. L. Schuler, J. R. Burg, et al. 1987. Evaluation of 60 chemicals in a prelimary developmental toxicity test. *Teratogen. Carcinogen. Mutagen.* 7:29–48.

Hardy, C. J., D. W. Coombs, D. J. Lewis, and H. J. Klimisch. 1997. Twenty-eight day repeated dose inhalation exposure of rats to diethylene glycol monoethyl ether. *Fundam. Appl. Toxicol.* 38:143–147.

Harrison, J. E., A. C. Watkinson, D. M. Green, J. Hadgraft, and K. Brain. 1996. The relative effect of Azone and Transcutol on permeant diffusivity and solubility in human stratum cornneum. *Pharm. Res.* 13:542–546.

Hoechst Celanese Corp. 1991. Initial submission: subchronic feeding study with 1,3-butanediol in dogs (final report) with cover letter. EPA/OTS; Document No. 88-920001732. NTIS/OTS0537195.

Johansen, J. D., G. B. Jemec, and S. C. Rastogi. 1995. Contact sensitization to dipropylene glycol in an eczema population. *Contact Dermatitis* 33:211–212.

Johansen, J. D., S. C. Rastogi, and G. B. E. Jemec. 1994. Dipropylene glycol allergy: a hidden cause of perfume contact dermatitis. *Am. J. Cont. Derm.* 5:98–101.

Kinnunen, T., and M. Hannuksela. 1989. Skin reactions to hexylene glycol. *Contact Dermatitis* 21:154–158.

Kinnunen, T., and M. Koskela. 1991. Antibacterial and antifungal properties of propylene glycol, hexylene glycol, and 1,3-butylene glycol in vitro. *Acta Dermatol. Venereol.* 71:148–150.

Levi-Schaffer, F., N. Dayan, and E. Touitou. 1996. Diethylene glycol monoethyl ether (Transcutol) displays antiproliferative properties alone and in combination with xanthines. *Skin Pharmacol.* 9:53–59.

Li, D., J. F. Brady, M. J. Lee, and C. S. Yang. 1989. Effect of 1,3,Butanediol on rat liver microsomal NDMA demethylation and other monooxygenase activities. *Toxicol. Lett.* 45:141–148.

Lundgren, J., M. L. Smith, A. M. Mans, and B. K. Siesjo. 1992. Ischemic brain damage is not ameliorated by 1,3-butanediol in hyperglycemic rats. *Stroke* 23:719–724.

Lundy, E. F., B. A. Luyckx, D. J. Combs, G. B. Zelenock, and L. G. D'Alecy. 1984. Butanediol induced cerebral protection from ischemic-hypoxia in the instrumented Levine rat. *Stroke* 15:547–552.

Mankes, R. F., V. Renak, J. Fieseher, and R. Lefevre. 1986. Birthweight depression in male rats contiguous to male siblings in utero exposed to high doses of 1,3-butanediol during organogenesis. *J. Am. Coll. Toxicol.* 5:189–196.

Marie, C., A. M. Bralet, and J. Bralet. 1987. Protective action of 1,3-butanediol in cerabral ischemia. A neurologic, histologic, and metabolic study. *J. Cereb. Flow Metab*. 7(6):794–800.

Meenakshi, C., K.L. Kumari, and C.S. Devi. 1995. Biochemical studies on the effect of *S*-1,3-butanediol of diabetes induced rats. *Indian J. Physiol. Pharmacol*. 39:145–148.

Mellon Institute. 1994. Letter from union carbide corp to USEPA regarding toxicity studies of various chemicals referenced in 40 CFR part 716, 58 FED REG 68311-68322 (1227/93) w/attachments dated 042694. EPA/OTS Document No. 86940001887. NTIS/OTS0557477.

Mills, S. E., R. R. Lyle, D. C. Beitz, and J. W. Young. 1984. In vitro hepatic gluconeogenesis during experimental ketosis produced in steers by 1,3-butanediol and phlorizin. *J. Dairy Sci.* 37:2265–2273.

Mura, P., M. T. Faucci, G. Bramanti, and P. Corti. 2000. Evalutaiton of transcutol as clonazepam transdermal permeation enhancer from hydrophilic gel formulations. *Eur. J. Pharm. Sci.* 9:365–372.

Murphy, M. J., A. C. Ray, L. P. Jones, and J. C. Reagor. 1984. 1,3 Butanediol treatment of ethylene glycol toxicosis in dogs. *Am. J. Vet. Res.* 45:2293–2295.

Nelson, B. K., J. V. Setzer, W. S. Brithwell, et al. 1984. Comparative inhalation teratogenicity of four glycol ether solvents and an amino derivative in rats. *Environ. Health Perspect.* 57:261–271.

Panchagnula, R., and W. A. Ritschel. 1991. Development and evaluation of an intracutaneous depot formulation of corticosteriods using Transcutol as a cosolvent: in-vitro, ex-vivo and in-vivo rat studies. *J. Pharm. Pharmacol.* 43:609–614.

Pilon, D., J. Brodeur, and G. L. Plaa. 1986. 1,3-Butanediol-induced increases in ketone bodies and potentiation of carbon tetrachloride hepatotoxicity. *Toxicology*. 40:165–180.

Proctor & Gamble Co. 1995. Support: Draft summary of results of range-finding developmental toxicity study with 2-methyl-2,4-pentanediol in rats, with cover letter dated 11/22/95. EPA/OTS Document No. 89960000011. NTIS/OTS0572134-1.

Schuler, R. L., B. D. Hardin, R. W. Niemeier, et al. 1984. Results of testing fifteen glycol ethers in a short-term in vivo reproductive toxicity assay. *Environ. Health Perspect.* 57:141–146.

Sims, N. R., and S. L. Heward. 1994. Delayed treatment with 1,3-butanediol reduces loss of CA1 neurons in the hippocampus of rats following brief forebrain ischemia. *Brain Res.* 662:216–222.

Spence, C. A., R. D. Boyd, C. D. Wray, and D. M. Whitehead. 1985. Effect of 1,3-butanediol and short chain acids in sow gestation diets on maternal plasma metabolites and fetal energy storage. *J. Anim. Sci.* 60:1280–1287.

Stahly, T. S., G.L. Cromwell, and H.J. Monegue. 1986. Effects of dietary addition of 1,3-butanediol or lard for sows on survival of neonatal pigs. *J. Anim. Sci.* 63:1156–1162.

Sugiura, M., and R. Hayakawa. 1997. Contact dermatitis due to 1,3-butylene glycol. *Contact Dermatitis* 37:90.

Watanabe, M., K. Watanabe, K. Suzuki, O. Nikaido, I. Ishii, H. Konishi, N. Tanaka, and T. Sugahara. 1989. Use of primary rabbit cornea cells to replace the Draize rabbit eye irritancy test. *Toxicol In Vitro* 3:329–334.

Williams, R., J. R. Reel, J. D. George, and J. C. Lamb. 1990. Reproductive effects of diethylene glycol and diethylene glycol monoethyl ether in Swiss CD-1 mice assessed by continuous breeding protocol. *Fundam. Appl. Toxicol*. 14:622–635.

Xie, Z., R. Hayakawa, M. Sugiura, Y. Kato, and Y. Takeuchi. 1999a. Causes of 15 cases with occupational contact dermatitis in the secondary industries. *Environ. Dermatol.* 6:22–25.

Xie, Z., R. Hayakawa, M. Sugiura, Y. Kato, and Y. Takeuchi. 1999b. Causative agents and prognosis of 66 patients with occupational contact dermatitis. *Environ. Dermatol.* 6:33–141.

Yazdanian, M., and E. Chen. 1995. The effect of diethylene glycol monoethyl ether as a vehicle for topical delivery of ivermectin. *Vet. Res. Commun.* 19:309–319.

## CETEARYL OCTANOATE (CETEARYL ETHYLHEXANOATE)

A safety assessment of Cetearyl Octanoate was published in 1982 with the conclusion that this ingredient is safe as a cosmetic ingredient in the present practices of use (Elder 1982). Studies available since that safety assessment was completed have been considered by the CIR Expert Panel, 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—Ceteraryl Ethylhexanoate is the current terminology (Pepe et al. 2002).

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 come 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.

Although 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 was used in 243 cosmetic products in 1976 (Elder 1982). The highest concentrations were in eye makeup, makeup, and skin care preparations. Currently there are 229 reported uses of Cetearyl Ethylhexanoate reported to FDA (FDA 2002), with the highest concentrations (up to 35%) in makeup (CTFA 2002). 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 and concentraton information. The most recent information now constitutes the present practices of use.

## REFERENCES

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(1):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 061787. NTIS Report No. OTS0525538.

CMA. 1987b. Letter from Chemical Manufacturers Association to USEPA submitting 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]

[6]Available for review: Director, Cosmetic Ingredient Review (CIR), 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

**TABLE 5**
Historical and current cosmetic product uses and concentrations for Cetearyl Ethylhexanoate

| Product category | 1976 uses (Elder 1982) | 2002 uses (FDA 2002) | 1976 concentrations (Elder 1982) % | 2002 concentrations (CTFA 2002a) % |
|---|---|---|---|---|
| **Baby care** | | | | |
| Lotions, oils, powders, and creams | — | 1 | — | — |
| **Bath** | | | | |
| Oils, tablets, and salts | 1 | — | Unknown | — |
| Capsules | — | — | — | 9 |
| Other bath | 2 | — | 1–10 | — |
| **Eye makeup** | | | | |
| Eyeliners | 1 | — | 0.1–1 | — |
| Eye shadows | 22 | 4 | 0–25 | 26–28 |
| Mascara | 6 | — | 0.1–1 | 0.07 |
| Other eye makeup | 2 | 3 | 0.1–5 | 3–5 |
| **Fragrances** | | | | |
| Powders | — | 2 | — | — |
| Other fragrances | — | 12 | — | — |
| **Noncoloring hair care** | | | | |
| Conditioners | 5 | — | 0–5 | — |
| Sprays (aerosol fixatives) | 5 | 5 | 0–5 | — |
| Straighteners | 1 | — | 0.1–1 | — |
| Rinses | 1 | — | 0.1–1 | — |
| Shampoos | — | — | — | 0.2 |
| Tonics, dressings, etc. | 1 | 32 | 0.1–1 | 0.1 |
| Wave sets | 1 | — | 1–5 | — |
| Other noncoloring hair | 3 | 2 | 0–5 | — |
| **Makeup** | | | | |
| Blushers | 19 | 3 | 1–25 | 3 |
| Face powders | 10 | 6 | 0.1–1 | 1–4 |
| Foundations | — | 5 | — | 0.1–34 |
| Lipstick | — | 4 | — | 0.1–8 |
| Makeup bases | 25 | — | 0.1–5 | — |
| Rouges | 2 | — | 5–25 | — |
| Makeup fixatives | 1 | — | 5–10 | — |
| Other makeup | 10 | — | 0.1–5 | 35 |
| **Nail care** | | | | |
| Nail creams and lotions | 1 | — | 10–25 | — |
| **Personal hygiene** | | | | |
| Underarm deodorants | — | — | — | 3 |
| Feminine deodorants | 1 | — | 1–5 | — |
| **Shaving** | | | | |
| Aftershave lotion | — | 2 | — | — |
| Mens talcum | — | 1 | — | — |
| Preshave lotions | 1 | — | 1–5 | — |
| Other shaving | 1 | — | 1–5 | — |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 15 | 7 | >0–10 | 13 |
| Face and neck skin care | 35* | 21 | >0–25* | 3 |
| Body and hand skin care | | 38 | | 3–10 |
| Moisturizers | 39 | 23 | 0.1–25 | 2–34 |
| Night skin care | 16 | 13 | 0.1–10 | 2–7 |
| Paste masks/mud packs | 3 | 8 | 0.1–5 | — |
| Skin fresheners | 1 | 2 | 0.1–1 | — |
| Other skin care | 4 | 21 | 1–25 | 6 |
| **Suntan** | | | | |
| Suntan gels, creams, and liquids | 7 | 9 | 0-5 | 0.5–9 |
| Indoor tanning | — | 2 | — | 3 |
| Other suntan | 1 | 3 | 5–10 | — |
| **Total uses/ranges for Cetearyl Ethylhexanoate** | **243** | **229** | **0–25** | **0.07–35** |

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

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 MatTek Epiocular Model. Unpublished data submitted by CTFA. March 22, 2002. 14 pages.[6]

Cosmetic, Toiletry, and Fragrance Association (CTFA). 1990a. Report regarding the primary eye irritation of neopentyl glycol diethylhexanoate; 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]

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. 1993a. Phototoxicity. Unpublished data submitted by the CTFA. May 8, 2002.[6]

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

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

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

CTFA. 1995. Human Repeat Insult Patch Test. Unpublished data submitted by CTFA. May 8 2002.[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-Ethylhexanoic 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. Coll. 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. 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.

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.

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-ehtylhexanoic 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.

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

Pradhan, M. 2002. Personal communication—toxicologist's evaluation of toxicological data, exposure levels, and assessment, 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 valproic acid, and potentiation 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 & 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]

## CHOLESTEROL

A safety assessment of Cholesterol was published in 1986 with the conclusion that this ingredient is safe as presently used in cosmetic products (Elder 1986). The CIR Expert Panel reviewed new studies available since that time, along with updated information regarding types and concentrations of use, and determined to not reopen this safety assessment.

According to the entry in the *International Cosmetic Ingredient Dictionary and Handbook*, Cholesterol functions as an emulsion stabilizer, miscellaneous skin-conditioning agent, and nonaqueous viscocity-increasing agent in cosmetic products (Gottschalck and McEwen 2004).

Frequency of use data provided by industry to FDA for 2002 show that cholesterol is used in 258 cosmetic products (FDA 2002), an increase compared to 145 uses reported in 1981 (Elder 1986). In 1981, Cholesterol use concentrations (again, as reported by industry to FDA) ranged from $\leq$0.1% to 5% (Elder 1986). A survey by the Cosmetic, Toiletry, and Fragrance Association (CTFA) in 2004 found the range of use concentrations to be 0.002% to 3%, with majority of products around 0.1%.

Historical and current cosmetic product uses and concentrations for Cholesterol are given in Table 6. The most recent information now constitutes the present practices of use.

## REFERENCES

Barbu, V., C. Roux, D. Lampert, R. Dupuis, J. Gardette, J. C. Maziere, C. Maziere, E. Elefant, and J. Polonovski. 1988. Cholesterol prevents the teratogenic action of AY 9944: Importance of the timing of cholesterol supplementation to rats. *J. Nutri*. 118:774–779.

Contag, B. 1991. Specific crystal chemical interactions between carcinogenic aromatic compounds and cholesterol. *Z. Naturforsch.* 46:663–672.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2004a. Cholesterol use concentration data from industry survey. Unpublished data submitted by CTFA, 2004 (1 page).[7]

CTFA. 2004b. Sources of cholesterol. Unpublished data submitted by CTFA, 2004 (1 page).[7]

Cross, N. L. 1996. Effect of Cholesterol and Other Sterols on Human Sperm Acrosomal Responsiveness. *Mol. Reprod. Dev.* 45:212–217.

Dehart, D. B., L. Lanoue, G. S. Tint, and K. K. Sulik. 1995. Altered cholesterol biosynthesis in rats: A model for Smith-Lemli-Opitz syndrome. *Teratology* 51:165.

Elder, R. L. ed. 1986. Final report on the safety assessment of Cholesterol. *J. Am. Coll. Toxicol*. 5:491–516.

Food and Drug Administration (FDA). 2002. Frequency of Use of Cosmetic Ingredients. *FDA database.* Washington, DC: FDA.

Gottschalck, T. E., and G. N. McEwen, Jr., eds. 2004. *International Cosmetic Ingredient Dictionary and Handbook*, 10th ed., 151. Washington, DC: CTFA.[7]

Innis, S. M., and N. C. Haave. 1988. Effect of chronic modification of diet fat and cholesterol during gestation on plasma hormones and hepatic enzyme activities in rat fetus. *Biol. Neonate* 53:355–361.

Kurtin, W. E., W. H. Schwesinger, and R. M. Stewart. 1991. Effect of dietary ethanol on gallbladder absorption and cholesterol gallstone formation in the prairie dog. *Am. J. Surg.* 161:470–474.

Lewis, R. J., ed. 2000. Cholesterol. In: *Sax's Dangerous Properties of Industrial Materials*. 919. New York: John Wiley & Sons, Inc.

Lynn, W. S., D. Mathews, A. Thompson, and M. Cloyd. 1988. Role of calcium and cholesterol in cytotoxicity. *Clin. Res.* 36:606A.

Mallinkrodt Baker, Incorporated. 2004. MSDS: Cholesterol. Internet site accessed http://www.jtbaker.com/msds/englishhtml/c3993.htm. October, 2004.

Morgan, B. P., and M. Moynihan. 1990. Steroids. In *Kirk-Othmer concise encyclopedia of chemical technology*, 4th ed., 1894–1900. New York: John Wiley & Sons, Inc.

Poulos, A. 1995. Cholesterol in prenatal development. *Teratology.* 51:286.

Rao, K. N. 1986. Regulatory aspects of cholesterol metabolism in cells with different degrees of replication. *Toxicol. Pathol.* 14:430–437.

Rao, A. V., S. A. Janezic, D. Friday, and C. W. Kendall. 1992. Dietary cholesterol enhances the induction and development of colonic preneoplastic lesions in C57BL/6J and BALB/cJ mice treated with azoxymethane. *Cancer Lett.* 63:249–257.

Repetto, M., J. C. Maziere, D. Citadelle, R. Dupuis, M. Meier, S. Biade, D. Quiec, and C. Roux. 1990. Teratogenic effect of the cholesterol synthesis inhibitor AY 9944 on rat embryos in vitro. *Teratology* 42:611–618.

Ridker, P. M., and T. Michel. 1989. Streptokinase therapy and cholesterol embolization. *Am. J. Med.* 87:357–358.

Thacker, B. J., B. M. Trivedi, Y. D. Shah, D. A. Shah, P. D. Bharadia, et al. 1988. Comparative study of different methods of isolation of cholesterol. *Indian J. Pharm.* 50:331–332.

Yadav, S., and U. M. Rawal. 1992. Cholesterol and lipid peroxidation in 3beta-(2-diethylaminoethoxy) androst-5-en-17-one hydrochloride (U18666A) induced cataractogenesis in rats. *Indian J. Exp. Biol.* 30:147–148.

Wrensch, M., L. Gruenke, N. Petrakis, R. Miike, V. Ernster, and J. Craig. 1987. Breast fluid cholesterol and cholesterol—epoxides relation to breast cancer risk factors. *Am. J. Epidemiol.* 126:770.

## CHLOROXYLENOL

A safety assessment of Chloroxylenol was published in 1985 with the conclusion that this ingredient was safe as a cosmetic ingredient in the practices of use at that time (Elder 1985). New studies, 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.

As given in the *International Cosmetic Ingredient Dictionary and Handbook*, the functions of Chloroxylenol in cosmetic products are now described as a cosmetic biocide, deodorant agent, and preservative (Gottschalck and McEwen 2006).

[7]Available for review: Director, Cosmetic Ingredient Review (CIR), 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

**TABLE 6**
Historical and current cosmetic product uses and concentrations for Cholesterol

| Product category | 1981 uses (Elder 1984) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1984) % | 2004 concentrations (CTFA 2004) % |
|---|---|---|---|---|
| **Bath** | | | | |
| Soaps and detergents | — | 2 | — | — |
| **Eye makeup** | | | | |
| Eyeliners | 6 | 1 | >0.1–1 | — |
| Eye shadow | 15 | — | <0.1–1 | 0.01 |
| Eye lotions | — | 1 | — | 0.04–0.3 |
| Eye makeup remover | — | — | — | 0.002 |
| Mascara | 16 | 2 | >0.1–5 | — |
| Other eye makeup | 3 | 4 | >0.1–5 | — |
| **Fragrances** | | | | |
| Other fragrances | 1 | 2 | >0.1–1 | — |
| **Noncoloring hair care** | | | | |
| Conditioners | 7 | 13 | ≤0.1–1 | 0.3 |
| Straighteners | — | — | — | 0.003 |
| Rinses | — | 1 | — | — |
| Shampoos | 1 | 5 | >0.1–1 | — |
| Tonics, dressings, etc. | — | 3 | — | 2 |
| Other noncoloring hair care | — | 4 | — | 0.2 |
| **Hair coloring** | | | | |
| Dyes and colors | — | 27 | — | — |
| **Makeup** | | | | |
| Face powders | — | 3 | — | — |
| Foundations | 7 | 7 | ≤0.1–1 | 3 |
| Lipsticks | — | 5 | — | 0.1 |
| Makeup bases | 12 | 3 | ≤0.1–1 | 0.02 |
| Rouges | — | 1 | — | — |
| Makeup fixatives | — | 2 | — | — |
| Other makeup | 14 | 4 | ≤0.1–1 | — |
| **Nail care** | | | | |
| Cuticle softeners | — | 1 | — | 0.1 |
| Nail polish and enamel removers | — | 1 | — | — |
| **Shaving** | | | | |
| Aftershave lotions | 1 | 3 | >0.1–1 | 0.1 |
| Shaving cream | — | — | — | 0.1 |
| Other shaving | 1 | — | >0.1–1 | — |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 5 | 11 | ≤0.1–1 | 1 |
| Face and neck skin care | 11* | 22 | ≤0.1–5* | 0.3–2 |
| Body and hand skin care | | 19 | | 0.01–0.5 |
| Foot powders and sprays | — | 3 | — | 0.5 |
| Moisturizers | 19 | 61 | ≤0.1–5 | 0.005–1 |
| Night skin care | 15 | 24 | ≤0.1–5 | 0.1–1 |
| Wrinkle smoothers** | 2 | — | ≤0.1–5 | — |
| Paste masks/mud packs | — | 4 | — | 0.5 |
| Skin fresheners | — | 3 | — | — |
| Other skin care | 8 | 13 | ≤0.1–5 | — |
| **Suntan** | | | | |
| Suntan gels, creams, liquids, and sprays | 1 | 1 | >0.1–1 | 0.02–0.4 |
| Indoor tanning | — | — | — | 0.005 |
| Other suntan | — | 2 | — | — |
| **Total uses/ranges for Cholesterol** | **145** | **258** | **≤0.1–5** | **0.002–3** |

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

In 1984, Chloroxylenol was used as an antimicrobial compound in 93 cosmetic products, with the maximum concentrations at up to 5% in fragrance powders, noncoloring shampoos, and other hair preparations (Elder 1985). In 2002, industry reports of Chloroxylenol use to the FDA included 43 cosmetic products (FDA 2002). Based on an industry survey, CTFA (2002) reported that Chloroxylenol was used in cosmetic products at a maximum concentration of use of 0.5% in skin cleansing products.

Table 7 summarizes these data. The most recent information now constitutes the present practices of use.

## REFERENCES


Aly, R., and H. I. Maibach. 1988. Comparative antibacterial efficacy of a 2-minute surgical scrub with chlorhexidine gluconate, povidone-iodine, and chloroxylenol sponge-brushes. *Am. J. Infect. Control* 16:173–177.

Chan, T. Y. K., and J. A. J. H. Critchley. 1994. Is chloroxylenol nephrotoxic like phenol? A study of patients with DETTOL poisoning. *Vet. Human Toxicol*. 36:250–251.

Cosmetic, Toiletry, and Fragrance Association. 2004. Ingredient use data—chloroxylenol. Unpublished data submitted by CTFA on March 15, 2004. 1 page.[8]

Davila, J. C., A. Dorantes, S. A. Stavchansky, and D. Acosta. 1991. The cytotoxicity of p-chloro-m-xylenol in primary culture of rat hepatocytes. *Pharmaceu. Res.* 8:656–657.

Dorantes, A., and S. Stavchansky. 1992. Pharmacokinetic and metabolic disposition of p-chloro-m-xylenol (PCMX) in dogs. *Pharmaceut. Res*. 9:677–682.

Elder, R. L. 1985. Final report on the safety assessment of chloroxylenol. *J. Am. Coll. Toxicol*. 4:147–169.

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

Gatti, R., P. Roveri, D. Bonazzi, and V. Cavrini. 1997. HPLC-fluorescence determination of chlorocresol and chloroxylenol in pharmaceuticals. *J. Pharmaceut. Biomed. Anal*. 16:405–412.

Goh, C. L. 1989. Contact sensitivity to topical antimicrobials. (ii) Sensitizing potentials of some topical antimicrobials. *Contact Dermatitis* 21:166–171.

Gudipati, R. M., and S. A. Stavchansky. 1995. Percutaneous absorption of parachlorometaxylenol. *Int. J. Pharmaceu.* 118:41–45.

Holder, I. A., L. Vanderpool, and J. Wesselman. 1985. Para-chloro-meta-xylenol (PCMX): a new, potential topical antimicrobial agent. *J. Burn Care Rehab*. 6:58–61.

Lear, J. C., J.-Y. Maillard, P. W. Dettmar, P. A. Goddard, and A. D. Russell. 2002. Chloroxylenol- and triclosan-tolerant bacteria from industrial sources. *J. Ind. Microbiol. Biotech*. 29:238–242.

Libow, L. F., A. M. Ruszkowski, and V. A. DeLeo. 1989. Allergic contact dermatitis from para-chloro-meta-xylenol in Lurosep soap. *Contact Dermatitis* 20:67–68.

Malakar, S., and S. Panda. 2001. Post-inflammatory depigmentation following allergic contact dermatitis to chloroxylenol. *Br. J. Dermatol*. 144:1275–1276.

Malaveille, C., G. Brun, and H. Bartsch. 1991. Genotoxicity of ochratoxin A and structurally related compounds in *Escherichia coli* strains: Studies on their mode of action. In: *Mycotoxins, Endemic Nephropathy and Urinary Tract Tumours*, ed. M. Castegnaro, R. Pleština, G. Dirheimer, I. N. Chernozemsky, and H. Bartsch, 261–266. Lyon, France: IARC.


[8]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.


Miner, N., and M. Armstrong. 1994. Comparative ability of various prescription and over-the-counter topical antifungal drug products to inhibit growth of *C. albicans*. *Adv. in Wound Care* 7:53–56.

Momma, J., K. Takada, Y. Aida, H. Yoshimoto, K. Naito, Y. Suzuki, Y. Nakaji, Kurokawa, and M. Tobe. 1988. Combined ling-term toxicity and carcinogenicity test of p-chloro-m-xylenol (PCMX) applied to female mouse skin. *Eisei Shikenjo Hokoku* 106:39–47.

Mowad, C. 1998. Chloroxylenol causing hand dermatitis in a plumber. *Am. J. Contact Dermatitis* 9:128–129.

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.

Papageorgiou, P. P., and A. C. Chu. Chloroxylenol and zinc oxide containing cream (Nels cream®) vs. 5% benzoyl peroxide cream in the treatment of acne vulgaris. A double-blind, randomized, controlled trial. *Clin. Exp. Dermatol*. 25:16–20.

Schäfer, E., and K. Bössmann. 1999. Antimicrobial effect of camphorated chloroxylenol (ED84) in the treatment of infected root canals. *J. Endod.* 25:547–551.

Schäfer, E., and K. Bössmann. 2001. Antimicrobial efficacy of chloroxylenol and chlorohexidine in the treatment of infected root canals. *Am. J. Dent*. 14:233–237.

Stubbs, W. P., J. R. Bellah, D. Vermaas-Hekman, B. Purich, and P. S. Kubilis. 1996. Chlorohexidine gluconate versus chloroxylenol for preoperative skin preparation in dogs. *Vet. Surg*. 25:487–494.

Yamano, T., M. Shimizu, and T. Noda. 2003. Allergenicity evaluation of *p*-chloro-*m*-cresol and *p*-chloro-*m*-xylenol by non-radioactive murine local lymph-node assay and multiple dose guinea pig maximization test. *Toxicology* 190:259–266.


## DIISOPROPANOLAMINE, ISOPROPANOLAMINE, TRIISOPROPANOLAMINE, AND MIXED ISOPROPANOLAMINES

A safety assessment of Diisopropanolamine, Triisopropanolamine, Isopropanolamine, and Mixed lsopropanolamines was published in 1987 with the conclusion that these ingredients are safe as cosmetic ingredients in the present practices of use and concentration, if not used in products containing N-nitrosating agents (Elder 1987). The CIR Expert Panel considered new studies, along with updated information regarding types and concentrations of use. The Panel determined not to reopen this safety assessment.

No uses of Mixed Isopropanolamines were reported in the original safety assessment, in frequency of use data collected by FDA in 2002 (FDA 2002) or in a recent industry survey (CTFA 2004).

Diisopropanolamine reportedly was used in 66 products in 1981, at concentrations of $\leq$10%, and in 33 products in 2002, at concentrations of up to 0.7% (from the 2004 survey).

Isopropanolamine was used in 11 cosmetic products in 1981, at concentrations of $\leq$1%, and in 27 products in 2002, at the same concentrations (from the 2004 survey).

Triisopropanolamine had 36 cosmetic uses in 1981, at concentrations of $\leq$ 5%, and 25 uses in 2002, at concentrations up to 1% (from the 2004 survey).

Table 8 summarizes the historical and recent uses of Diisopropanolamine, Isopropanolamine, and Triisopropanolamine in

**TABLE 7**
Historical and current cosmetic product uses and concentrations for Chloroxylenol

| Product category | 1979 uses (Elder 1985) | 2002 uses (FDA 2002) | 1979 concentrations (Elder 1985) % | 2003 concentrations (CTFA 2004) % |
|---|---|---|---|---|
| **Baby care** | | | | |
| Lotions, oils, powders, and creams | — | — | — | 0.1 |
| **Bath** | | | | |
| Soaps and detergents | 2 | 1 | >0.1–1 | — |
| **Eye makeup** | | | | |
| Eye shadow | — | 1 | — | — |
| Eye makeup remover | 2 | — | ≤1 | — |
| **Fragrances** | | | | |
| Powders | 2 | — | >1–5 | — |
| **Noncoloring hair care** | | | | |
| Conditioners | 8 | 3 | ≤1 | — |
| Straighteners | 4 | — | >0.1–1 | — |
| Shampoos | 29 | 3 | ≤5 | — |
| Tonics, dressings, etc. | 3 | 6 | >0.1–1 | — |
| Wave sets | 1 | — | ≤0.1 | — |
| Other noncoloring hair care | 3 | — | ≤5 | — |
| **Hair coloring** | | | | |
| Dyes and colors | 1 | — | ≤1 | — |
| Rinses | 2 | — | >0.1–1 | — |
| **Makeup** | | | | |
| Blushers | 1 | — | >0.1–1 | — |
| Rouges | — | 1 | — | — |
| Makeup fixatives | 1 | — | >0.1–1 | — |
| Other makeup | — | 5 | — | — |
| **Nail care** | | | | |
| Basecoats and undercoats | 1 | — | ≤1 | — |
| Cuticle softeners | 1 | — | >0.1–1 | — |
| **Oral hygiene** | | | | |
| Other oral hygiene | — | — | — | 0.4 |
| **Personal hygiene** | | | | |
| Underarm deodorants | 1 | 1 | >0.1–1 | — |
| Feminine deodorants | 1 | — | ≤0.1 | — |
| Other personal hygiene | 8 | 11 | ≤1 | — |
| **Shaving** | | | | |
| Shaving cream | — | 1 | — | — |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 5 | 4 | ≤1 | 0.5 |
| Depilatories | 1 | — | >0.1–1 | — |
| Face and neck skin care | 7* | — | ≤1* | 0.2 |
| Body and hand skin care | | 2 | | — |
| Moisturizers | — | 1 | — | 0.1 |
| Paste masks/mud packs | 2 | — | ≤1 | — |
| Skin fresheners | 1 | — | ≤1 | — |
| Other skin care | 5 | 3 | ≤1 | — |
| **Suntan products** | | | | |
| Suntan gels, creams, liquids and sprays | 1 | — | 0.1–1 | — |
| **Total uses/ranges for Chloroxylenol** | **93** | **43** | **≤5** | **0.1–0.5** |

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

**TABLE 8**
Historical and current uses and use concentrations for Diisopropanolamine, Isopropanolamine, and Triisopropanolamine in cosmetic products

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2004 concentrations (CTFA 2004) % |
|---|---|---|---|---|
| | *Diisopropanolamine* | | | |
| **Fragrances** | | | | |
| Colognes and toilet waters | 2 | 1 | ≤0.1 | — |
| Other fragrances | 13 | 10 | ≤1 | — |
| **Noncoloring hair care** | | | | |
| Conditioners | 1 | 1 | >0.1–1 | — |
| Sprays | 1 | — | >1–5 | — |
| Permanent waves | 7 | 3 | >0.1–10 | — |
| Tonics, dressings, etc. | 2 | 5 | ≤1 | 0.7 |
| Wave sets | 1 | 1 | >0.1–1 | — |
| Other noncoloring hair care | 2 | 1 | >1–5 | — |
| **Hair coloring** | | | | |
| Hair dyes and colors | — | 3 | — | — |
| **Makeup** | | | | |
| Makeup foundations | 2 | — | >1–5 | — |
| Other makeup | 5 | — | >0.1–5 | — |
| **Shaving** | | | | |
| Aftershave lotion | 4 | 2 | ≤1 | — |
| Other shaving | 2 | 3 | ≤1 | — |
| **Skin care preparations** | | | | |
| Cleansing creams, lotions, etc. | — | — | — | <0.01 |
| Face, body, and hand skin care | 10 | — | >0.1–1 | — |
| Moisturizers | 4 | — | ≤5 | — |
| Night skin care | 1 | — | >0.1–1 | — |
| Paste masks/mud packs | 2 | 1 | >0.1–5 | — |
| Skin fresheners | 2 | 1 | ≤1 | — |
| Wrinkle smoothers** | 1 | —** | >0.1–1 | —** |
| Other skin care | 1 | 1 | >0.1–1 | — |
| **Suntan preparations** | | | | |
| Suntan gels, creams, and liquids | 2 | — | >0.1–1 | — |
| Indoor tanning | 1 | — | >0.1–1 | — |
| **Total uses/ranges for Diisopropanolamine** | **66** | **33** | **≤10** | **<0.01–0.7** |
| | *Isopropanolamine* | | | |
| **Eye makeup** | | | | |
| Eyeliner | — | 1 | — | — |
| Mascara | 3 | 22 | ≤1 | — |
| **Noncoloring hair care** | | | | |
| Tonics, dressings, etc. | 1 | 1 | ≤0.1 | — |
| **Hair coloring** | | | | |
| Hair dyes and colors | — | — | — | 1 |
| **Shaving** | | | | |
| Aftershave lotions | 2 | — | >0.1–1 | — |
| **Skin care** | | | | |
| Depilatories | 1 | — | ≤0.1 | — |
| Body and hand skin care | — | 1 | — | — |
| Moisturizers | 3 | 1 | ≤1 | — |

*(Continued on next page)*

**TABLE 8**
Historical and current uses and use concentrations for Diisopropanolamine, Isopropanolamine, and Triisopropanolamine in cosmetic products *(Continued)*

| Product category | 1981 uses (Elder, 1985) | 2002 uses (FDA, 2002) | 1981 concentrations (Elder, 1985) % | 2004 concentrations (CTFA, 2004) % |
|---|---|---|---|---|
| **Suntan** | | | | |
| Suntan gels, creams, and lotions | 1 | 1 | ≤0.1 | — |
| **Total uses/ranges for Isopropanolamine** | **11** | **27** | **≤1** | **1** |
| | | *Triisopropanolamine* | | |
| **Baby care** | | | | |
| Lotions, oils, powders, and sprays | 1 | — | >0.1–1 | — |
| **Noncoloring hair care** | | | | |
| Conditioners | 4 | — | >0.1–5 | — |
| Sprays | 9 | 9 | ≤1 | 0.4 |
| Tonics, dressings, etc. | 13 | 12 | ≤5 | 0.7 |
| Wave sets | 2 | 3 | >0.1–1 | — |
| Other hair care | 2 | 1 | >0.1–1 | 1* |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 1 | — | >1–5 | — |
| Face and neck skin care preparations | 1*** | — | >0.1–1*** | — |
| Body and hand skin care preparations | | — | | — |
| Moisturizers | 3 | — | >0.1–1 | — |
| **Total uses/ranges for Triisopropanolamine** | **36** | **25** | **≤5** | **0.4–1** |

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

cosmetic products. The most recent information now constitutes the present practices of use.

The CIR Expert Panel did note that Diisopropanolamine has a structure that is related to diethanolamine (DEA), which has been implicated as an animal carcinogen. Data were provided suggesting a mechanism for DEA carcinogenicity in animals is related to choline metabolism. Data also were provided demonstrating that Diisopropanolamine does not act by the same mechanism. It was suggested, therefore, that Diisopropanolamine is unlikely to present any risk of carcinogenicity.

The Panel acknowledged the use of Diisopropanolamine 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 depostion. The mean aerodynamic diameter of pump hair spray particles is approximately 80 $\mu$m, and 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, Diisoprpanolamine would not be respirable in formulation. Therefore, exposure of the lung by inhalation was not considered likely.

## REFERENCES

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

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2004. Use concentration data on sodium lauryl sulfoacetate from industry survey. Unpublished data submitted by CTFA, 2004 (1 page).[9]

Cooper, S. M., and S. Shaw. 1999. Contact allergy to isopropanolamine in Traxam® gel. *Contact Dermatitis* 41:233–234.

Elder, R. L. 1987. Final report on the safety assessment of diisopropanolamine, triisopropanolamine, isopropanolamine, and mixed isopropanolmaine. *J. Am. Coll. Toxicol.* 6:53–76.

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

Fujimoto, K., S. Hashimoto, T. Kozuka, and K. Yoshikawa. 1989. Contact dermatitis due to diisopropanolamine. *Contact Dermatitis* 21:56.

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

Oisu, N., K. Fukai, and M. Ishii. 2003. Triple allergic contact sensitivities due to ferbanic, crotamiton, and diisopropanolamine. *Contact Dermatitis* 49:261–263.

Oakes, D. J., and J. K. Pollak. 1999. Effects of a herbicide formulation, Tordon 75D®, and its individual components on the oxidative functions of mitochondria. *Toxicology* 136:41–52.

[9]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

**TABLE 9**
Historical and current uses and use concentrations for Diethylhexyl Adipate and Diisopropyl Adipate

| Product category | 1981 uses (Elder 1984) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1984) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| | *Diethylhexyl Adipate* | | | |
| **Bath** | | | | |
| Oils, tablets, salts | 4 | — | >10–25 | — |
| **Eye makeup** | | | | |
| Lotion | — | — | — | 0.6 |
| Other eye makeup | — | 2 | — | 0.4-2 |
| **Fragrances** | | | | |
| Colognes and toilet waters | 6 | — | >1–5 | — |
| Other fragrance | — | 5 | — | — |
| **Makeup** | | | | |
| Blushers | 1 | 3 | ≥ 0.1 | 13 |
| Foundations | 4 | 2 | >0.1–10 | 16 |
| Makeup bases | — | 6 | — | 6 |
| Lipsticks | 5 | 1 | >1–5 | — |
| Other makeup | 1 | 2 | >1–5 | — |
| **Nail care** | | | | |
| Nail polish & enamel remover | 2 | — | >1–5 | — |
| Nail creams and lotions | — | 1 | — | — |
| Cuticle softeners | — | 1 | — | — |
| **Personal hygiene** | | | | |
| Underarm deodorants | 1 | — | >0.1–1 | 8 |
| Other personal hygiene | — | 4 | — | — |
| **Shaving** | | | | |
| Aftershave lotions | 1 | — | >1–5 | 1 |
| Shaving cream | — | 5 | — | — |
| **Skin care** | | | | |
| Face and neck skin care | 1* | 2 | >1–5* | — |
| Body and hand skin care | | 2 | | — |
| Moisturizers | — | 4 | — | — |
| Other skin care | — | 5 | — | — |
| **Suntan** | | | | |
| Suntan gels, creams, and liquids | — | 1 | — | 38 |
| Indoor tanning | — | 2 | — | 12 |
| Other suntan | 1 | 1 | — | — |
| **Total uses/ranges for Diethylhexyl Adipate** | **27** | **49** | **≥0.1–25** | **0.4–38** |
| | *Diisopropyl Adipate* | | | |
| **Bath** | | | | |
| Oils, tablets, and salts | 7 | 5 | >1–25 | 5 |
| Bubble baths | 1 | — | >1–5 | — |
| Other bath | — | 1 | — | 8 |
| **Eye makeup** | | | | |
| Eyeliner | 1 | — | >1–5 | — |
| Eye shadow | 1 | — | >10–25 | — |
| **Fragrances** | | | | |
| Colognes and toilet waters | 15 | 16 | >0.1–5 | 8 |
| Perfumes | 20 | 14 | >1–10 | 8 |

*(Continued on next page)*

**TABLE 9**
Historical and current uses and use concentrations for Diethylhexyl Adipate and Diisopropyl Adipate *(Continued)*

| Product category | 1981 uses (Elder 1984) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1984) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| Sachets | 1 | — | >10–25 | — |
| Other fragrances | 9 | 2 | >0.1–25 | 15 |
| **Noncoloring hair care** | | | | |
| Conditioners | 3 | — | ≥0.1–1 | 0.1 |
| Sprays | 1 | 1 | >1–5 | 3 |
| Tonics, dressings, etc. | 4 | 2 | >1–5 | — |
| Wave sets | 2 | — | >0.1–5 | — |
| **Makeup** | | | | |
| Blushers | 1 | — | >1–5 | — |
| Face powders | 1 | — | >1–5 | — |
| Foundations | 1 | — | >0.1–1 | 5 |
| **Nail care** | | | | |
| Nail polish and enamel removers | — | 1 | — | 3 |
| **Personal hygiene** | | | | |
| Underarm deodorants | — | — | — | 0.01 |
| Other personal hygiene | 1 | — | >0.1–1 | — |
| **Shaving** | | | | |
| Aftershave lotions | 16 | 10 | >1–5 | 1 |
| Preshave lotions | 1 | — | >5–10 | 5 |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 5 | 1 | >0.1–1 | — |
| Face and neck skin care | —* | 1 | —* | — |
| Body and hand skin care | | 1 | | 2–3 |
| Foot powders and sprays | 1 | — | >0.1–1 | — |
| Moisturizers | 2 | 5 | >0.1–5 | 0.2 |
| Night skin care | 1 | — | >5–10 | — |
| Skin fresheners | 11 | 2 | — | — |
| Other skin care | 2 | — | >1–10 | 4 |
| **Suntan** | | | | |
| Suntan gels, creams, and liquids | 2 | 3 | >5–10 | 4 |
| Indoor tanning | 2 | — | >1–5 | — |
| Other suntan | — | 1 | — | — |
| **Total uses/ranges for Diisopropyl Adipate** | **112** | **66** | **≥0.1–25** | **0.1–15** |

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

Stott, W.T. 2004. CIR Board diisopropanolamine review presentation on research by Dow Chemical Company. Dec. 2, 2004.[9]

Wigfield, Y. Y., M. D. Lacroix, M. Lanouette, and N. P. Gurprasad. 1988. Gas chromatographic determination of *N*-nitrosodialkanolamines I herbicide di- or trialkanolamine formulations. *J. Assoc. Off. Anal. Chem*. 71:328–333.

## DIOCTYL ADIPATE AND DIISOPROPYL ADIPATE

A safety assessment of Dioctyl Adipate and Diisopropyl Adipate was published in 1984 with the conclusion that these ingredients are safe as presently used in cosmetics (Elder 1984). 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.

The name of Dioctyl Adipate as listed in the *International Cosmetic Ingredient Dictionary and Handbook* has been changed to Diethylhexyl Adipate (Pepe et al. 2002).

**Diethylhexyl Adipate**, according to information provided by industry to FDA under a voluntary reporting program, was used in 27 cosmetic products in 1981, with the maximum use concentration at 25%. Use increased in 2002 to 49 cosmetic products. As reported in an industry survey, the maximum use concentration increased to 38% in 2003.

**Diisopropyl Adipate** was used in 112 cosmetic products in 1981, with the maximum use concentration in the 10% to 25% range. Use decreased to 66 reported uses in 2002. The maximum use concentration was 15% in 2003, consistent with that reported in 1981.

Table 9 gives the available use and concentration data for Dioctyl Adipate and Diisopropyl Adipate. The most recent data now constitute the present practices of use.

The CIR Expert Panel noted that Dioctyl Adipate and Diisopropyl Adipate are used in cosmetic products that may be incidentally inhaled during use (e.g., 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 depostion.

The mean aerodynamic diameter of pump hair spray particles is approximately 80 $\mu$m, and 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, these ingredients would not be respirable in formulation. Therefore, exposure of the lung by inhalation was not considered likely.

The increase in the maximum concentration of use to 38% (in suntan lotion) was considered in the context of newly available reproductive and developmental toxicity data suggesting that Diethylhexyl Adipate can be fetotoxic in animal studies. This was a threshold effect and the systemic dose at which no adverse effects were seen (NOAEL) was 200 mg/kg day$^{-1}$. Using an estimated use of 40 g per day of suntan lotion containing Diethylhexyl Adipate at 38%, a 60-kg person would receive a dermal dose of 250 mg/kg day$^{-1}$. Given that Diethylhexyl Adipate is soluble in organic solvents, but not in water, dermal penetration of Diethyhexyl Adipate is likely to be less than 1%, yielding a maximum possible systemic dose of $<$2.5 mg/kg day$^{-1}$, well below the level demonstrated to have no fetotoxic effect.

## REFERENCES


Astill, B. D., R. Gingell, D. Guest, et al. 1996. Oncogenicity Testing of 2-Ethylhexanol in Fischer 344 Rats and B6C3F1 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.

Bowen, D. 1999. Unpublished information on hair spray particle size provided at the September 9, 1999 CIR Expert Panel meeting.[10]


[10]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.


British Indus. Bio Res Assn. 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 Mfg. Assn. 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.

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.* 12:265–268.

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.

Dalgaard, M., H. Ulla, A. M. Vinggaard, et al. 2003. Di(2-ethylhexyl) adipate (DEHA) induced deveopmental 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. Coll. 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. Membr.* 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. O'Brien. 1993. Industrial hygiene. In: *Aerosol measurement. Principles techniques and applications*, ed. K. Willeke, and P. A. Baron, New York: John Wiley and Sons. 538–540.

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. 1983. 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 Res Ctr. 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. Wilkd, 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.

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.

## FORMALDEHYDE

A safety assessment of Formaldehyde was published in 1984 (Elder 1984) with the conclusion that this ingredient is safe in cosmetic products to the great majority of consumers, however, because of skin sensitivity of some individuals to this agent, the formulation and manufacture of a cosmetic product should be such as to ensure use at the minimal effective concentration of formaldehyde, not to exceed 0.2% measured as free formaldehyde. Furthermore, it cannot be concluded that formaldehyde is safe in cosmetic products intended to be aerosolized. An extensive number of 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.

Data reported to the FDA by industry in 1981 indicated that Formaldehyde was used in a total of 805 cosmetic products, but that figure decreased to 120 reported uses in 2002. The maximum use concentration reported to FDA in 1981 was in the $\leq$0.1% to 10% range. Data from an industry use concentration survey in 2003 indicate a maximum use concentration of 0.08%.

Table 10 presents the recent and historical frequency of use and concentration of use data as a function of product category.

The discussion section in the original safety assessment acknowledged that Formaldehyde can be a skin irritant and sensitizer in clinical tests, and a developmental toxin, a genotoxin, and a neoplastic agent in experimental animal studies. The new clinical studies confirmed that Formaldehyde can be a skin irritant and sensitizer, but at levels higher than the 0.2% free Formaldehyde upper limit established by the CIR Expert Panel.

The developmental toxicity, genotoxicity, and carcinogenicity of high doses of Formaldehyde was also confirmed in the new studies. These studies demonstrate that there is a threshold effect; that is, high doses are required before any effect is seen. Again, the limit on the amount of free Formaldehyde established by the CIR Expert Panel precludes any risk as a result of use of cosmetic products containing Formaldehyde.

## REFERENCES

Adams, D. O., T. A. Hamilton, L. D. Lauer, and J. H. Dean. 1987. The effect of formaldehyde exposure upon the mononuclear phagocyte system of mice. *Toxicol. Appl. Pharmacol.* 88:165–174.

Adams, R. M., and H. I. Maibach. 1985. A five-year study of cosmetic reactions. *J. Am. Acad. Dermatol.* 13:1062–1069.

Andersen, K. E. 1986. Contact allergy to chlororesorcinol, formaldehyde and other biocides. Guinea pig tests and clinical studies. *Acta Dermatol. Venereol. Suppl.* 125:1–21.

**TABLE 10**
Historical and recent uses and use concentrations of Formaldehyde in cosmetic products

| Product category | 1981 uses (Elder 1984) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1984) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| **Baby care** | | | | |
| Shampoos | 7 | — | ≤ 0.1–1 | — |
| Lotions, oils, powders and creams | 1 | — | >0.1–1 | — |
| **Bath** | | | | |
| Soaps and detergents | 5 | 5 | ≤0.1–1 | <0.002–0.08 |
| Oils, tablets and salts | 10 | 6 | ≤0.1–1 | 0.08 |
| Bubble baths | 109 | 4 | ≤0.1–1 | 0.08 |
| Other bath | 24 | 1 | ≤0.1–5 | 0.08 |
| **Eye makeup** | | | | |
| Mascara | 1 | — | ≤0.1 | 0.0002 |
| Other eye makeup | 3 | — | ≤0.1–1 | — |
| **Fragrance** | | | | |
| Sachets | 2 | — | ≤0.1–1 | — |
| Other fragrance | — | — | — | 0.02 |
| **Noncoloring hair care** | | | | |
| Conditioners | 95 | 11 | ≤0.1–5 | — |
| Permanent waves | 11 | 2 | ≤0.1–1 | — |
| Rinses | 32 | 2 | ≤0.1–1 | — |
| Shampoos | 316 | 59 | ≤0.1–5 | <0.005–0.08 |
| Tonics, dressings, etc. | 21 | 9 | ≤0.1–10 | <0.005 |
| Wave sets | 37 | 8 | ≤0.1–10 | — |
| Other hair | 13 | 3 | ≤0.1–5 | — |
| **Hair coloring** | | | | |
| Dyes and colors | 5 | — | ≤0.1 | — |
| Shampoos | 3 | 2 | ≤0.1–1 | — |
| **Makeup** | | | | |
| Face powders | 1 | — | >0.1–1 | — |
| Foundations | 2 | — | ≤0.1–1 | — |
| Leg and body paints | — | — | — | 0.02 |
| Makeup bases | 3 | — | ≤0.1–1 | — |
| Other makeup | — | — | — | 0.01 |
| **Nail care** | | | | |
| Cuticle softeners | 1 | — | ≤0.1 | — |
| Nail creams and lotions | 1 | 1 | ≤0.1 | — |
| Other manicuring | — | 1 | — | 2* |
| **Oral hygiene** | | | | |
| Dentifrices | — | — | — | 0.04 |
| Mouthwashes and breath fresheners | 2 | — | ≤0.1–1 | — |
| **Personal hygiene** | | | | |
| Underarm deodorants | 7 | — | >0.1–1 | — |
| Feminine hygiene deodorants | 1 | — | >1–5 | — |
| Other personal cleanliness | 1 | 1 | ≤0.1 | 0.07–0.08 |
| **Shaving** | | | | |
| Aftershave lotions | 1 | — | >0.1–1 | — |
| Shaving creams | 2 | 1 | ≤0.1 | — |
| Other shaving | 1 | — | >1–5 | — |

*(Continued on next page)*

**TABLE 10**
Historical and recent uses and use concentrations of Formaldehyde in cosmetic products *(Continued)*

| Product category | 1981 uses (Elder 1984) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1984) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 13 | 1 | ≤0.1–1 | <0.0001–0.002 |
| Face and neck skin care | 47** | — | ≤0.1–1** | — |
| Body and hand skin care | | 2 | | <0.0001 |
| Foot powders and sprays | 1 | — | >0.1–1 | — |
| Moisturizers | 11 | 1 | ≤0.1–1 | — |
| Night skin care | 5 | — | ≤0.1–1 | — |
| Paste masks/mud packs | 3 | — | ≤0.1–1 | — |
| Skin fresheners | 1 | — | >0.1–1 | — |
| Other skin care | 4 | — | >0.1–1 | 0.06 |
| **Suntan** | | | | |
| Suntan gels, creams, and liquids | 2 | — | ≤0.1–1 | — |
| **Total uses/ranges for Formaldehyde** | **805** | **120** | **≤0.1–10** | **<0.0001–0.08** |

*This product was sold only in Europe and no longer marketed

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


Andersen, K. E., A. Boman, A. Volund, and J. E. Wahlberg. 1985. Induction of formaldehyde contact sensitivity: Dose response relationship in the guinea pig maximization test. *Acta. Dermatol. Venereol.* 65:472–478.

Appelman, L. M., R. A. Woutersen, A. Zwart, H. E. Falke, and V. J. Feron. 1988. One-year inhalation toxicity study of formaldehyde in male rats with a damaged or undamaged nasal mucosa. *J. Appl. Toxicol*. 8:85–90.

Baran, R. 2002. Nail Cosmetics. Allergies and Irritations. *Am. J. Clin. Dermatol.* 3:547-555.

Bartnik, F. G., C. Gloxhuber, and V. Zimmerman. 1985. Percutaneous absorption of formaldehyde in rats. *Toxicol. Lett*. 25:167–172.

Beall, J. R., and A. G. Ulsamer. 1984. Formaldehyde and hepatotoxicity: A review.*J. Toxicol. Environ. Health* 13:1–21.

Bender, J. 2002. The use of noncancer endpoints as a basis for establishing a reference concentration for formaldehyde. *Reg. Toxicol. Pharmacol.* 35:23–31.

Bender, J. R., L. S. Mullin, G. J. Graepel, and W. E. Wilson. 1983. Eye irritation response of humans to formaldehyde. *Am. Ind. Hyg. Assoc. J*. 44:463–465.

Bergh, M., and A. T. Karlberg. 1999. Sensitizing potential of acetaldehyde and formaldehyde using a modified cumulative contact enhancement test (CCET). *Contact Dermatitis* 40:139–145.

Berne, B., A. Bostrum, A. F. Grahnen, and M. Tammela. 1996. Adverse effects of cosmetics and toiletries reported to the Swedish Medical Products Agency 1989-1994. *Contact Dermatitis* 34:359–362.

Bernstein, R. S., L. T. Stayner, L. J. Elliott, R. Kimbrough, H. Falk, and L. Blade. 1984. Inhalation exposure to formaldehyde: An overview of its toxicology, epidemiology, monitoring, and control. *Am. Ind. Hyg. Assoc. J*. 45:778–785.

Bhalla, D. K., V. Mahavni, T. Nguyen, and T. McClure. 1991. Effects of acute exposure to formaldehyde on surface morphology of nasal epithelia in rats. *J. Toxicol. Environ. Health* 33:171–188.

Biagini, R. E., W. J. Moorman, E. A. Knecht, J. C. Clark, and I. L. Bernstein. 1989. Acute airway narrowing in monkeys from challenge with 2.5 ppm formaldehyde generated from formalin. *Arch. Environ. Health* 44:12–17.

Burgaz, S., G. Cakmak, O. Erdem, M. Yilmaz, and A. E. Karakaya. 2001. Micronuclei frequencies in exfoliated nasal mucosa cells from pathology and anatomy laboratory workers exposed to formaldehyde. *Neoplasma* 48:144–147.

Casanova, M., H. D. Heck, J. I. Everitt, W. W. Harrington, Jr., and J. A. Popp. 1988. Formaldehyde concentrations in the blood of rhesus monkeys after inhalation exposure. *Food Chem. Toxicol*. 26:715–716.

Charpin, D., H. Dutau, and S. Falzon. 2000. Hypersensitivity to formaldehyde. *Allergy* 55:986–987.

Chia, S. E., C. N. Ong, S. C. Foo, and H. P. Lee. 1992. Medical students exposure to formaldehyde in a gross anatomy dissection laboratory. *J. Am. Coll. Health* 41:115–119.

Collins, J. J., N. A. Esmen, and T. A. Hall. 2001a. A review and meta-analysis of formaldehyde exposure and pancreatic cancer. *Am. J. Ind. Med*. 39:336–345.

Collins, J. J., R. Ness, R. W. Tyl, N. Krivanek, N. A. Esmen, and T. A. Hall. 2001b. A review of adverse pregnancy outcomes and formaldehyde exposure in human and animal studies. *Regul. Toxicol. Pharmacol.* 34:17–34.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2003. Formaldehyde concentrations of use, updated May 8, 2003. Unpublished data submitted by CTFA.[11]

Dallas, C. E., P. Badeaux, J. C. Theiss, and E. J. Fairchild. 1989. The influence of inhaled formaldehyde on rat lung cytochrome P450. *Environ. Res*. 49:50–59.

Dallas, C. E., M. J. Scott, J. B. Ward, Jr., and J. C., Theiss. 1992. Cytogenetic analysis of pulmonary lavage and bone marrow cells of rats after repeated formaldehyde inhalation. *J. Appl. Toxicol*. 12:199–203.

Dallas, C. E., J. C. Theiss, R. B. Harrist, and E. J. Fairchild. 1986. Respiratory responses in the lower respiratory tract of Sprague-Dawley rats to formaldehyde inhalation. *J. Environ. Pathol. Toxicol. Oncol.* 6:1–12.

Dearman, R. J., D. A. Basketter, P. Evans, and I. Kimber. 1999. Comparison of cytokine secretion profiles provoked in mice by glutaraldehyde and formaldehyde. *Clin. Exp. Allergy* 29:124–132.

De Flora, S., A. Camoirano, P. Zanacchi, and C. Bennicelli. 1984. Mutagenicity testing with TA97 and TA102 of 30 DNA-damaging compounds, negative with other Salmonella strains. *Mutat. Res*. 134:159–165.

de Groot, A. C., E. G. Beverdam, C. T. Ayong, P. J. Coenraads, and J. P. Nater. 1988a. The role of contact allergy in the spectrum of adverse effects caused by cosmetics and toiletries. *Contact Dermatitis* 19:195–201.


[11] Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

de Groot, A. C., D. P. Bruynzeel, J. D. Bos, H. L. van der Meeren, T. van Joost, B. A. Jagtman, and J. W. Weyland. 1988b. The allergens in cosmetics. *Arch. Dermatol* 124:1525–1529.

de Groot, A. C., and F. Gerkens. 1989. Contact urticaria from a chemical textile finish. *Contact Dermatitis* 20:63–64.

Dillon, D., R. Combes, and E. Zeiger. 1998. The effectiveness of Salmonella strains TA100, TA102, and TA104 for detecting mutagenicity of some aldehydes and peroxides. *Mutagenesis* 13:19–26.

Dossou, K. G., C. Sicard, G. Kalopissis, D. Reymond, and H. Schaefer. 1985. Method for assessment of experimental allergy in guinea pigs adapted to cosmetic ingredients. *Contact Dermatitis* 13:226–234.

Elder R. L., ed. 1984. Final report on the safety assessment of Formaldehyde.*J. Am. Coll. Toxicol.* 3:157–184.

European Commission (EC). 1976. Annex VI of the Cosmetic Directive 76.768/EC. *Off. J. European Communities* No. L1 67/1.

EC. 2002. Opinion concerning the determination of certain Formaldehyde releasers in cosmetic products. The Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers. http://europa.eu.int/comm/food/fs/sc/sccp/out188_en.pdf.

Environmental Protection Agency (EPA). 2002a. Sources of Indoor Air Pollution—Formaldehyde. http://www.epa.gov/iaq/formalde.html.

EPA. 2003b. IRIS entry for Formaldehyde, http://www.epa.gov/iris/subst/0419.htm.

Food and Drug Administration (FDA). 1981. Formaldehyde frequencies and concentrations of use.*FDA database*. Washington, DC: FDA.

FDA. 1996. CVM Update. April 9, 1996. FDA approves food additive petition for formaldehyde. http://fda.gov/cvm/index/updates/forma.html.

FDA. 2002. Formaldehyde frequencies of use. *FDA database*. Washington, DC: FDA.

Feron, V. J., J. H. Arts, C. F. Kuper, P. J. Slootweg, and R. A. Woutersen. 2001. Health Risks Associated with Inhaled Nasal Toxicants. *Crit. Rev. Toxicol.* 31:313–347.

Feron, V. J., H. P. Til, F. de Vrijer, R. A. Woutersen, F. R. Cassee, and P. J. van Bladeren. 1991. Aldehydes: Occurrence, carcinogenic potential, mechanism of action and risk assessment. *Mutat. Res*. 259:363–385.

Feron, V. J., H. P. Til, and R. A. Woutersen. 1990. Letter to the editor. *Toxicol. Indust. Health* 6:637–638.

Fowler, J. F., Jr., S. M. Skinner, and D. V. Belsito. 1992. Allergic contact dermatitis from formaldehyde resins in permanent press clothing: An underdiagnosed cause of generalized dermatitis. *J. Am. Acad. Dermatol*. 27:962–968.

Frenzelli, G., E. Bosco, and R. Barale. 2000. Validation of single cell gel assay in human leukocytes with 18 reference compounds. *Mutat. Res*. 468:93–108.

Gerin, M., J. Siemiatycki, L. Nadon, R. Dewar, and D. Krewski. 1989. Cancer risks due to occupational exposure to formaldehyde: Results of a multi-site case-control study in Montreal. *Int. J. Cancer* 44:53–58.

Gorski, P., and A. Krakowiak. 1991. Formaldehyde-induced bronchial asthma — does it really exist? *Polish J. Occup. Med. Environ. Health* 4:317–320.

Grafstrom, R. C., R. D. Curren, L. L. Yang, and C. C. Harris. 1985. Genotoxicity of formaldehyde in cultured human bronchial fibroblasts. *Science* 228:89–91.

Grafstrom, R. C., I. C. Hsu, and C. C. Harris. 1993. Mutagenicity of formaldehyde in Chinese hamster lung fibroblasts: Synergy with ionizing radiation and *N*-nitroso-*N*-methylurea. *Chem.-Biol. Interact*. 86:41–49.

Green, D. J., R. Bascom, E. M. Healey, J. R. Hebel, L. R. Sauder, and T. J. Kulle. 1989. Acute pulmonary response in healthy, nonsmoking adults to inhalation of formaldehyde and carbon. *J. Toxicol. Environ. Health*. 28:261–275.

Green, D. J., L. R. Sauder, T. J. Kulle, and R. Bascom. 1987. Acute response to 3.0 ppm formaldehyde in exercising healthy nonsmokers and asthmatics. *Am. Rev. Respir. Dis*. 135:1261–1266.

Guy, E. R., and F. V. Abbott. 1992. The behavioral response to formalin in preweanling rats. *Pain* 51:81–90.

Haikel, Y., J. J. Braun, H. Zana, A. Boukari, F. de Blay, and G. Pauli. 2000. Anaphylactic shock during endodontic treatment due to allergy to formaldehyde in a root canal sealant. *J. Endodon*. 26:529–531.

Hamaguchi, F., and T. Tsutsui. 2000. Assessment of genotoxicity of dental antiseptics: Ability of phenol, guaiacol, *p*-phenolsulfonic acid, sodium hypochlorite, *p*-chlorophenol, *m*-cresol or formaldehyde to induce unscheduled DNA synthesis in cultured Syrian hamster embryo cells. *Jpn. J. Pharmacol*. 83:273–276.

Hayasaka, Y., S. Hayasaka, and Y. Nagaki. 2001. Ocular changes after intravitreal injecton of methanol, formaldehyde, or formate in rabbits. *Pharmacol. Toxicol*. 89:74–78.

Heck, H., and M. Casanova. 1999. Pharmacodynamics of formaldehyde: Applications of a model for the arrest of DNA replication by DNA-Protein cross-links. *Toxicol. Appl. Pharmacol*. 160:86–100.

Higginson, J., O. M. Jensen, L. Kinlen, W. H. Kirsten, B. MacMahon, G. M. Matanoski, T. J. Smith, and D. C. Thomas. 1988. Epidemiology of chronic occupational exposure to formaldehyde: Report of the ad hoc panel on health effects of formaldehyde. *Toxicol. Ind. Health* 4:77–90.

Holcátová, I., and V. Bencko. 1997. Health aspects of formaldehyde in the indoor environment. Czech and Slovak experience. *Cent. Eur. J. Pub. Health.* 5:38–42.

Holness, D. L., and J. R. Nethercott. 1989. Health status of funeral service workers exposed to formaledhyde. *Arch. Environ. Health.* 44:222–228.

Holness, D. L., and J. R. Nethercott. 1990. Dermatitis in hairdressers. *Dermatol. Clin.* 8:119–126.

Hooper, K., and L. S. Gold. 1986. Ranking the carcinogenic hazards of occupational exposures: Exposure-potency index (EPI) values for nine volatile chemicals. *Prog. Clin. Biol. Res*. 207:217–228.

Kamata, E., M. Nakadate, O. Uchida, Y. Ogawa, S. Susuki, T. Kaneko, M. Saito, and Y. Kurokawa. 1997. Results of a 28-month chronic inhalation toxicity study of formaldehyde in male Fisher-344 rats. *J. Toxicol. Sci*. 22:239–254.

Kerns, W. D., K. L. Pavkov, D. J. Donofrio, E. J. Gralla, and J. A. Swenberg. 1983. Carcinogenicity of formaldehyde in rats and mice after long-term inhalation exposure. *Cancer Res.* 43:4382–4392.

Kieć-Świerczyńska, M., B. Kręcisz, B. Krysiak, E. Kuchowicz, and K. Rydzyński. 1998. Occupational allergy to aldehydes in health care workers. Clinical observations. Experiments. *Int. J. Occup. Med. Environ. Health.* 11:349–358.

Kilburn, K. H., R. Warshaw, C.T. Boylen, S.J. Johnson, B. Seidman, R. Sinclair, and T. Takaro, Jr. 1985. Pulmonary and neourobehavioral effects of formaldehyde exposure. *Arch. Environ. Health*. 40:254–260.

Kim, C. W., J. S. Song, Y. S. Ahn, S. H. Park, J. W. Park, J. H. Noh, and C. S. Hong. 2001. Occupational asthma due to formaldehyde. *Yonsei Med. J.* 42:440–445.

Kimbell, J. S., R.P. Subramaniam, E.A. Gross, P.M. Schlosser, and K.T. Morgan. 2001. Dosimetry modeling of inhaled formaldehyde: Comparisons of local flux predictions in the rat, monkey, and human nasal passages. *Toxicol. Sci.* 64:100–110.

Krakowiak, A., P. Gorski, K. Pazdrak, and U. Ruta. 1998. Airway response to formaldehyde inhalation in asthmatic subjects with suspected respiratory formaldehyde sensitization. *Am. J. Indust. Med*. 33:274–281.

Lachapelle, J. M., D. Tennstedt, A. Fyad, M. L. Masmoudi, and H. Nouaigui. 1988. Ring-shaped positive allergic patch test reactions to allergens in liquid vehicles. *Contact Dermatitis* 18:234–236.

Le Curieux, F., D. Marzin, and F. Erb. 1993. Comparison of three short-term assays: Results on seven chemicals. Potential contribution to the control of water genotoxicity. *Mutat. Res*. 319:223–236.

Liebling, T., K. D. Rosenman, H. Pastides, R. G. Griffith, and S. Lemeshow. 1984. Cancer mortality among workers exposed to formaldehyde. *Am. J. Ind. Med*. 5:423–428.

Liu, X. J., T. D. White, and J. Sawynok. 2001. Involvement of primary sensory afferents, postganglionic sympathetic nerves and mast cells in the formalin-evoked peripheral release of adenosine. *Eur. J. Pharmacol*. 429:147–155.

Lodén, M. 1986. The in vitro permeability of human skin to benzene, ethylene glycol, formaldehyde, and n-hexane. *Acta Pharmacol. Toxicol*. 58:382–389.

Majumder, P. K., and V. L. Kumar. 1995. Inhibitory effects of formaldehyde on the reproductive system of male rats. *Indian J. Physiol. Pharmacol*. 39:80–82.

Martin, W. J. 1990. A teratology study of inhaled formaldehyde in the rat. *Reprod. Toxicol*. 4:237–239.

Massone, L., A. Anonide, S. Borghi, and V. Isola. 1989. 4-Day patch test reactions to neomycin and formaldehyde. *Contact Dermatitis* 21:344–345.

Maurer, J. K., A. Molai, R. D. Parker, L. I. Li, G. J. Carr, W. M. Petroll, H. D. Cavanagh, and J. V. Jester. 2001. Pathology of ocular irritation with acetone, cyclohexanol, parafluoroaniline, and formaldehyde in the rabbit low-volume eye test. *Toxicol. Pathol*. 29:187–199.

Minamoto, K., M. Nagano, T. Inaoka, and M. Futatsuka. 2002. Occupational dermatoses among fiberglass-reinforced plastics factory workers. *Contact Dermatitis* 46:339–347.

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.

Monticello, T. M., J. A. Swenberg, E. A. Gross, J. R. Leininger, J. S. Kimball, S. Seilkop, T. B. Starr, J. E. Gibson, and K. T. Morgan. 1996. Correlation of regional and nonlinear formaldehyde-induced nasal cancer with proliferating populations of cells. *Cancer Res*. 56:1012–1022.

Morgan, K. T., E. A. Gross, and D. L. Patterson. 1986. Distribution, progression, and recovery of acute formaldehyde-induced inhibition of nasal mucociliary function in F-344 rats. *Toxicol. Appl. Pharmacol*. 86:448–456.

Muller, W., G. Englehart, B. Herbold, R. Jackh, and R. Jung. 1993. Evaluation of mutagenicity testing with *Salmonella typhimurium* TA102 in three different laboratories. *Env. Health Perspect. Suppl.* 3:33–36.

Norton, L. A. 1991. Common and uncommon reactions to formaldehyde-containing nail hardeners. *Seminars in Dermatol*. 10:29–33.

Odeigah, P. G. C. 1997. Sperm head abnormalities and dominant lethal effects of formaldehyde in albino rats. *Mutat. Res*. 389:141–148.

Omote, K., T. Kawamata, M. Kawamata, and A. Namiki. 1998. Formalin-induced release of excitatory amino acids in the skin of the rat hindpaw. *Brain Res*. 787:161–164.

Overman, D. O. 1985. Absence of embryotoxic effects of formaldehyde after percutaneous exposure in hamsters. *Toxicol. Lett*. 24:107–110.

Paustenbach, D., Y Alarie, T. Kulle, N. Schachter, R. Smith, J. Swenberg, H. Witschi, and S.B. Horowitz. 1997. A recommended occupational exposure limit based on irritation. *J. Toxicol. Environ. Health* 21:217–263.

Pazdrak, K., P. Gorski, A. Krakowiak, and U. Ruta. 1993. Changes in nasal lavage fluid due to formaldehyde inhalation. *Int. Arch. Occup. Environ. Health*. 64:515–519.

Pitten, F.-A., A. Kramer, K. Herrmann, J. Bremer, and S. Koch. 2000. Formaldehyde neurotoxicity in animal experiments. *Pathol. Res. Pract*. 196:193–198.

Purchase, I. F., and G. M. Paddle. 1989. Does formaldehyde cause nasopharyngeal cancer in man? *Cancer Lett*. 46:79–85.

Rastogi, S. C. 1992. A survey of formaldehyde in shampoos and skin creams on the Danish market. *Contact Dermatitis* 27:235–240.

Rastogi, S. C. 2000. Analytical control of preservative labelling on skin creams. *Contact Dermatitis* 43:339–343.

Restani, P., and C. L. Galli. 1991. Oral toxicity of formaldehyde and its derivatives. *Crit. Rev. Toxicol*. 21:315–328.

Riedel, F., E. Hasenauer, P. J. Barth, A. Koziorowski, and C. H. Rieger. 1996. Formaldehyde exposure enhances inhalative allergic sensitization in the guinea pig. *Allergy*. 51:94–99.

Ritchie, I. M., and R. G. Lehnen. 1987. Formaldehyde-related health complaints of residents living in mobile and conventional homes. *Am. J. Public Health* 77:323–328.

Rudzki, E., P. Rebandel, and Z. Grzywa. 1989. Patch tests with occupational contactants in nurses, doctors, and dentists. *Contact Dermatitis* 20:247–250.

Rusch, G. M., J. J. Clary, W. E. Rinehart, and H. F. Bolte. 1983. A 26-week inhalation toxicity study with formaldehyde in the monkey, rat, and hamster. *Toxicol. Appl. Pharmacol*. 68:329–343.

Saillenfait, A.M., P. Bonnet, and J. de Ceaurriz. 1989. The effects of maternally inhaled formaldehyde on embryonal and foetal development in rats. *Food Chem. Toxicol*. 27:545–548.

Sauder, L. R., D. J. Green, M. D. Chatham, and T. J. Kulle. 1987. Acute pulmonary response of asthmatics to 3.0 ppm formaldehyde. *Toxicol. Indust. Health* 3:569–578.

Schachter, E. N., T. J. Wick, Jr., D. J. Brody, T. Tosun, G. J. Beck, and B. P. Leaderer. 1987. A study of respiratory effects from exposure to 2.0 ppm formaldehyde in occupationally exposed workers. *Environ. Res*. 44:188–205.

Schmid, E., W. Gogglemann, and M. Bauchinger. 1986. Formaldehyde-induced cytotoxic, genotoxic and mutagenic response in human lymphocytes and *Salmonella typhimurium*. *Mutagenesis.* 1:427–431.

Schnuch, A., W. Uter, J Geier, P.J. Frosch, and T. Rustemeyer. 1998. Contact allergies in healthcare workers. Results from the IVDK. *Acta Dermatol. Venereol.* 78:358–363.

Shaham, J., Y. Bomstein, A. Melzer, and J. Ribak. 1997. DNA-protein crosslinks and sister chromatid exchanges as biomarkers of exposure to formaldehyde. *Int. J. Occup. Environ. Health* 3:95–104.

Sheppard, D., W. L. Eshenbacher, and J. Epstein. 1984. Lack of a bronchomotor response to up to 3 ppm formaldehyde in subjects with asthma. *Environ. Res.* 35:133–139.

Snyder, R. D., and B. Van Houten. 1986. Genotoxicity of formaldehyde and an evaluation of its effects on the DNA repair process in human diploid fibroblasts. *Mutat. Res*. 165:21–30.

Soffritti, M., F. Belpoggi, L. Lambertini, M. Lauriola, M. Padovani, and C. Maltoni. 2002. Results of long-term experimental studies on the carcinogenicity of formaldehyde and acetaldehyde in rats. *Ann. N.Y. Acad. Sci*. 982:87–105.

Soffritti, M., C. Maltoni, F. Maffei, and R. Biagi. 1989. Formaldehyde: An experimental multipotential carcinogen. *Toxicol. Indust. Health* 5:699–730.

Solomons, K., and J. W. Cochrane. 1984. Formaldehyde toxicity. Part II. Review of acute and chronic effects on health. *S. Afr. Med. J.* 66:103-106.

Szabad, J., I. Soos, G. Polgar, and G. Hejja. 1983. Testing the mutagenicity of malondialdehyde and formaldehyde by the *Drosophila* mosaic and the sex-linked recessive lethal tests. *Mutat. Res*. 113:117–133.

Tas, E., M. Pletscher, and A.J. Bircher. IgE-mediated urticaria from formaldehyde in a dental root canal compound. *J. Invest. Allergol. Clin. Immunol*. 12:130–133.

Temcharoen, P., and W. G. Thilly. 1983. Toxic and mutagenic effects of formaldehyde in *Salmonella typhimurium*. *Mutat. Res*. 119:89–93.

Thrasher, J. D., and K. H. Kilburn. 2001. Embryo toxicity and teratogenicity of formaldehyde. *Arch. Environ. Health* 56:300–311.

Til, H. P., R. A. Woutersen, V. J. Feron, V. H. Hollanders, H. E. Falke, and J. J. Clary. 1989. Two-year drinking water study of formaldehyde in rats. *Food Chem. Toxicol*. 27:77–87.

Tobe, M., K. Naito, and Y. Kurokawa. 1989. Chronic toxicity study on formaldehyde administered orally to rats. *Toxicology* 56:79–86.

Uba, G., D. Pachorek, J. Bernstein, D.H. Garabrant, J.R. Balmes, W.E. Wright, and R.B. Amar. 1989. Prospective study of respiratory effects of formaldehyde among healthy and asthmatic medical students. *Am. J. Ind. Med*. 15:91–101.

Ushio, H., K. Nohara, and H. Fujimaki. 1999. Effect of environmental pollutants on the production of pro-inflammatory cytokines by normal human dermal keratinocytes. *Toxicol. Lett*. 105:17–24.

Wang, H., A.V. Del Grosso, and J.C. May. 2003. Development of an HPLC method for the determination of formaldehyde in human vaccines. http://cfsan.fda.gov/~frf/forum03/D-09.HTM.

Wieslander, G., D. Norback, E. Bjornsson, C. Janson, and G. Boman. 1997. Asthma and the indoor environment: The significance of emission of formaldehyde and volatile organic compounds from newly painted indoor surfaces. *Int. Arch. Occup. Environ. Health* 69:115–124.

Wilmer, J. W., R. A. Woutersen, L. M. Appelman, W. R. Leeman, and V. J. Feron. 1987. Subacute (4-week) inhalation toxicity study of formaldehyde in

male rats: 8-hour intermittent *Versus* 8-hour continuous exposures. *J. Appl. Toxicol*. 7:15–16.

Wilmer, J. W., R. A. Woutersen, L. M. Appelman, W. R. Leeman, and V. J. Feron. 1989. Subchronic (13-week) inhalation toxicity study of formaldehyde in male rats: 8-Hour intermittent versus 8-hour continuous exposures. *Toxicol. Lett*. 47:287–293.

Witek, T. J., Jr., E. N. Schachter, T. Tosun, G. J. Beck, and B. P. Leaderer. 1987. An evaluation of respiratory effects following exposure to 2.0 ppm formaldehyde in asthmatics: lung function, symptoms, and airway reactivity. *Arch. Environ. Health* 42:230–237.

Wolf, D. C., E. A. Gross, O. Lyght, E. Bermudez, L. Recio, and K. T. Morgan. 1995. Immunohistochemical localization of p53, PCNA, and TGF-$\alpha$ proteins in formaldehyde-induced rat nasal squamous cell carcinomas. *Toxicol. Appl. Pharmacol*. 132:27–35.

Woodruff, R. C., J. M. Mason, R. Valencia, and S. Zimmering. 1985. Chemical mutagenesis testing in *Drosophila*. V. Results of 53 coded compounds tested for the National Toxicology Program. *Environ. Mutagen*. 7:677–702.

Woutersen, R. A., L. M. Appelman, J. W. Wilmer, H. E. Falke, and V. J. Feron. 1987. Subchronic (13-week) inhalation toxicity study of formaldehyde in rats. *J. Appl. Toxicol*. 7:43–49.

Woutersen, R. A., A. van Garderen-Hoetmer, J. P. Bruijntjes, A. Zwart, and V. J. Feron. 1989. Nasal tumours in rats after severe injury to the nasal mucosa and prolonged exposure to 10 ppm formaldehyde. *J. Appl. Toxicol*. 9:39–46.

Xu, B., K. Aoyama, M. Takeuchi, T. Matsushita, and T. Takeuchi. 2002. Expression of cytokine mRNAs in mice cutaneously exposed to formaldehyde. *Immunol. Lett*. 84:49–55.

Yang, X., Y. P. Zhang, D. Chen, W. G. Chen, and R. Wang. 2001. Eye irritation caused by formaldehyde as an indoor air pollution—a controlled human exposure experiment. *Biomed. Environ. Sci.* 14:229–236.

Zimmerman, F. K., and A. Mohr. 1992. Formaldehyde, glyoxal, urethane, methyl carbamate, 2,3-butanedione, 2,3-hexanedione, ethyl acrylate, dibromoacetonitrile, and 2-hydroxypropionitrile induce chromosome loss in *Saccharomyces cerevisiae*. *Mutat. Res*. 270:151–166.

## HYDROLYZED COLLAGEN

A safety assessment of Hydrolyzed Collagen concluded that this ingredient is safe as a cosmetic ingredient in the present practices of use and concentration (Elder 1985). New studies, along with the updated information regarding types and concentrations of use, were considered by the CIR Expert Panel. The Panel determined not to reopen this safety assessment.

Data reported to the FDA by industry in 1981 indicated that Hydrolyzed Collagen was used in 936 cosmetic products at concentrations ranging from $\leq$0.1% to >50% (Elder 1985). Uses reported to FDA in 2002 (Hydrolyzed Animal Protein and Hydrolyzed Animal Collagen were listed in this FDA database) decreased to 569 (FDA 2002) and an industry survey of use concentrations yielded a maximum use concentration of 1% (CTFA 2004).

Table 11 presents the historical and recent uses and concentrations of Hydrolyzed Collagen in cosmetic products. The most recent data now constitute the present practices of use and concentration.

The CIR Expert Panel did note that the description of Hydrolyzed Collagen has been expanded recently to include specific mention of animal and fish collagen as the source material (Hydrolyzed Collagen is the hydrosylate of animal or fish collagen derived by acid, enzyme, or other method of hydrolysis) (Gottschalck and McEwen 2004).

The CIR Expert Panel is aware of the concerns about infectious prions in products obtained from mammalian tissues. As with all animal-derived ingredients, the use of Hydrolyzed Collagen should comply with FDA regulations to ensure that this ingredient is free of infectious agents, including bovine spongiform encephalopathy.

### REFERENCES

Challoner, N. I., S. P. Chahal, and R. T. Jones. 1997. Cosmetic proteins for skin care. *Cosmet. Toiletries* 112:51–63.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2004. Concentration of use—hydrolyzed collagen. Unpublished data submitted by CTFA on May 11, 2004. (2 pages.)[12]

Elder, R. L. 1985. Final Report on the safety assessment of hydrolyzed collagen. *J. Am. Coll. Toxicol*. 4:199–221.

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

Gottschalck, T. E., and G. N. McEwen, Jr., eds. 2004. *International Cosmetic Ingredient Dictionary and Handbook*, 10th ed., DC: Washington CTFA.

Niinimäki, A., M. Niinimäki, S. Mäkinen-Kiljunen, and M. Hannuksela. 1998. Contact urticaria from protein hydrosylates in hair conditioners. *Allergy* 53:1078–1082.

Pearson, A., E. G. Salole, and J. Currie. 1986. Utilizing collagen in drug formulation. *Manuf. Chem*. 57:64–65, 67.

## ISOSTEARYL NEOPENTANOATE

A safety assessment of Isostearyl Neopentanoate concluded that this ingredient is safe as a cosmetic ingredient in the present practices of use and concentration (Elder 1985). One new study, along with the updated information regarding types and concentrations of use, were considered by the CIR Expert Panel. The Panel determined not to reopen this safety assessment.

Data reported to the FDA by industry in 1981 indicated that Isostearyl Neopentanoate was used in 208 cosmetic products at concentrations >1% to 50% (Elder 1985). Uses reported to FDA in 2002 decreased to 71 (FDA 2002) and an industry survey of use concentrations yielded a use concentration range from 0.2% to 14% (CTFA 2003).

Table 12 presents the historical and recent uses of Hydrolyzed Collagen in cosmetic products. The most current data are now considered the present practices of use.

The CIR Expert Panel did note a new use in lipsticks at concentrations of use of 9% to 14%. Oral toxicity studies in the original report suggest no concerns relating to this new use.

### REFERENCES

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2003. Use concentration data on Isostearyl Neopentanoate from industry survey. Unpublished data submitted by CTFA, July, 2003. (1 page.)[13]

Elder, R. L. ed. 1985. Final Report on the Safety Assessment of Isostearyl Neopentanoate. *J. Am. Coll. Toxicol.* 4:1–22.

[12]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

[13]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

**TABLE 11**
Historical and recent uses and use concentrations of Hydrolyzed Collagen in cosmetic products

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2004 concentrations (CTFA 2004) % |
|---|---|---|---|---|
| **Baby care** | | | | |
| Shampoos | 1 | — | ≤0.1 | — |
| **Bath** | | | | |
| Oils, tablets and salts | 2 | — | >1–5 | — |
| Bubble baths | 2 | 2[a] | >0.1–1 | — |
| Soaps and detergents | 3 | 13[a] | >0.1–5 | 0.1 |
| Other bath | 2 | 2[a] | >0.1–1 | — |
| **Eye makeup** | | | | |
| Eyebrow pencils | — | 1[a], 1 | — | — |
| Eyeliners | 1 | 1[a] | ≤0.1 | 1 |
| Eye shadow | 6 | 7[a] | ≤1 | — |
| Eye lotion | — | — | — | 3 |
| Eye makeup remover | — | 1[a] | — | — |
| Mascara | 28 | 9[a] | ≤1 | 0.02–1 |
| Other eye makeup | 5 | 1[a] | ≤5 | 0.000004 |
| **Noncoloring hair** | | | | |
| Hair conditioners | 174 | 126[a] | >50 | — |
| Hair sprays/aerosol fixatives | 7 | 3[a] | ≤1 | — |
| Hair Straighteners | 7 | 7[a] | >0.1–1 | — |
| Permanent waves | 70 | 13[a] | ≤25 | 0.05 |
| Rinses | 34 | 7[a] | ≤10 | — |
| Shampoos | 224 | 116[a] | ≤10 | 0.02 |
| Hair tonics, dressings, etc. | 35 | 40[a] | >50 | — |
| Wave sets | 39 | 4[a] | ≤25 | — |
| Other noncoloring hair | 18 | 15[a] | ≤10 | 0.03–0.2 |
| **Hair coloring** | | | | |
| Tints | 14 | 2[a] | ≤5 | — |
| Rinses | 24 | — | ≤0.1 | — |
| Shampoos | — | 2[a] | — | — |
| Bleaches | 7 | — | ≤5 | — |
| Other hair coloring | 1 | — | >0.1–1 | — |
| **Makeup** | | | | |
| Blushers | 5 | 2[a] | >0.1–1 | 0.5 |
| Face powders | 5 | 4[a] | ≤1 | 0.5 |
| Foundations | 10 | 7[a] | ≤1 | 0.5–4 |
| Lipsticks | 15 | 7[a] | ≤1 | 1 |
| Makeup bases | 15 | 4[a] | ≤1 | — |
| Other makeup | — | — | — | 0.2 |
| **Nail care** | | | | |
| Basecoats | — | 1[a] | — | — |
| Cuticle softeners | 3 | 2[a] | ≤1 | — |
| Creams and lotions | 6 | 5[a] | ≤50 | — |
| Polishes and enamels | 1 | — | >1–5 | — |
| Polish and enamel removers | 2 | — | ≤0.1 | — |
| Other nail care | 6 | 1[a] | ≤5 | — |
| **Personal hygiene** | | | | |
| Other personal hygiene | — | 4[a] | — | — |

**TABLE 11**
Historical and recent uses and use concentrations of Hydrolyzed Collagen in cosmetic products *(Continued)*

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2004 concentrations (CTFA 2004) % |
|---|---|---|---|---|
| **Shaving** | | | | |
| Aftershave lotions | 3 | 1[a] | >0.1–1 | 0.007 |
| Other shaving | — | 1[a] | — | 0.007 |
| **Skin Care** | | | | |
| Cleansing creams, lotions, etc. | 27 | 17[a] | ≤5 | — |
| Face and neck skin care | 46[c] | 18[a] | ≤10[c] | 0.06–6 |
| Body and hand skin care | | 20[a] | | 1 |
| Moisturizers | 43 | 36[a] | ≤25 | 1 |
| Night skin care | 11 | 15[a] | >0.1–25 | 0.02 |
| Paste masks/mud packs | 6 | 8[a] | ≤5 | 0.008 |
| Skin fresheners | 7 | 8[a] | ≤5 | — |
| Wrinkle smoothers[d] | 1 | —[d] | >1–5 | —[d] |
| Other skin care preparations | 7 | 27[a] | ≤0.1–5 | 0.5 |
| **Suntan Preparations** | | | | |
| Suntan gels, creams and liquids | — | 7[a] | — | 0.000004 |
| Other suntan preparations | — | 2[a] | — | 0.05 |
| **Total uses/ranges for Hydrolyzed Collagen** | **923** | **569[a], 1[b]** | **≤0.1− >50** | **.000004–6** |

[a]Ingredient identified as "Hydrolyzed Animal Protein" in the FDA database.
[b]Ingredient identified as "Hydrolyzed Animal Collagen" in the FDA database.
[c]This category was combined when the original safety assessment was performed and is now two separate categories.
[d]No longer a cosmetic product category.

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

Fulton, J. E., S. R. Pay, and J. E. Fulton. 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*, 8th ed., vol. 1. Washington, DC: CTFA.

## 2-NITRO-*p*-PHENYLENEDIAMINE AND 4-NITRO-*o*-PHENYLENEDIAMINE

A safety assessment of 2-Nitro-*p*-Phenylenediamine and 4-Nitro-*o*-Phenylenediamine was published in 1985 with the conclusion "for those persons not sensitized, the Expert Panel concludes that 2-Nitro-*p*-Phenylenediamine and 4-Nitro-*o*-Phenylenediamine are safe as hair dye ingredients at the current concentration of use" (Elder 1985). Studies available since that safety assessment was completed, along with updated information regarding uses and use concentrations, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

**2-Nitro-*p*-Phenylenediamine** was reported to be used in 28 hair dyes and colors in 1981 at concentrations from ≤0.1% to 1% (Elder 1985). In 2002, voluntary reports provided by industry to FDA indicated that 2-Nitro-*p*-Phenylenediamine was used in 113 hair dyes and colors (FDA 2002). Use concentration data from a survey of industry practices by the Cosmetic, Toiletry, and Fragrance Association (CTFA) indicated use at concentrations from 0.1% to 1% in cosmetic products (CTFA 2003).

**4-Nitro-*o*-Phenylenediamine** was reported to be used in 26 hair dyes and colors in 1981, at concentrations of ≤ 0.1% to 1% (Elder 1985). Industry reports to FDA in 2002 included 22 uses as hair dyes and colors. Use concentration data from an industry survey in 2003 indicated use at concentrations of 0.1% to 0.2% (CTFA 2003).

The available use and concentration as a function of product type is given in Table 13. The most recent information now constitutes the current practices of use and concentration.

In 2003, an updated review of the available hair dye epidemiology literature was prepared (Helzlsouer et al. 2003). The authors found insufficient evidence to support a causal association between personal hair dye use and a variety of tumors and cancers. The review highlighted well-designed studies with an exposure assessment that included hair dye type, color, and frequency or duration of use, which found associations between personal hair dye use and development of bladder cancer, non-Hodgkin's lymphoma, and multiple myeloma. These findings, however, were not consistently observed across studies.

In considering all these data, the CIR Expert Panel concluded that the available epidemiology studies are insufficient to conclude there is a causal relationship between hair dye use and cancer and other endpoints. The Panel stated that use of direct

**TABLE 12**
Historical and recent uses and use concentrations of Isostearyl Neopentaoate in cosmetic products

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| **Eye makeup** | | | | |
| Eyeliner | 5 | — | >5–10 | 8–13 |
| Eye shadow | 135 | 5 | >1–10 | 1–13 |
| Eye makeup remover | 1 | 1 | >10–25 | — |
| Eye lotion | — | — | — | 2 |
| Other eye makeup preparations | 3 | 1 | >1–10 | 13 |
| **Fragrances** | | | | |
| Perfumes | — | 1 | — | — |
| Powders | — | 1 | — | — |
| Other fragrances | — | 4 | — | — |
| **Makeup** | | | | |
| Blushers | 20 | 8 | >1–50 | 2–10 |
| Foundations | 10 | 9 | >1–10 | — |
| Face powders | — | 2 | — | 3–6 |
| Lipstick | — | 3 | — | 9–14 |
| Foundations | — | — | — | 1–10 |
| Makeup bases | 16 | 9 | >1–50 | 1–2 |
| Rouges | 2 | — | >1–5 | — |
| Other makeup | 1 | 4 | >10–25 | 0.2–12 |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 1 | 2 | >5–10 | 3–8 |
| Face and neck skin care | 1* | 1 | >1–5* | 4 |
| Body and hand skin care | | 1 | | 2–5 |
| Body and hand sprays | — | — | — | 6 |
| Moisturizers | 8 | 11 | >0.1–10 | — |
| Night skin care | 1 | 1 | >1–5 | — |
| Paste masks/mud packs | — | 1 | — | 4 |
| Other skin care | 1 | 5 | >1–5 | 1–7 |
| **Suntan** | | | | |
| Suntan gels, creams, and liquids | 2 | — | >1–5 | 2–4 |
| Indoor tanning | — | 1 | — | — |
| Other suntan | 1 | — | >1–5 | — |
| **Total uses/ranges for Isostearyl Neopentaoate** | **208** | **71** | **>0.1–50** | **0.2–14** |

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

**TABLE 13**
Historical and current uses and use concentrations for 2-Nitro-*p*-phenylenediamine and 4-Nitro-*o*-phenylenediamine

| Product category | 1981 use (Elder 1980) | 2002 use (FDA 2002) | 1981 concentrations (Elder 1980) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| | 2-Nitro-*p*-phenylenediamine | | | |
| Hair dyes and colors | 28 | 113 | ≤0.1–1 | 0.1–1 |
| **Total uses/ranges for 2-Nitro-*p*-phenylenediamine** | **28** | **113** | **≤0.1–1** | **0.1–1** |
| | 4-Nitro-*o*-phenylenediamine | | | |
| Hair dyes and colors | 26 | 22 | ≤0.1–1 | 0.1–0.2 |
| **Total uses/ranges 4-Nitro-*o*-phenylenediamine** | **26** | **22** | **≤0.1–1** | **0.1–0.2** |

hair dyes, although not the focus in all investigations, appears to have little evidence of an association with adverse events as reported in epidemiology studies. However, direct hair dyes are a diverse group of chemicals and the determination of safety may hinge on other safety test data.

Discussion of the most recent available hair dye epidemiology data is available at http://www.cir-safety.org/findings.shtml.

## REFERENCES


Adam, M. 1985. Evaluation of mutagenicity of some aromatic amines used as hair dyes by chromosomal aberration tests in-vivo. *Genet. Pol.* 26:109–116.

Batiste-Alentorn, M., N. Xamena, A. Creus, and R. Marcos. 1995. Genotoxicity testing of five compounds in three Drosophila short-term somatic assays. *Mutat. Res.* 341:161–167.

Blair, L. C., M. J. Plewa, and J. M. Gentile. 1985. Impurities of commercial 4-nitro-*o*-phenylenediamine and a novel plant activated promutagen. *Environ. Mutagen.* 7:40.

Broeckx, W., A. Blondeel, A. Dooms-Goossens, and G. Achten. 1987. Cosmetic intolerance. *Contact Dermatitis* 16:189–194.

Bronaugh, R. L., and E. R. Congdon. 1984. Percutaneous absorption of hair dyes: Correlation with partition coefficients. *J. Invest. Dermatol*. 83:124–127.

Bronaugh, R. L., and H. I. Maibach. 1985. Percutaneous absorption of nitroaromatic compounds: In vivo and in vitro studies in the human and monkey. *J. Invest. Dermatol*. 84:180–183.

Chen, S. C., and K. T. Chung. 2000. Mutagenicity and antimutagenicity studies of tannic acid and its related compounds. *Food Chem. Toxicol.* 38:1–5.

Chen, S. C., T. Y. Wong, and K. T. Chung. 1997. Base-pair mutation caused by four nitro-group containing amines in *Salmonella typhimurium* TA100, TA104, TA4001, and TA4006. *Mutat. Res.* 395:223–227.

Chung, K., T. J. Hughes, and L. D. Claxton. 2000. Comparison of the mutagenic specificity induced by four nitro-group-containing aromatic amines in *Salmonella typhimurium* his genes. *Mutat. Res.* 465:165–171.

Chung, K. T., C. A. Murdock, S. E. Stevens, Jr., Y. S. Li, C. I. Wei, T. S. Huang, and M. W. Chou. 1995. Mutagenicity and toxicity studies of *p*-phenylenediamine and its derivatives. *Toxicol. Lett.* 81:23–32.

Chung, K. T., C. A. Murdock, Y. Zhou et al. 1996. Effects of the nitro-group on the mutagenicity and toxicity of some benzamines. *Environ. Mol. Mutagen*. 27:67–74.

Clive, D., and J. F. S. Spector. 1975. Laboratory procedure for assessing specific locus mutations at the TK locus in cultured L5178Y mouse lymphoma cells. *Mutat. Res.* 31:17–29.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2003. Use concentration data on 2-Nitro-*p*-phenylenediamine and 4-Nitro-*o*-phenylenediamine from industry survey. Unpublished data submitted by CTFA, September 3, 2003 (1 page).[14]

Crank, G., and M. I. H. Makin. 1984. Oxidations of aromatic amines by superoxide ion. *Aust. J. Chem*. 37:845–856.

Dunkel, V. C., E. Zeiger, D. Brusick et al. 1985. Reproducibility of microbial mutagenicity assays. 2. Testing of carcinogens and noncarcinogens in *Salmonella typhimurium* and *Escherichia coli*. *Environ. Mutagen*. 7:1–248.

Elder, R. L. 1985. Final report on the safety assessment of 2-nitro-*p*-phenylenediamine and 4-nitro-*o*-phenylenediamine. *J. Am. Coll. Toxicol.* 4:161–202.

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.

Fautz, R., A. Fuchs, H. van der Walle, V. Henny, and L. Smits. 2002. Hair dye-sensitized hairdressers: The cross-reaction pattern with new generation hair dyes. *Contact Dermatitis* 46:319–324.


[14]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.


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

Frosch, P. J., D. Burrows, and J. G. Camarasa. 1993. Allergic reactions to a hairdressers' series: Results from 9 European Centers. *Contact Dermatitis* 28:180–183.

Gentile, J. M., G. J. Gentile, S. Townsend, and M. J. Plewa. 1985a. The in vitro enhancement of the mutagenicity of 4-nitro-*o*-phenylenediamine by plant S-9. *Environ. Mutagen*. 7:73–85.

Gentile, J. M., G. J. Gentile, S. Townsend, and M. J. Plewa. 1985b. Mutagenicity of phenylenediamines to Salmonella following plant and mammalian hepatic activation. *Environ. Mutagen*. 7:23.

Goosens, A., M. H. Beck, E. Haneke, J. P. McFadden, S. Nolting, G. Durupt, and G. Ries. 1999. Adverse allergic reactions to cosmetic allergens. *Contact Dermatitis* 40:112–113.

Guerra, L., A. Tosti, F. Bardazzi, et al. 1992. Contact dermatitis in hairdressers: The Italian experience. *Contact Dermatitis* 26:101–107.

Heil, J., and G. Reifferscheid. 1992. Detection of mammalian carcinogens with an immunological DNA synthesis-inhibition test. *Carcinogenesis* 13:2389–2394.

Hellmäer, L., and G. Bolcsfoldi. 1992. An evaluation of the E. coli K-12 uvrB/recA DNA repair host-mediated assay. II. In vivo results for 36 compounds tested in the mouse. *Mutat. Res.* 272:161–173.

Helzlsouer, K., D. Rollison, and S. Pinney. 2003. Association between hair dye use and health outcomes: Review of the literature published since 1992. Unpublished data submitted by Clairol, Inc. 107 pages.[14]

Hera, C., and C. Pueyo. 1988. Response of the L-arabinose forward mutation assay of Salmonella typhimurium to frameshift-type mutagens. *Mutat. Res.* 203:39–45.

International Agency for Research on Cancer (IARC). 1978. Some aromatic amines and related nitro compounds—hair dyes, colouring agents and miscellaneous industrial chemicals. *IARC Monographs* 16:73–82.

IARC. 1993. 1,4-Diamino-2-nitrobenzene (2-nitro-para-phenylenediamine). *IARC Monographs* 57:185–200.

Kerckaert, G. A., R. A. LeBoeuf, and R. J. Isfort. 1998. Assessing the predictiveness of the Syrian hamster embryo cell transformation assay for determining the rodent carcinogenic potential of single ring aromatic/nitroaromatic amine compounds. *Toxicol. Sci.* 41:189–197.

Keystone Aniline Corporation. 1999. *Technical Guide and Formulary*. Chicago: Keystone Aniline Corporation.[14]

Kvelland, I. 1985. Mutagenicity of 5 hair dyes in bacteriophage T-4D. *Hereditas* 102:151–154.

LeBoeuf, R. A., G. A. Kerckaert, M. J. Aardema, D. P. Gibson, R. Brauninger, and R. J. Isfort. The pH 6.7 Syrian hamster embryo cell transformation assay for assessing the carcinogenic potential of chemicals. *Mutat. Res.* 356:85–127.

Lee, H., N. J. Hao, and J.-Y. Lin. 1988. Effects of butylhydroxyanisole on the genotoxicity of three hair dye components in Ames *Salmonella* test and sister chromatid exchange assay. *J. Chin. Biochem. Soc.* 17:112–118.

Lee, H., L.-Y. Perng, S.-J. Shiow, M.-Y. Chou, M.-C. Chou, and J.-Y. Lin. 1986. Induction of sister chromatid exchange in cultured Chinese hamster cells by short-term treatment with hair dye components. *J. Chin. Biochem. Soc.* 15:34–38.

Maron, D. M., and B.N. Ames. 1983. Revised methods for the *Salmonella* mutagenicity test. *Mutat. Res.* 113:173–215.

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 in rodent bioassays. *Environ. Health Perspect.* 101:347–482.

McFee, A. F., P. P. Jauhar, K. W. Lowe, J. T. MacGregor, and C. M. Wehr. 1989. Assays of three carcinogen/non-carcinogen chemical pairs for in vivo induction of chromosome aberrations, sister chromatid exchanges and micronuclei. *Environ. Mol. Mutagen.* 14:207–220.

Ministry of Health, Labor and Welfare (MHLW). June 29, 2001. MHW Ordinance No. 332. Ingredients of quasi-drugs. Products to be used directly on the body. MHLW, Pharmaceutical and Medical Safety Bureau, Inspection and

Guidance Division, 2-2, 1-chome, Kasumigaseki, Chiyoda-ku, Tokyo 100-8045, Japan.
Misra, R. 1992. Clastogenic potential testing of some hair dye components by the bone marrow micronucleus analysis. *Cytologia* 57:149–154.
Mitchell, A. D., C. J. Rudd, and W. J. Caspary. 1988. Evaluation of the L5178Y mouse lymphoma cell mutagenesis assay: Intralaboratory results for sixty-three coded chemicals tested at SRI International. *Environ. Mol. Mutatgen.* 12:37–194.
Myhr, B. C., and W. J. Caspary. 1988. Evaluation of the L5178Y mouse lymphoma cell mutagenesis assay: Intralaboratory results for sixty-three coded chemicals tested at Litton Bionetics, Inc. *Environ. Mol. Mutagen.* 12:103–194.
Nakao, M., Y. Gotoh, A. Hiratsuka, and T. Watabe. 1991. Reductive metabolism of nitro-p-phenylenediamine by rat liver. *Chem. Pharm. Bull.* 39:177–180.
Nakao, M., Y. Gotoh, Y. Matsuki, A. Hiratsuka, and T. Watabe. 1987. Metabolism of the hair dye component, nitro-p-phenylenediamine, in the rat. *Chem. Pharm. Bull.* 35:785–791.
Neal, S. B., and G. S. Probst. 1983. Chemically-induced sister-chromatid exchange in vivo in bone marrow of Chinese hamsters. An evaluation of 24 compounds. *Mutat. Res.* 113:33–43.
Neal, S. B., and G. S. Probst. 1984. Assessment of sister chromatid exchange in spermatogonia and intestinal epithelium in Chinese hamsters. *Basic Life Sci*. 29:613–628.
Oberly, T. J., B. J. Bewsey, and Probst, G. S. 1984. An evaluation of the L5178Y TK+/− mouse lymphoma forward mutation assay using 42 chemicals. *Mutat. Res*. 125:291–306.
Pepe, R. C., J. A. Wenninger, and G. N. McEwen, Jr., eds. 2002. *International Cosmetic Ingredient Dictionary and Handbook*, 9th ed., 1032. Washington, DC: CTFA.
Popkin, D. J., and M. J. Prival. 1985. Effects of pH on weak and positive control mutagens in the Ames Salmonella plate assay. *Mutat. Res.* 142:109–114.
Rodriguez-Arnaiz, R., and J. H. Aranda. 1994. Activity of aromatic amines in the eye: w/w+ somatic assay of *Drosophila melanogaster*. *Environ. Mol. Mutagen.* 24:75–79.
Sasaki, Y. F., K. Fujikawa, K. Ishida, et al. 1999. The alkaline single cell gel electrophoresis assay with mouse multiple organs: Results with 30 aromatic amines evaluated by the IARC and U.S. NTP. *Mutat. Res.* 440:1–18.
Soler-Niedziela, L., X. Shi, J. Nath, and T. Ong. 1991. Studies on three structurally related phenylenediamines with the mouse micronucleus assay system. *Mutat. Res.* 259:43–48.
Suter, W., R. Ahiabor, B. Blanco et al.1996. Evaluation of the in vivo genotoxic potential of three carcinogenic aromatic amines using the Big Blue transgenic mouse mutation assay. *Environ. Mol. Mutagen*. 28:354–362.
van Erp, Y. H. M., M. J. E. Koopmans, P. R. C. M. Heirbaut, J. C. M. Van der Hoeven, and P. J. J. M. Weterings. 1992. Unscheduled DNA synthesis in human hair follicles after in vitro exposure to 11 chemicals: Comparison with unscheduled DNA synthesis in rat hepatocytes. *Mutat. Res.* 271:201–208.
Van Joost, T., F. Heule, and J De Boer. 1987. Sensitization to methylene-dianiline and para-structures. *Contact Dermatitis* 16:246–248.
Vogel, E. W., U. Graf, H. J. Frei, and M. M. Nivard. 1999. The results of assays in Drosophila as indicators of exposure to carcinogens. *IARC Sci. Publ.* 146:427–470.
Williams, G. M. 1997. Liver cell culture methods for measuring DNA alterations produced by chemicals and radiation. *Cell Biol. Toxicol.* 13:317–321.
Williams, G. M., H. Mori, and C. A. McQueen. 1982. Reliability of the hepatocyte primary culture/DNA repair test in testing in coded carcinogens and noncarcinogens. *Mutat. Res.* 97:359–370.
Wilschut, A., W. F. Ten Berge, P. J. Robinson, and T. E. McKone. 1995. Estimating skin permeation. The validation of five mathematical skin permeation models. *Chemosphere* 30:1275–1296.
Wolfram, L. J., and H. I. Maibach. 1985. Percutaneous penetration of hair dyes. *Arch. Dermatol. Res.* 277:235–241.
Yourick, J. J., and R. L. Bronaugh. 2000. Percutaneous absorption and metabolism of 2-nitro-*p*-phenylenediamine in human and fuzzy rat skin. *Toxicol. Appl. Pharmacol*. 166:13–23.

## OLEIC ACID, LAURIC ACID, PALMITIC ACID, MYRISTIC ACID, AND STEARIC ACID

A safety assessment of the Oleic Acid group was published in 1987 with a conclusion that these ingredients are safe in present practices of use and concentration in cosmetics. New studies regarding these fatty acids available since then, along with updated information regarding uses and use concentrations, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

**Oleic Acid** usage increased from 424 in 1981 to 1131 in 2002, based on industry voluntary reports provided to FDA (Elder 1987; FDA 2002). An industry survey in 2004 indicated that use concentrations range from 0.00004% to 20%, within the range reported in 1981 (Elder 1987).

**Lauric Acid** usage increased from 22 in 1981 to 121 in 2002, based on industry voluntary reports provided to FDA (Elder 1987; FDA 2002). An industry survey in 2004 indicated that use concentrations range from 0.00003% to 11%, within the range reported in 1981 (Elder 1987).

**Palmitic Acid** usage increased from 29 in 1981 to 132 in 2002, based on industry voluntary reports provided to FDA (Elder 1987; FDA 2002). An industry survey in 2004 indicated that use concentrations range from 0.00006% to 20%, within the range reported in 1981 (Elder 1987).

**Myristic Acid** usage increased from 36 in 1981 to 73 in 2002, based on industry voluntary reports provided to FDA (Elder 1987; FDA 2002). An industry survey in 2004 indicated that use concentrations range from 0.00001% to 38%, within the range reported in 1981 (Elder 1987).

**Stearic Acid** usage decreased from 2465 in 1981 to 2133 in 2002, based on industry voluntary reports provided to FDA (Elder 1987; FDA 2002). An industry survey in 2004 indicated that use concentrations range from 0.000002% to 43%, within the range reported in 1981 (Elder 1987).

The available use and concentration data are given in Table 14. The most recent information now constitutes the present practices of use and concentration.

The newly available studies reported findings consistent with the data in the original safety assessment. One area not covered in the original report was reproductive and developmental toxicity. One new study was available that demonstrated little or no toxicity to sperm cells by Oleic Acid, Palmitic Acid, and Stearic Acid.

These fatty acids may be plant derived. In such cases, established limits for pesticide and heavy metal residues should not be exceeded (lead $\leq$10 ppm, arsenic $\leq$3 ppm, mercury $\leq$1 ppm, total PCB/pesticide $\leq$40 ppm, with $\leq$10 ppm for any specific pesticide residue).

These fatty acids may also be derived from animal sources, including beef. The Panel agrees with the Food and Drug Administration's position that tallow derivatives, including these fatty acids, would not present any risk of transmissible encephalopathies.

**TABLE 14**
Historical and current cosmetic product uses and concentrations for Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, and Stearic Acid

| Product category | 1981 uses (Elder 1987) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1987) % | 2004 concentrations (CTFA 2005) % |
|---|---|---|---|---|
| | | *Oleic Acid* | | |
| **Baby care** | | | | |
| Shampoos | 1 | 1 | >10–25 | — |
| Lotions, oils, powders, and creams | 1 | 1 | >1–5 | 1 |
| Other baby care | 2 | 4 | >1–25 | 2 |
| **Bath** | | | | |
| Oils, tablets, and salts | 1 | 1 | >5–10 | — |
| Soaps and detergents | 5 | 20 | >1–10 | 0.000004–15 |
| Other bath | — | 10 | — | — |
| **Eye makeup** | | | | |
| Eyeliners | 16 | 10 | >0.1–25 | 0.1–3 |
| Eye shadow | 5 | — | >0.1–5 | 0.4 |
| Eye makeup remover | 2 | — | >1–5 | — |
| Mascara | 41 | 38 | >0.1–10 | 1–4 |
| Other eye makeup | 1 | 1 | >1–5 | 2–5 [a] |
| **Fragrances** | | | | |
| Colognes and toilet waters | — | — | — | 0.001 |
| Sachets | 4 | 2 | >0.1–1 | — |
| Other fragrances | 8 | 5 | >0.1–5 | — |
| **Noncoloring hair care** | | | | |
| Conditioners | 1 | — | >25–50 | — |
| Permanent waves | 1 | 2 | ≤0.1 | — |
| Rinses | — | 1 | — | — |
| Shampoos | 9 | 5 | >1–25 | 0.000007 |
| Tonics, dressings, etc. | 1 | 1 | >0.1–1 | 0.6 |
| Other noncoloring hair care | — | — | — | 20 [b] |
| **Hair coloring** | | | | |
| Dyes and colors | 205 | 946 | ≤0.1–25 | 19 |
| Tints | 14 | 9 | >1–25 | — |
| Shampoos | 7 | — | >0.1–5 | — |
| Color sprays | — | 1 | — | — |
| Lighteners with color | 1 | 1 | >1–5 | — |
| Bleaches | 8 | 17 | >1–50 | — |
| **Makeup** | | | | |
| Blushers | 10 | 2 | >1–5 | 0.4 |
| Face powders | 1 | — | >0.1–1 | 0.0001 |
| Foundations | 20 | 9 | >0.1–5 | 0.4–2 |
| Lipsticks | 1 | 5 | >5–10 | 16 |
| Makeup bases | 5 | 3 | ≤0.1–5 | 0.4 |
| Rouges | — | 1 | — | 0.00005 |
| Other makeup | 4 | 3 | >0.1–25 | 2 |
| **Nail care** | | | | |
| Basecoats and undercoats | 1 | 1 | >10–25 | — |
| Nail polish and enamels | — | — | — | 0.0008 |
| Other nail care | — | 1 | — | — |

*(Continued on next page)*

**TABLE 14**
Historical and current cosmetic product uses and concentrations for Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, and Stearic Acid *(Continued)*

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2004 concentrations (CTFA 2005) % |
|---|---|---|---|---|
| **Personal hygiene** | | | | |
| Underarm deodorants | — | — | — | 0.0007–0.6 |
| Other personal hygiene | 3 | 4 | >1–10 | 6[e] |
| **Shaving** | | | | |
| Aftershave lotions | 3 | — | ≤0.1–1 | 0.00008 |
| Shaving cream | 2 | 3 | >1–5 | 0.7–4 |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 10 | 5 | >0.1–5 | 0.00002–9 |
| Face and neck skin care | 11[c] | — | >0.1–25[c] | 2 |
| Body and hand skin care | | 2 | | 0.2–0.4 |
| Moisturizers | 14 | 7 | >0.1–5 | 0.2–0.4 |
| Night skin care | — | — | — | 0.5 |
| Other skin care | 2 | 3 | >0.1–5 | — |
| Hormone preparations[d] | 1 | NA[d] | >1–5 | NA[d] |
| **Suntan products** | | | | |
| Suntan gels, creams, liquids, and sprays | 2 | 5 | >1–5 | 0.02 |
| Indoor tanning preparations | — | 1 | — | — |
| **Total uses/ranges for Oleic Acid** | **424** | **1131** | **≤0.1–50** | **0.000004–20** |
| | | *Lauric Acid* | | |
| **Bath** | | | | |
| Soaps and detergents | — | 16 | — | 0.1–8 |
| Other bath | — | 20 | — | 2–11 |
| **Noncoloring hair care** | | | | |
| Conditioners | — | 1 | — | 0.000004–4 |
| Sprays | — | — | — | 0.00002 |
| Shampoos | 3 | 1 | >1–25 | 0.2–0.5 |
| Tonics, dressings, etc. | 3 | 5 | >0.1–1 | 0.00003 |
| **Fragrances** | | | | |
| Colognes and toilet waters | — | — | — | 0.001 |
| Perfumes | — | — | — | 0.00002 |
| **Hair coloring** | | | | |
| Dyes and colors | — | 43 | — | — |
| **Makeup** | | | | |
| Foundations | — | — | — | 1 |
| Lipsticks | — | 1 | — | 0.00003 |
| **Personal hygiene** | | | | |
| Underarm deodorants | 5 | 3 | ≤0.1–1 | 0.3 |
| Other personal hygiene | 4 | 3 | ≤0.1–10 | 5[e] |
| **Shaving** | | | | |
| Aftershave lotions | — | — | — | 0.0003 |
| Shaving cream | 3 | 1 | >1–10 | 0.003 |
| Other shaving | — | — | — | 0.2[g] |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 3 | 25 | >1–5 | — |
| Face and neck skin care | —[c] | — | —[c] | — |
| Body and hand skin care | | — | | 0.00006 |
| Moisturizers | 1 | 2 | >0.1–1 | — |

**TABLE 14**
Historical and current cosmetic product uses and concentrations for Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, and Stearic Acid *(Continued)*

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2004 concentrations (CTFA 2005) % |
|---|---|---|---|---|
| Night skin care | — | — | — | 0.00003–0.5 |
| Other skin care | — | — | — | 2–3 |
| **Suntan** | | | | |
| Suntan gels, creams and liquids | — | — | — | 1 |
| **Total uses/ranges for Lauric Acid** | **22** | **121** | **≤0.1–25** | **0.000004–11** |
| | | *Palmitic Acid* | | |
| **Bath** | | | | |
| Soaps and detergents | 1 | 10 | >5–10 | 0.3–10 |
| Other | — | 11 | — | 0.000006–2 |
| **Eye makeup** | | | | |
| Eyeliners | — | — | — | 0.1–0.7 |
| Eye shadow | 1 | — | >5–10 | 0.006–0.3 |
| Eye lotion | — | — | — | 0.05 |
| Mascara | — | 1 | — | 0.02–4 |
| Other eye makeup | — | 2 | — | 0.003 |
| **Fragrance** | | | | |
| Colognes and toilet waters | — | — | — | 0.01–0.8 |
| Other fragrances | — | 1 | — | 3 |
| **Noncoloring hair care** | | | | |
| Conditioners | — | 1 | — | 0.00002–0.4 |
| Shampoos | 2 | 26 | >1–5 | 0.001–3 |
| Tonics, dressings, etc. | — | — | — | 0.00003–2 |
| Other noncoloring hair care | — | 3 | — | — |
| **Hair coloring** | | | | |
| Other hair coloring | — | 1 | — | — |
| **Makeup** | | | | |
| Blushers | — | — | — | 0.008–0.2 |
| Face powders | — | 1 | — | 0.01–1 |
| Foundations | 2 | 10 | >0.1–5 | 0.3–2 |
| Lipsticks | — | 1 | — | 0.2–16 |
| Rouges | — | 1 | — | 0.00005 |
| Makeup fixatives | — | 1 | — | — |
| Other makeup | — | — | — | 0.01–2 |
| **Nail care** | | | | |
| Nail polishes and enamels | — | — | — | 0.02–0.03 |
| **Personal hygiene** | | | | |
| Underarm deodorants | — | 1 | — | 0.09–3 |
| Other personal hygiene | — | — | — | 0.3–4 |
| **Shaving** | | | | |
| Aftershave lotions | — | — | — | 0.006 |
| Shaving cream | 4 | 11 | >0.1–10 | 2–20 |
| Shaving soap | — | — | — | 0.4–8 |
| Other shaving | — | 17 | — | 10 |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 8 | 8 | >1–25 | 0.03–7 |
| Depilatories | — | — | — | 4 |

*(Continued on next page)*

**TABLE 14**
Historical and current cosmetic product uses and concentrations for Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, and Stearic Acid *(Continued)*

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2004 concentrations (CTFA 2005) % |
|---|---|---|---|---|
| Face and neck skin care | 3[c] | 1 | >0.1–5[c] | 0.2–3 |
| Body and hand skin care | | 3 | | 0.05–7 |
| Foot powders and sprays | — | 1 | — | — |
| Moisturizers | 3 | 8 | >0.1–5 | 0.2–2 |
| Night skin care | 3 | — | >1–25 | 0.05–1 |
| Paste masks/mud packs | — | — | — | 0.02 |
| Skin fresheners | — | 1 | — | — |
| Other skin care | 1 | 4 | >1–5 | 0.2–2 |
| **Suntan** | | | | |
| Suntan gels, creams, liquids, and sprays | 1 | 5 | >10–25 | 0.0009–3 |
| Indoor tanning | — | 1 | — | — |
| Other suntan | — | 1 | — | — |
| **Total uses/ranges for Palmitic Acid** | **29** | **132** | **>0.1–25** | **0.000006–20** |
| | | *Myristic Acid* | | |
| **Bath** | | | | |
| Soaps and detergents | 3 | 7 | >5–25 | 0.005-19 |
| Other bath | — | 11 | — | 0.00001–14 |
| **Eye makeup** | | | | |
| Mascara | 2 | — | >0.1–1 | 0.005–0.8 |
| **Fragrances** | | | | |
| Colognes and toilet waters | — | — | — | 0.001 |
| Other fragrances | — | 1 | — | — |
| **Noncoloring hair care** | | | | |
| Conditioners | — | 1 | — | — |
| Shampoos | 2 | 3 | >1–5 | 0.00006–0.2 |
| Tonics, dressings, etc. | — | — | — | 0.00002–0.08 |
| **Makeup** | | | | |
| Face powders | — | — | — | 0.05 |
| Foundations | — | 2 | — | 0.4 |
| Lipsticks | — | 1 | — | — |
| Rouges | — | — | — | 0.00005 |
| Other makeup | — | — | — | 0.00004 |
| **Oral hygiene** | | | | |
| Dentifrices | — | — | — | 0.0003 |
| **Personal hygiene** | | | | |
| Underarm deodorants | — | 1 | — | — |
| Other personal hygiene | 2 | 1 | >10–25 | 1–38[f] |
| **Shaving** | | | | |
| Aftershave lotions | — | — | — | 0.00008 |
| Beard softeners | 2 | — | >25–50 | — |
| Shaving cream | 16 | 13 | >1–10 | 3–33 |
| Shaving soap | — | — | — | 2 |
| Other shaving | 1 | 3 | >0.1–1 | — |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 5 | 26 | 1–25 | 0.0005–12 |
| Depilatories | — | — | — | 12 |
| Face and neck skin care | 2[c] | — | >0.1–5[c] | 14 |
| Body and hand skin care | | 1 | | 0.5–10 |
| Moisturizers | 1 | 1 | >0.1–1 | 0.0002–1 |

**TABLE 14**
Historical and current cosmetic product uses and concentrations for Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, and Stearic Acid *(Continued)*

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2004 concentrations (CTFA 2005) % |
|---|---|---|---|---|
| Night skin care | — | — | — | 0.0003 |
| Other skin care | — | 1 | — | 0.003–15 |
| **Total uses/ranges for Myristic Acid** | **36** | **73** | **>0.1–50** | **0.00001–38** |
| | | *Stearic Acid* | | |
| **Baby care** | | | | |
| Shampoos | — | — | — | 2 |
| Lotions, oils, powders, and creams | 9 | 11 | >0.1–10 | 2–3 |
| Other baby care | 1 | 7 | >10–25 | 0.1–2 |
| **Bath** | | | | |
| Soaps and detergents | 13 | 41 | >1–25 | 0.2–19 |
| Bubble baths | — | 1 | — | 1–2 |
| Other bath | 3 | 13 | >0.1–5 | 0.000007–7[h] |
| **Eye makeup** | | | | |
| Eyebrow pencils | 9 | 12 | >5–25 | 0.009–15 |
| Eyeliners | 55 | 74 | >0.1–50 | 0.7–22 |
| Eye shadow | 128 | 4 | >0.1–5 | 0.3–16 |
| Eye lotions | 1 | 4 | >1–5 | 0.05–3 |
| Eye makeup remover | 1 | 3 | >0.1–1 | 0.1–0.5 |
| Mascara | 139 | 95 | >0.1–50 | 1–21 |
| Other eye makeup | 26 | 32 | >0.1–10 | 1–14 |
| **Fragrances** | | | | |
| Colognes and toilet waters | 3 | — | >1–5 | 1 |
| Perfumes | 3 | — | >0.1–10 | — |
| Sachets | 32 | 4 | >0.1–10 | — |
| Other fragrances | 34 | 31 | >0.1–10 | 16 |
| **Noncoloring hair care** | | | | |
| Conditioners | 18 | 7 | ≤0.1–5 | 0.000002–0.5 |
| Sprays/aerosol fixatives | 1 | — | >1–5 | — |
| Straighteners | 6 | 8 | >0.1–10 | — |
| Shampoos | 17 | 10 | >0.1–25 | 0.000007–7 |
| Tonics, dressings, etc. | 18 | 4 | ≤0.1–>50 | 0.01–2 |
| **Hair coloring** | | | | |
| Dyes and colors | 76 | 132 | >1–5 | — |
| Tints | — | 1 | — | — |
| Rinses | — | 1 | — | — |
| Color sprays | — | 1 | — | — |
| Bleaches | 4 | — | >0.1–5 | — |
| Other hair coloring | 8 | 2 | >10–25 | — |
| **Makeup** | | | | |
| Blushers | 47 | 4 | >0.1–10 | 0.8–3 |
| Face powders | 2 | 6 | >0.1–1 | 0.1–1 |
| Foundations | 190 | 119 | >0.1–25 | 1–5 |
| Lipsticks | 27 | 40 | >0.1–25 | 0.02–9 |
| Makeup bases | 263 | 35 | >0.1–25 | 2–3 |
| Rouges | 9 | — | >0.1–10 | 0.00005–0.1 |
| Makeup fixatives | 1 | 4 | >1–5 | — |
| Other makeup | 20 | 22 | >0.1–25 | 0.01–6 |

*(Continued on next page)*

**TABLE 14**
Historical and current cosmetic product uses and concentrations for Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, and Stearic Acid *(Continued)*

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985)% | 2004 concentrations (CTFA 2005)% |
|---|---|---|---|---|
| **Nail care** | | | | |
| Cuticle softeners | 10 | 8 | >0.1–25 | 1–4 |
| Creams and lotions | 6 | 5 | >1–5 | 3–5 |
| Nail polishes and enamels | — | — | — | 0.04 |
| Other nail care | 2 | — | >1–10 | 0.05–4 |
| **Personal hygiene** | | | | |
| Underarm deodorants | 8 | 21 | >1–25 | 0.2–9 |
| Other personal hygiene | 8 | 6 | >1–25 | 5–6[e] |
| **Shaving** | | | | |
| Aftershave lotions | 5 | 9 | >0.1–5 | 0.5–2 |
| Shaving cream | 100 | 100 | >0.1–50 | 1–43 |
| Shaving soap | 1 | 1 | >25–50 | 0.4–2 |
| Other shaving | 6 | 4 | >1–25 | 0.5–8 |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 173 | 168 | ≤0.1–25 | 1–25 |
| Depilatories | — | — | — | 7 |
| Face and neck skin care | | 84 | | 3–7 |
| Body and hand skin care | 432[c] | 320 | >0.1–50[c] | 0.1–16 |
| Foot powders and sprays | — | 5 | — | 4 |
| Moisturizers | 327 | 356 | ≤1–50 | 0.3–10 |
| Night skin care | 67 | 62 | ≤0.1–25 | 0.4–2 |
| Paste masks/mud packs | 15 | 55 | >1–25 | 0.4–8 |
| Skin fresheners | 4 | 4 | >10–25 | — |
| Skin lighteners[d] | 11 | —[d] | >1–25 | —[d] |
| Hormone preparations[d] | 3 | —[d] | >1–25 | —[d] |
| Wrinkle smoothers[d] | 4 | —[d] | >1–5 | —[d] |
| Other skin care | 55 | 133 | >0.1–25 | 0.0005–5 |
| **Suntan** | | | | |
| Suntan gels, creams, liquids, and sprays | 48 | 42 | >0.1–25 | — |
| Indoor tanning | 3 | 9 | >0.1–1 | 0.3–2 |
| Other suntan | 13 | 13 | >0.1–5 | — |
| **Total uses/ranges for Stearic Acid** | **2465** | **2133** | **≤0.1–>50** | **0.000007–43** |

[a] The 5% concentration was for a definer.
[b] A hair care protective oil.
[c] These categories were combined in 1981, but are now separate.
[d] No longer considered as a cosmetic ingredient category.
[e] A hand wash product.
[f] The highest concentration was for a hand wash product.
[g] The 0.2% concentration was specifically reported in a shave lubricant product.
[h] The 7% concentration was for a body scrub product.

## REFERENCES

Boelsma, E., H. Tanojo, H. E. Bodde, and M. Ponec. 1996. Assessment of the potential irritancy of oleic acid on human skin: Evaluation in vitro and in vivo. *Toxicol. In Vitro* 10:729–742.

Cardoso, C. R., M. A. Souza, E. A. Ferro, et al. 2004. Influence of topical administration of n–3 and n–6 essential and n–9 nonessential fatty acids on the healing of cutaneous wounds. *Wound Repair Regen.* 12:235–243.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2005. Use concentration data from industry survey. Unpublished data submitted by CTFA.[15]

De Groot, A. C., H. L. van der Meeren, and J. W. Weyland. 1988. Cosmetic allergy from stearic acid and glyceryl stearate. *Contact Dermatitis* 19:77–78.

[15] Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

de Sousa Andrade, L. N., T. M. de Lima, R. Curi, and A. M. de Lauro Castrucci. 2005. Toxicity of fatty acids on murine and human melanoma cell lines. *Toxicol. In Vitro* 19:553–560.

Dobson, C. L., S. S. Davis, S. Chauhan, R. A. Sparrow et al. 1999. Effect of oleic acid on the human ileal brake and its implications for small intestinal transit of tablet formulations. *Pharm. Res.* 16:92–96.

Elder, R. L. 1985. Final report on the safety assessment of Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, and Stearic Acid. *J. Am. Coll. Toxicol.* 4:161–202.

Fermor, B. F., J. R. Masters, C. B. Wood, J. Miller et al. 1992. Fatty acid composition of normal and malignant cells and cytotoxicity of stearic, oleic, and sterculic acids in vitro. *Eur. J. Cancer* 28:1143–1147.

Garrison, M. D., L. M. Doh, R. O. Potts, and W. Abraham. 1994. Effect of oleic acid on human epidermis: Fluorescence spectroscopic investigation. *J. Controlled Release* 31:263–269.

Gottschalck, T. E., and G. N. McEwen, Jr. 2004. *International cosmetic ingredient dictionary and handbook*, 10th ed., p 970, 1106, 1163–1164, 1198, 1822. Washington, DC: CTFA.

Gouni-Berthold, I., H. K. Berhold, C. Seul, Y. Ko, et al. 2001. Effects of authentic and VLDL hydrolysis-derived fatty acids on vascular smooth muscle cell growth. *Br. J. Pharmacol.* 132:1725–1734.

Green, P. G., R. H. Guy, and J. Hadgraft. 1988. In vitro and in vivo enhancement of skin permeation with oleic and lauric acids. *Int. J. Pharmacol.* 48:103–111.

Huang, Z. H., D. Gu, and T. Mazzone. 2004. Oleic acid modulates the post-translational glycosylation of macrophage ApoE to increase its secretion. *J. Biol. Chem.* 279:29195–29201.

Khalil, M. H., J. F. Marceletti, L. R. Katz, D. H. Katz, et al. 2000. Topical application of docosanol- or stearic acid-containing creams reduces severity of phenol burn wounds in mice. *Contact Dermatitis* 24:79–81.

Khoo, D. E., B. Flaks, H. Oztas, R. C. Williamson, et al. 1991. Effects of dietary fatty acids on the early stages of neoplastic induction in the rat pancreas. Changes in fatty acid composition and development of atypical acinar cell nodules. *Int. J. Exp. Pathol*. 72:571–580.

Kim, H. J., J. H. Lee, C. H. Lee, S. H. Lee, et al. 2002. Experimental cerebral fat embolism: Embolic effects of triolein and oleic acid depicted by MR Imaging and electron microscopy. *Am. J. Neuroradiol.* 23:1516–1623.

Kinter, M., D. R. Spitz, and R. J. Roberts. 1996. Oleic acid incorporation protects cultured hamster fibroblasts from oxygen-induced cytotoxicity. *J. Nutr.* 126:2952–2959.

Koehler, A. E., M. E. Tobin, and R. T. Sugihara. 1995. Exploration of lauric acid as a potentiator for enhancing warfarin toxicity to rats. *Int. Biodeterior. Biodegrad*. 36:73–87.

Koyama, Y., H. Bando, F. Yamashita, Y. Takakura, et al. 1994. Comparative analysis of percutaneous absorption enhancement by *d*-limonene and oleic acid based on a skin diffusion model. *Pharm. Res*. 11:377–383.

Kravchenko, I. A., N. Y. Golovenko, V. B. Larionov, A. I. Aleksandrova, et al. 2003. Effect of lauric acid on transdermal penetration of phenazepam in vivo. *Pharmacol. Toxicol*. 136:579–581.

Lee, S. P., C. Tasman-Jones, and V. Carlisle. 1986. Oleic acid-induced cholelithiasis in rabbits. Changes in bile composition and gallbladder morphology. *Am. J. Pathol*. 124:18–24.

Medvedev, A. V., J. Robidoux, X. Bai, W. Cao, et al. 2002. Regulation of the uncoupling protien-2 gene in INS-1 $\beta$-cells by oleic acid. *J. Biol. Chem*. 277:42639–42644.

Müller, D., R. M. Nitsch, R. J. Wurtman, and S. Hoyer. 1998. Streptozotocin increases free fatty acids and decreases phospholipids in rat brain. *J. Neural. Transm*. 105:1271–1281.

Ogiso, T., M. Iwaki, Y. Kashitani, and K. Yamashita. 1991. Enhancement effect of lauric acid on the rectal absorption of propranolol from suppository in rats. *Chem. Pharm. Bull*. (*Tokyo*). 39:2657–2661.

Pershing, L. K., G. E. Parry, and L. D. Lambert. 1993. Disparity of in vitro and in vivo oleic acid-enhanced beta-estradiol percutaneous absorption across human skin. *Pharm. Res.* 10:1745–1750.

Siegel, I., A. B. Dudkiewicz, J. Friberg, M. Suarez et al. 1986. Inhibition of sperm motility and agglutination of sperm cells by free fatty acids in whole semen. *Fertil. Steril*. 45:273–279.

Tholstrup, T., C. Ehnholm, M. Jauhianen, M. Petersen, et al. 2004. Effects of medium-chain fatty acids and oleic acid on blood lipids, lipoproteins, glucose, insulin, and lipid transfer protein activities. *Am. J. Clin. Nutr*. 79:564–569.

Tanojo, H., E. Boelsma, H. E. Junginger, M. Ponec, et al. 1999. In vivo human skin permeability enhancement by oleic acid: Laser Doppler velocimetry study. *J. Controlled Release* 58:97–104.

Tanojo, H., H. E. Junginger, and H. E. Bodde. 1997. In vivo human skin permeability enhancement by oleic acid: Transepidermal water loss and Fourier-transform infrared spectroscopy studies. *J. Controlled Release* 47:31–39.

Ulloth, J. E., C. A. Casiano, and M. De Leon. 2003. Palmitic and stearic fatty acids induce caspase-dependent and independent cell death in nerve growth factor differentiated PC12 cells. *J. Neurochem*. 84:655–668.

Velasquez, O. R., A. R. Place, P. Tso, and K. D. Crissinger. 1994. Developing intestine is injured during absorption of oleic acid but not its ethyl ester. *J. Clin. Invest*. 93:479–485.

## PANTHENOL AND PANTOTHENIC ACID

A safety assessment of Panthenol and Pantothenic Acid was published in 1987 with the conclusion that these ingredients are safe as presently used in cosmetics (Elder 1987). Studies published since the last assessment, along with updated information concerning frequency of use and use concentrations, were considered by the CIR Expert Panel. The Panel determined to not reopen the safety assessment.

The safety assessment applies to Panthenol in both the D and the DL form.

The available use and concentration information is provided in Table 15. The most recent information now constitutes the present use of these ingredients.

**Panthenol** reported usage increased from 284 in 1981 to 1538 in 2002, based on industry voluntary reports provided to FDA (Elder 1987; FDA 2002). An industry survey in 2004 indicated that use concentrations range from 0.00005% to 6%, which is lower than the maximum use concentration range reported in 1981 (Elder 1987).

**Pantothenic Acid** was not reportedly used in cosmetics in 1981 (Elder 1987), but industry voluntary reports provided to FDA in 2002 included three uses in eye makeup and skin care products (FDA 2002). An industry survey in 2004 indicated that use concentrations range from 0.00001% to 0.01% in those product categories and in makeup and shaving preparations (categories in which no uses were reported to FDA).

## REFERENCES

Biro, K., D. Thaci, F. R. Ochsendorf, R. Kaufmann, and W. H. Boehncke. 2003. Efficiency of dexpanthenol in skin protection against irritation: A double-blind, placebo-controlled study. *Contact Dermatitis* 49:80–84.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2004. Concentration of use of Panthenol and Pantothenic Acid in cosmetic formulations. Unpublished data submitted by CTFA. 3 pages.[16]

[16]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

**TABLE 15**
Historical and current cosmetic product uses and concentrations for Panthenol and Pantothenic Acid

| Product category | 1981 uses (Elder 1987) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1987) % | 2004 concentrations (CTFA 2004) % |
|---|---|---|---|---|
| | | *Panthenol* | | |
| **Baby care** | | | | |
| Lotions, oils, powders, and creams | — | 3 | — | — |
| **Bath** | | | | |
| Oils, tablets and salts | — | — | — | 2 |
| Soaps and detergents | — | 15 | — | 0.05–4 |
| Bubble baths | — | 3 | — | 0.01–2 |
| Capsules | — | 1 | — | — |
| Other bath | — | 11 | — | 0.3–2 |
| **Eye makeup** | | | | |
| Eyebrow pencils | — | 3 | — | 0.01–2 |
| Eyeliners | 5 | — | >0.1–1 | 0.01–0.05 |
| Eye shadow | 23 | — | >0.1–1 | 0.5–1 |
| Eye lotions | — | 5 | — | 0.01–0.6 |
| Eye makeup remover | 2 | 8 | >0.1–1 | 0.001–1 |
| Mascara | 10 | 70 | >0.1–5 | 0.1–2 |
| Other eye makeup | 2 | 14 | >0.1–1 | 0.3–0.5 |
| **Fragrances** | | | | |
| Colognes and toilet waters | 1 | 5 | >0.1–1 | 0.003–0.1 |
| Perfumes | — | — | — | 1 |
| Powders | — | 3 | — | — |
| Other fragrances | — | 11 | — | 1 |
| **Noncoloring hair care** | | | | |
| Conditioners | 33 | 264 | ≤0.1–5 | 0.09–6 |
| Sprays/aerosol fixatives | 17 | 82 | ≤0.1–1 | 0.01–5 |
| Straighteners | — | 1 | — | — |
| Permanent waves | 2 | 6 | >0.1–1 | 5 |
| Rinses | 1 | 6 | >0.1–1 | 0.1–0.5 |
| Shampoos | 25 | 206 | ≤0.1–5 | 0.01–5 |
| Tonics, dressings, etc. | 11 | 187 | ≤0.1–1 | 0.01–5 |
| Wave sets | 31 | 12 | ≤0.1–5 | 0.9–1 |
| Other noncoloring hair care | 6 | 93 | ≤0.1–1 | 0.01–1* |
| **Hair coloring** | | | | |
| Dyes and colors | — | 52 | — | 0.01–0.1 |
| Tints | — | 1 | — | — |
| Color sprays | — | 2 | — | — |
| Bleaches | — | 1 | — | 0.5 |
| Other hair coloring | — | 6 | — | 0.00005–1 |
| **Makeup** | | | | |
| Blushers | 3 | 2 | >0.1–1<br>>10–25 | 0.2–1 |
| Face powders | 1 | 1 | >0.1–1 | 0.02–1 |
| Foundations | 8 | 45 | ≤0.1–1 | 0.2–1 |
| Lipsticks | 27 | 6 | ≤0.1–5 | 0.01–2 |
| Makeup bases | 1 | 8 | ≤0.1 | 0.5 |
| Rouges | 1 | — | >0.1–1 | — |
| Other makeup | 2 | 4 | >0.1–1 | <1–6 |

**TABLE 15**
Historical and current cosmetic product uses and concentrations for Panthenol and Pantothenic Acid *(Continued)*

| Product category | 1981 uses (Elder 1987) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1987) % | 2004 concentrations (CTFA 2004) % |
|---|---|---|---|---|
| **Nail care** | | | | |
| Basecoats and undercoats | — | 9 | — | 0.03–0.2 |
| Cuticle softeners | 1 | 4 | >0.1–1 | 0.1–0.2 |
| Creams and lotions | 1 | 1 | >0.1–1 | 0.05–0.5 |
| Polishes and enamels | — | 10 | — | 0.2–1 |
| Polish and enamel removers | — | 5 | — | 0.03–0.5 |
| Other nail care | — | 11 | — | 0.1–0.2 |
| **Personal hygiene** | | | | |
| Underarm deodorants | 1 | 3 | >0.1–1 | 0.05–0.5 |
| Douches | — | — | — | 0.1–0.8 |
| Other personal hygiene | — | 8 | — | 0.1 |
| **Shaving** | | | | |
| Aftershave lotions | 3 | 14 | ≤0.1–1 | 0.03–3 |
| Preshave lotions | 1 | — | >0.1–1 | — |
| Shaving cream | — | 1 | — | 0.1–0.3 |
| Other shaving | 1 | 2 | >0.1–1 | 0.4–1 |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 5 | 38 | >0.1–1 | 0.05–3 |
| Depilatories | — | — | — | 1 |
| Face and neck skin care | 8** | 29 | ≤0.1–1** | 0.001–6 |
| Body and hand skin care | | 32 | | 0.1–5 |
| Body and hand sprays | — | — | — | 2 |
| Foot powders and sprays | — | — | — | 0.5 |
| Moisturizers | 22 | 98 | ≤0.1–5 | 0.1–3 |
| Night skin care | 14 | 29 | >0.1–1 | 0.08–2 |
| Paste masks/mud packs | 1 | 24 | ≤0.1 | 0.1–5 |
| Skin fresheners | 2 | 15 | >0.1–1 | 0.01–3 |
| Other skin care | 5 | 46 | ≤0.1–1 | 0.1–5 |
| **Suntan** | | | | |
| Suntan gels, creams, liquids, and sprays | 5 | 10 | >0.1–1 | 0.1–2 |
| Indoor tanning | — | 2 | — | 0.1–2 |
| Other suntan | 2 | 10 | >0.1–1 | 0.5 |
| **Total uses/ranges for Panthenol** | **284** | **1538** | **≤0.1–25** | **0.00005–6** |
| | *Pantothenic Acid* | | | |
| **Eye makeup** | | | | |
| Mascara | — | — | — | 0.001–0.01 |
| Other eye makeup | — | 1 | — | — |
| **Makeup** | | | | |
| Face powders | — | — | — | 0.001 |
| Foundations | — | — | — | 0.002 |
| **Shaving** | | | | |
| Aftershave lotions | — | — | — | 0.001 |
| Shaving cream | — | — | — | 0.00001 |
| **Skin Care** | | | | |
| Moisturizers | — | 1 | — | 0.003 |
| Other skin care | — | 1 | — | 0.001 |
| **Total uses/ranges for Pantothenic Acid** | **—** | **3** | **—** | **0.00001–0.01** |

*Includes two non-aerosol hair sprays.
**These categories were combined originally, but are now separate.

Ebner, F., A. Heller, F. Rippke, and I. Tausch. 2002. Topical use dexpanthenol in skin disorders. *Am. J. Clin. Dermatol*. 3:427–433.

Egger, S. F., V. Huber-Spitzy, E. Alzner, et al. 1999. Corneal wound healing after superficial foreign body injury: Vitamin A and dexpanthenol versus a calf blood extract. A randomized double-blind study. *Ophthalmologica* 213:246.

Elder, R. L. 1987. Final Report on the Safety Assessment of Panthenol and Pantothenic Acid. *J. Am. Coll. Toxicol*. 6:139–162.

Gehring, W., and M. Gloor. 2000. Effect of topically applied dexpanthenol on epidermal barrier function and stratum corneum hydration. Results of a human in vivo study." *Arzneimittelforschung*. 50:659–663.

Gottschalck, T. E., and G. N. McEwen, Jr., eds. 2004. *International cosmetic ingredient dictionary and handbook.* 10th ed., vol. 2. Washington, DC: CTFA.

Hemmer, W., R. Bracun, S. Wolf-Abdolvahab, M. Focke, M. Gotz, and R. Jarisch. 1997. Maintenance of hand eczema by oral pantothenic acid in a patient sensitized to dexpanthenol. *Contact Dermatitis* 37:51.

Jeanmougin, M., J. R. Manciet, J. P. Moulin, P. Blanc, A. Pons, and J. Civatte. 1988. Contact allergy to dexpanthenol in sunscreens. *Contact Dermatitis* 18:240.

Klocker, N., T. Verse, and P. Rudolph. 2003. The protective effect of dexpanthenol in nasal sprays. First results of cytotoxic and ciliary-toxic studies in vitro. *Larynogorhinootologie* 82:177–182.

Lokkevik, E., E. Skovlund, J. B. Reitan, E. Hannisdal, and G. Tanum. 1996. Skin treatment with bepanthen cream versus no cream during radiotherapy—a randomized controlled trial. *Acta Oncol*. 35:1021–1026.

Pugliese, P. T., J. C. Farina, and Y. Chautems. 1995. Efficacy of dexpanthenol in wound healing: A double-blind assessment of excised wound tissue by ultrasound and histologic examination. *Nouv. Dermatol*. 14:130.

Romitti, P., and N. Romitti. 2002. Dexpanthenol cream significantly improves mucocutaneous side effects associated with isotretinoin therapy. *Pediatr. Dermatol*. 19:368.

Schalock, P. C., F. J. Storrs, and L. Morrison. 2000. Contact urticaria from panthenol in hair conditioner. *Contact Dermatitis* 43:223.

Schepler, H., J. Kessler, and B. Hartmann. 2002. Abuse of silver-nitrate solution for planing periorbital folds. *Burns* 28:90–91.

Schmid-Grendelmeier, P., M. Wyss, and P. Elsner. 1995. Contact allergy to dexpanthenol. A report of 7 cases and review of the literature. *Dermatosen in Beruf und Umwelt* 43:175–178.

Schulze-Dirks, A., and P.J. Frosch. 1988. Contact allergy to dexpanthenol. *Hautarzt* 39:375–377.

Slyshenkov, V. S., M. Rakowska, A. G. Moiseenok, et al. 1995. Pantothenic acid and its derivatives protect tumor cells against lipid peroxidation. *Free Radical Biol. Med*. 19:767–772.

Slyshenkov, V. S., M. Rakowska, and L. Wojtczak. 1996. Protective effect of pantothenic acid and related compounds against permeabilitzation of Ehrlich ascites tumor cells by digitonin. *Acta Biochim. Polon*. 43:407–410.

Slyshenkov, V. S., S. N. Omelyanchik, A. G. Moiseenok, R. V. Trebukhina, and L. Wojtczak. 1998. Pantothenol protects rats against some deleterious effects of gamma radiation. *Free Radical Biol. Med*. 24:894–899.

Stables, G. I., and S. M. Wilkinson. 1998. Allergic contact dermatitis due to panthenol. *Contact Dermatitis* 38:236–237.

Weiser, H., and G. Erlemann. 1988. Acceleration of superficial wound healing by panthenol zinc oxide. *Cosmet. Toiletries* 103:79–81, 84.

## *p*-PHENYLENEDIAMINE

A safety assessment on *p*-Phenylenediamine was published in 1985 in which the CIR Expert Panel acknowledged that *p*-Phenylenediamine is a known sensitizer and some persons may be sensitized under intended conditions of use. For those persons not sensitized, the Expert Panel concluded that *p*-Phenylenediamine is safe as a hair dye ingredient at the current concentrations of use (Elder 1985). Studies available since that safety assessment was completed, along with updated information regarding uses and use concentrations, were considered by the CIR Expert Panel. The Panel determined to not reopen the safety assessment.

Although the safety of *p*-Phenylenediamine as a hair dye ingredient was reaffirmed, the Panel did agree with FDA that other uses of this dye are unapproved. The Panel expressed particular concern over the practice of combining *p*-Phenylenediamine with henna (so-called dark henna) for use in temporary tattoos—*p*-Phenylenediamine is a known sensitizer, highly inappropriate for such use as evidenced by reports of severe adverse skin reactions to dark henna temporary tattoos. The Panel urged users to report adverse reactions to the FDA (for more information, see the FDA website at http://www.cfsan.fda.gov/~dms/costatt.html). The Panel also will work with the Consumer Federation of America to help the public understand the need to avoid using such unapproved and potentially dangerous products.

The CIR Expert Panel also reviewed hair dye epidemiology data. In 1993, an International Agency for Research on Cancer (IARC) working group evaluated 78 epidemiology literature citations and concluded that "personal use of hair colourants cannot be evaluated as to its carcinogenicity" and that occupation as a hairdresser or barber entails exposures that are probably carcinogenic" (IARC 1993). The IARC report did not distinguish between personal use of oxidative/permanent versus direct hair dyes, or distinguish among the multiple chemical exposures in addition to hair dyes to which a hairdresser or barber might be exposed.

In 2003, an updated review of the available epidemiology literature was prepared (Helzlsouer et al. 2003). This review considered 83 literature citations available since the IARC review. The authors found insufficient evidence to support a causal association between personal hair dye use and a variety of tumors and cancers.

In considering this information, the CIR Expert Panel agreed that the available epidemiology studies are insufficient to conclude there is a causal relationship between hair dye use and cancer and other end points described in the Helzlsouer et al. (2003) review.

The Panel also stated that use of direct hair dyes, although not the focus in all investigations, appear to have little evidence of an association with adverse events as reported in epidemiology studies. However, direct hair dyes are a diverse group of chemicals and the determination of safety may hinge on other safety test data.

*p*-Phenylenediamine was used in 500 hair-coloring products in 1981, at concentrations of $\leq$0.1% to 5%. In 2002, *p*-Phenylenediamine was used in 1178 hair-coloring products and in 2 nail care products. Use concentration data provided in 2004 indicated use at concentrations of $\leq$0014% to $\leq$4% in hair coloring products. The 2004 use concentration data were provided by CTFA (CTFA 2004).

Available use and concentration information is shown in Table 16. The most recent information now constitutes the present practices of use.

**TABLE 16**
Historical and current cosmetic product uses and concentrations for *p*-Phenylenediamine

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2004 concentrations (CTFA 2005) % |
|---|---|---|---|---|
| **Hair coloring** | | | | |
| Dyes and colors | 493 | 1167 | ≤0.1–5 | ≤4 |
| Tints | 7 | 9 | ≤0.1 | — |
| Rinses | — | — | — | ≤0.0014 |
| Color sprays | — | 1 | — | — |
| Lighteners with color | — | 1 | — | — |
| **Nail care** | | | | |
| Basecoats and undercoats | — | 2 | — | — |
| **Total uses/ranges for *p*-Phenylenediamine** | **500** | **1180** | **≤0.1–5** | **≤0.0014–≤4** |

## REFERENCES


Abdulla, K. A., and N. M. Davidson. 1996. A woman who collapsed after painting her soles. *Lancet* 348:658.

Adams, R. M., and H. I. Maibach. 1985. A five-year study of cosmetic reactions. *J. Am. Acad. Dermatol*. 13:1062–1069.

Ahn, H. J., and W. S. Lee. 2002. An ultrastructural study of hair fiber damage and restoration following treatment with permanent hair dye. *Int. J. Dermatol*. 41:88–92.

Armstrong, D. K., A. B. Jones, H. R. Smith, J. S. Ross, I. R. White, R. J. Rycroft, and J. P. McFadden. 1999. Occupational sensitization to p-phenylenediamine: A 17-year review. *Contact Dermatitis* 41:348–349.

Ashar, A. 2003. Acute angioedema in paraphenylenediamine poisoning. *J. Pak. Med. Assoc.* 53:120–122.

Ashraf, W., S. Dawling, and L. J. Farrow. 1994. Systematic paraphenylenediamine (PPD) poisoning: A case report and review. *Hum. Exp. Toxicol.* 13:167–170.

Averbukh, Z., D. Modai, and Y. Leonov. 1989. Rhabdomyolysis and acute renal failure induced by paraphenylenediamine. *Hum. Toxicol.* 8:345–348.

Bajaj, A. K., S. C. Gupta, A. K. Chatterjee, K. G. Singh, S. Basu, and A. Kant. 1996. Hair dye depigmentation. *Contact Dermatitis* 35:56–57.

Bajaj, A. K., A. Misra, K. Misra, and S. Rastogi. 2000. The azo dye solvent yellow 3 produces depigmentation. *Contact Dermatitis* 42:237–238.

Bajaj, A. K., R. K. Pandey, K. Misra, A. K. Chatterji, A. Tiwari, and S. Basu. 1998. Contact depigmentation caused by an azo dye in alta. *Contact Dermatitis* 38:189–193.

Balato, N., G. Lembo, C. Patruno, and F. Ayala. 1990. Prevalence of textile dye contact sensitization. *Contact Dermatitis* 23:111–112.

Batiste-Aletorn, M., N. Xamena, A. Creus, and R. Marcos. 1995. Genotoxicity testing of five compounds in three *Drosophila* short-term somatic assays. *Mutat. Res.* 34:161–167.

Berne, B., A. Bostrom, A. F. Grahnen, and M. Tammela. 1996. Adverse effects of cosmetics and toiletries reported to the Swedish Medical Products Agency, 1989–1994. *Contact Dermatitis* 34:359–362.

Bork, K. 1993. Allergic contact dermatitis on a violinist's neck from paraphenylenediamine in a chin rest stain. *Contact Dermatitis* 28:250–251.

Bracher, M., C. Faller, W. Grotsch, R. Marshall, and J. Spengler. 1990. Studies on the potential mutagenicity of *p*-phenylenediamine in oxidative hair dye mixtures. *Mutat. Res.* 241:313–323.

Brancaccio, R., and D.E. Cohen. 1995. Contact leukoderma secondary to paraphenylenediamine. *Contact Dermatitis* 32:313.

Brancaccio, R. R., L. H. Brown, Y. T. Chang, J. P. Fogelman, E. A. Mafong, and D. E. Cohen. 2002. Identification and quantification of paraphenylenediamine in a temporary black henna tattoo. *Am. J. Contact Dermat* 13:15–18.

Brasch, J., T. Henseler, and W. Aberer. 1994. Reproducibility of patch tests. A multicenter study of synchronous left-versus right-sided patch tests by the German contact Dermatitis Research Group. *J. Am. Acad. Dermatol.* 31:584–591.

Broeckx, W., A. Blondeel, A. Dooms-Goossens, and G. Achten. 1987. Cosmetic intolerance. *Contact Dermatitis* 16:189–194.

Bronaugh, R. L., and E. R. Congdon. 1984. Percutaneous absorption of hair dyes: Correlation with partition coefficients. *J. Invest. Dermatol.* 83:124–127.

Bronaugh, R. L., C. D. Roberts, and J. L. McCoy. 1994. Dose-response relationship in skin sensitization. *Food Chem. Toxicol.* 32:113–117.

Brown, J. H., M. G. McGeown, B. Conway, and C. M. Hill. 1987. Chronic renal failure associated with topical application of paraphenylenediamine. *Br. Med. J. (Clin. Res. Ed.)* 294:155.

Bruckner-Tuderman, L., A. Konig, and U. W. Schnyder. 1992. Patch test results of the dermatology clinic Zurich in 1989: Personal computer-aided statistical evaluation. *Dermatology* 184:29–33.

Burnett, C. M., and E. I. Goldenthal. 1988. Multigeneration reproduction and carcinogenicity studies in Sprague-Dawley rats exposed topically to oxidative hair-colouring formulations containing *p*-phenylenediamine and other aromatic amines. *Food Chem. Toxicol.* 26:467–474.

Calzavara-Pinton, P., R. Capezzera, C. Zane, A. Brezzi, G. Pasolini, A. Ubiali, and F. Tacchetti. 2002. Lymphomatoid allergic contact dermatitis from paraphenylenediaimine. *Contact Dermatitis* 47:173–174.

Chung, W. H., Y. C. Chang, L. J. Yang, S. I. Hung, W. R. Wong, J. Y. Lin, and H. L. Chan. 2002. Clinicopathologic features of skin reactions to temporary tattoos and analysis of possible causes. *Arch Dermatol.* 138:88–92.

Chung, K. T., C. A. Murdock, S. E. Stevens Jr., Y. S. Li, C. I. Wei, T. S. Huang, and M. W. Chou. 1995. Mutagenicity and toxicity studies of *p*-phenylenediamine and its derivatives. *Toxicol. Lett.* 81:23–32.

Chung, K. T., C. A. Murdock, Y. Zhou, et al. 1996. Effects of the nitro-group on the mutagenicity and toxicity of some benzamines. *Environ. Mol. Mutagen.* 27:67–74.

Chung, W. H., C. M. Wang, and H. S. Hong. 2001. Allergic contact dermatitis to temporary tattoos with positive para-phenylenediamine reactions: Report of four cases. *Int. J. Dermatol.* 40:754–756.

Correa, A., et al. 1998. Final Report to Clairol, Inc.: Hair Dye Use Questionnaires: Development and Reliability Assessment. Unpublished data submitted by Clairol, Inc.[17]

Correia, S., and F. M. Brandao. 1986. Contact dermatitis of the feet. *Derm. Beruf. Umwelt*. 34:102–106.


[17] Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2004. Use concentration data on *p*-phenylenediamine from industry survey. Unpublished data submitted by CTFA, February 6, 2004 (1 page).[17]

Cronin, E. 1985. Clinical patterns of hand eczema in women. *Contact Dermatitis* 13:153–161.

De la Cuadra Oyanguren, J., A. Marquina Vila, A. Martorell Aragones, J. Sanz Ortega, and A. Aliaga Boniche. 1989. Contact allergic dermatitis in childhood: 1972–1987. *Ann. Esp. Pediatr.* 30:363–366.

Devos, S. A., and P. G. Van Der Valk. 2001. The risk of active sensitization to PPD. *Contact Dermatitis* 44:273–275.

Dickel, H., O. Kuss, A. Schmidt, and T.L. Diepgen. 2002. Occupational relevance of positive standard patch-test results in employed persons with an initial report of an occupational skin disease. *Int. Arch Occup. Environ. Health* 75:423–434.

Dickel, H., J. S. Taylor, P. Evey, and H. F. Merk. 2000. Delayed readings of a standard screening patch test tray: Frequency of lost, found, and persistent reactions. *Am. J. Contact Dermatitis* 11:213–217.

Dickel, H., J. S. Taylor, P. Evey, and H. F. Merk. 2001. Comparison of patch test results with a standard series among white and black racial groups. *Am. J. Contact Dermatitis* 12:77–82.

Dossou, K. G., C. Sicard, G. Kalopissis, D. Reymond, and H. Schaefer. 1985. Method for assessment of experimental allergy in guinea-pigs adapted to cosmetic ingredients. *Contact Dermatitis* 13:226–234.

Edwards, E. K. Jr., and E. K. Edwards. 1984. Contact urticaria and allergic contact dermatitis caused by paraphenylenediamine. *Cutis* 34:87–88.

E. I. DuPont de Nemours & Company. 1990. Acute oral neurotoxicity studies of para, meta, and ortho-phenylenediamine in rats with cover letter dated 9/17/90. OTS 40-9036454.

E. I. DuPont de Nemours & Company.1992. Subchronic oral neurotoxicity study of ortho-, meta-, and para-phenylenediamine in rats with attachments and cover letter dated 6/30/92. OTS 40-9236508.

Elder, R. L. 1985. Final report on the safety assessment of p-phenylenediamine. *J. Am. Coll. Toxicol.* 4:203–266.

Emmons, W. W., and J. G. Jr. Marks. 1985. Immediate and delayed reactions to cosmetic ingredients. *Contact Dermatitis* 13:258–265.

Estlander, T. 1988. Allergic dermatoses and respiratory diseases from reactive dyes. *Contact Dermatitis* 18:290–297.

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.

Fan, W. X., and B. Zhao. 1990. Study on Chinese common allergens of contact dermatitis. *Derm. Beruf. Umwelt* 38:158–161.

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

Fowler, J. F., Jr. 1987. Occupational dermatitis from stamp pad ink. *Contact Dermatitis* 16:38.

Frosch, P. J., D. Burrows, and J. G. Camarasa, et al. 1993. Allergic reactions to a hairdressers' series: Results from 9 European centres. *Contact Dermatitis* 28:180–183.

Fuchs, T., and R. Wahl. 1992. Immediate reactions to rubber products. *Allergy Proc.* 13:61–66.

Fukunaga, T., R. Kawagoe, H. Hozumi, and T. Kanzaki. 1996. Contact anaphylaxis due to para-phenylenediamine. *Contact Dermatitis* 35:185–186.

Gagliardi, L., M. Ambroso, J. Mavro, F. Furno, and G. Discalzi. 1992. Exposure to p-phenylenediamine in hairdressing parlours. *Int. J. Cosmet. Sci.* 14:19–31.

Gago-Dominguez, M., J. E. Castelao, J. M. Yuan, M. C., Yu, and R. K. Ross. 2001. Use of permanent hair dyes and bladder-cancer risk. *Int. J. Cancer.* 91:575–579.

Gago-Dominguez, M., D. A. Bell, M. A. Watson, et al. 2003. Permanent hair dyes and bladder cancer: Risk modification by cytochrome P4501A2 and N-acetyltransferases 1 and 2. *Carcinogenesis.* 24:483–489.

Gallo, R., G. Ghigliotti, E. Cozzani, and S. Balestrero. 1999. Contact dermatitis from para-phenylenediamine used as a skin paint: A further case. *Contact Dermatitis* 40:57.

Gentile, J. M., G. J. Gentile, and M. J. Plewa. 1987. Mutagenicity of selected aniline derivatives to Salmonella following plant activation and mammalian hepatic activation. *Mutat. Res.* 188:185–196.

Goetz, N., P. Lasserre, P. Bore, and G. Kalopissis. 1988. Percutaneous absorption of *p*-phenylenediamine during an actual hair dyeing procedure. *Int. J. Cosmet. Sci.* 10:63–74.

Goh, C. L. 1992. Comparative study of TRUE test and Finn chamber patch test techniques in Singapore. *Contact Dermatitis* 27:84–89.

Goh, C. L., S. F. Kwok, and V. S. Rajan. 1984. Cross sensitivity in colour developers. *Contact Dermatitis* 10:280–285.

Goldberg, B. J., F. F. Herman, and I. Hirata. 1987. Systemic anaphylaxis due to an oxidation product of *p*-phenylenediamine in a hair dye. *Ann. Allergy.* 58:205–208.

Gonzalo, M. A., F. Revenga, F. Caravaca, and J. L. Pizarro. 1997. Epidemiologic study of contact dermatitis in hemodialysis patients. *J. Invest. Allergol. Clin. Immunol.* 7:20–23.

Goossens, A., M. H. Beck, E. Haneke, J. P. McFadden, S. Nolting, G. Durupt, and G. Ries. 1999. Adverse cutaneous reactions to cosmetic allergens. *Contact Dermatitis* 40:112–113.

Guerra, L., A. Tosti, and F. Bardazzi, et al. 1992b. Contact dermatitis in hairdressers: The Italian experience. *Contact Dermatitis* 26:101–107.

Guillot, J. P., and J. F. Gonnet. 1985. The epicutaneous maximization test. *Curr. Probl. Dermatol*. 14:220–247.

Gupta, V., V. Misra, R. Shanker, and P.N. Viswanathan. 1991. Effect of *p*-phenylenediamine on the activity of glutathione-*S*-transferase in guinea pig skin. *J. Toxicol. Cutaneous Ocul. Toxicol*. 10:187–194.

Hagiwara, A., S. Tamano, M. A. Shibata, M. Arai, and H. Tsuda. 1990. Lack of modifying effects of *p*-phenylenediamine on induction of gamma-glutamyl transpeptidase-positive foci in a medium-term bioassay system using F344 rats. *Toxicol. Lett.* 52:261–268.

Helzlsouer, K., D. Rollison, and S. Pinney. 2003. Association between hair dye use and health outcomes: Review of the literature published since 1992. Unpublished data submitted by Clairol, Inc. 107 pages.[17]

Hsu, T. S., M. D. Davis, R. el-Azhary, J. F. Corbett, and L. E. Gibson. 2001. Beard dermatitis due to para-phenylenediamine use in Arabic men. *J. Am. Acad. Dermatol.* 44:867–869.

Imaida, K., Y. Ishihara, O. Nishio, K. Nakanishi, and N. Ito. 1983. Carcinogenicity and toxicity tests on *p*-phenylenediamine in F344 rats. *Toxicol. Lett.* 16:259–269.

International Agency for Research on Cancer (IARC). 1978. Some aromatic amines and related nitro compounds-hair dyes, coloring agents, and miscellaneous industrial chemicals. *IARC Monographs on the Carcinogenic Risks to Humans,* Lyon: IARC. Vol. 16, 125–142.

International Agency for Research on Cancer (IARC). 1987. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. *IARC Monographs on the Carcinogenic Risks to Humans,* Vol 16, supplement 7, 70–142 Lyon: IARC.

International Agency for Research on Cancer (IARC). 1993. Occupational exposures of hairdressers and barbers and personal use of hair colourants; some hair dyes, cosmetic colourants, industrial dyestuffs and aromatic amines. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol 57, 43–118, Lyon, France: IARC.

International Agency for Research on Cancer (IARC). 2004. Personal communication to determine basis for 1987 IARC conclusion on *p*-Phenylenediamine. Electronic mail dated January 30, 2004.[17]

Ioannou, Y. M., and H. B. Matthews. 1985. *p*-Phenylenediamine dihydrochloride: Comparative disposition in male and female rats and mice. *J. Toxicol. Environ. Health* 16:299–313.

Jappe, U., B. M. Hausen, and D. Petzoldt. 2001. Erythema-multifore-like eruption and depigmentation following allergic contact dermatitis from a paint-on

henna tattoo, due to para-phenylenediamine contact hypersensitivity. *Contact Dermatitis* 45:249–250.

Kalish, R. S., and J. A. Wood. 1995. Sensitization of mice to paraphenylenediamine and structurally-related compounds adjuvant effects of vitamin A supplementation. *Contact Dermatitis* 33:407–413.

Katsarou, A., M. Armenaka, I. Ale, V. Koufou, and D. Kalogeromitros. 1999. Frequency of immediate reactions to the European standard series. *Contact Dermatitis* 41:276–279.

Katsarou, A., B. Koufou, K. Takou, D. Kalogeromitros, G. Papanayiotou, and A. Vareltzidis. 1995. Patch test results in hairdressers with contact dermatitis in Greece. *Contact Dermatitis* 33:347–348.

Kawakubo, Y., H. F. Merk, T. Al Masaoudi, S. Sieben, and B. Blomeke. 2000. *N*-acetylation of paraphenylenediamine in human skin and keratinocytes. *J. Pharmacol. Exp. Ther.* 292:150–155.

Keystone Aniline Corporation. 1999. *Technical Guide and Formulary*. Chicago: Keystone Aniline Corporation.

Kim, H. O., R. C. Wester, J. A. McMaster, D. A. Bucks, and H. I. Maibach. 1987. Skin absorption from patch test systems. *Contact Dermatitis* 17:178–180.

Kokelj, F., and A. Cantarutti. 1986. Contact dermatitis in leg ulcers. *Contact Dermatitis* 15:47–49.

Krasteva, M., A. Cristaudo, B. Hall, et al. 2002. Contact sensitivity to hair dyes can be detected by the consumer open test. *Eur. J. Dermatol.* 12:322–326.

Kulkarni, P. D., J. B. Herron, W. B. Moores, and H. B. Hahn. 2001. What is your diagnosis? Allergic contact dermatitis to paraphenylenediamine in a temporary henna tattoo. *Cutis* 68:187, 229–230.

Kvelland, I. 1984. An investigation of the mutagenic activity of four hair dyes in bacteriophage T4D. *Hereditas.* 100:295–298.

Läuchli, S., S. Lautenschlager, and S. Lauchi. 2001. Contact dermatitis after temporary henna tattoos—An increasing phenomenon. *Swiss Med. Wkly.* 131:199–202.

Le Coz, C. J., C. Lefebvre, F. Keller, and E. Grosshans. 2000. Allergic contact dermatitis caused by skin painting (pseudotattooing) with black henna, a mixture of henna and *p*-phenylenediamine and its derivatives. *Arch. Dermatol.* 136:1515–1517.

Lee, H., L.-Y. Perng, S.-J. Shiow, M.-Y. Chou, M.-C. Chou, and J.-Y. Lin. 1986. Induction of sister chromatid exchange in cultured Chinese hamster cells by short-term treatment with hair dye components. *J. Chin. Biochem. Soc.* 15:34–38.

Leino, T., L. Tammilehto, M. Hytonen, E. Sala, H. Paakkulainen, and L. Kanerva. 1998. Occupational skin and respiratory diseases among hairdressers. *Scan. J. Work Environ. Health* 24:398–406.

Leino, T., T. Estlander, and L. Kanerva. 1998a. Occupational allergic dermatoses in hairdressers. *Contact Dermatitis* 38:166–167.

LeVine, M. J. 1984. Idiopathic photodermatitis with a positive paraphenylenediamine photopatch test. *Arch. Dermatol.* 120:1488–1490.

Li, L. F., and J. Wang. 2002. Contact hypersensitivity in hand dermatitis. *Contact Dermatitis* 47:206–209.

Li, Q., H. Inagaki, and M. Minami. 1996. Evaluation of cross-sensitization among dye-intermediate agents using a modified lymphocyte transformation test. *Arch. Toxicol*. 70:414–419.

Lisboa, C., M. A. Barros, and A. Azenha. 1994. Contact dermatitis from textile dyes. *Contact Dermatitis* 31:9–10.

Lodi, A., L. L. Mancini, M. Ambonati, A. Coassini, G. Ravanelli, and C. Crosti. 2000. Epidemiology of occupational contact dermatitis in a North Italian population. *Eur. J. Dermatol.* 10:128–132.

Mainka, E. 1983. Contact dermatitis in metallurgy workers. *Przegl Dermatol.* 70:65–68.

Marcoux, D., P. M. Coutureo-Trudel, G. Riboulet-Delmas, and D. Sasseville. 2002. Sensitization to para-phenylenediamine from a streetside temporary tattoo. *Pediatr. Dermatol.* 19:498–502.

Marks, J. G., Jr., D. V. Belsito, V. A. Deleo, et al. 1998. North American Contact Dermatitis Group patch test results for the detection of delayed-type hypersensitivity to topical allergens. *J. Am. Acad. Dermatol.* 38:911–918.

Marks, J. G., Jr., D. V. Belsito, V. A. Deleo, et al. 2000. North American Contact Dermatitis Group patch-test results, 1996–1998. *Arch. Dermatol.* 136:272–273.

Massone, L., A. Anonide, V. Isola, and S. Borghi. 1991. 2 cases of multiple azo dye sensitization. *Contact Dermatitis* 24:60–62.

Mathur, A. K., B. N. Gupta, S. Narang, et al. 1990. Biochemical and histopathological changes following dermal exposure to paraphenylene diamine in guinea pigs. *J. Appl. Toxicol.* 10:383–386.

Matsunaga, K., K. Hosokawa, M. Suzuki, Y. Arima, and R. Hayakawa. 1988. Occupational allergic contact Dermatitis in beauticians. *Contact Dermatitis* 18:94–96.

Maurer, T., and R. Hess. 1989. The maximization test for skin sensitization potential—updating the standard protocol and validation of a modified protocol. *Food Chem. Toxicol*. 27:807–811.

Maurer, T., E. G. Weirich, and R. Hess. 1984. Predictive contact allergenicity influence of the animal strain used. *Toxicology* 31:217–222.

McFadden, J. P., S. H. Wakelin, D. B. Halloway, and D. A. Basketter. 1998. The effect of patch duration on the elicitation of para-phenylenediamine contact allergy. *Contact Dermatitis* 39:79–81.

Ministry of Health, Labor and Welfare (MHLW). June 29, 2001. 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.

Mohamed, M., and R. Nixon. 2000. Severe allergic contact dermatitis induced by paraphenylenediamine in paint-on temporary "tattoos." *Austr. J. Dermatol.* 41:168–171.

Nakagawa, M., and K. Kawai. 1996. Multiple azo disperse dye sensitization mainly due to group sensitizations to azo dyes. *Contact Dermatitis* 34:6–11.

Neri, I., E. Guareschi, F. Savoia, and A. Patrizi. 2002. Childhood allergic contact dermatitis from henna tattoo. *Pediatr. Dermatol.* 19:503–505.

Nethercott, J. R., M. MacPherson, B. C. Choi, and P. Nixon. 1986. Contact dermatitis in hairdressers. *Contact Dermatitis* 14:73–79.

Nikkels, A. F., F. Henry, and G. E. Pierard. 2000. Allergic reactions to decorative skin paintings. *J. Eur. Acad. Dermatol. Venereol.* 15:140–142.

O'Hagan, A. H., and E. A. Bingham. 2001. Cellist's finger dermatitis. *Contact Dermatitis* 45:319.

Önder, M., C. A. Atahan, P. Oztas, and M. O. Oztas. 2001. Temporary henna tattoo reactions in children. *Int. J. Dermatol*. 40:577–579.

Pegas, J. R., P. R. Criado, R. F. Criado, C. Vasconcellos, and M. C. Pires. 2002. Allergic contact dermatitis to temporary tattoo by *p*-phenylenediamine. *J. Investig. Allergol. Clin. Immunol*. 12:62–64.

Pepe, R. C., J. A. Wenninger, and G. N. McEwen, Jr., eds. 2002. *International Cosmetic Ingredient Dictionary and Handbook*, 9th ed. Washington, DC: CTFA, 1238.

Picardo, M., C. Cannistraci, A. Cristaudo, C. De Luca, and B. Santucci. 1990. Study on cross-reactivity to the para group. *Dermatologica* 181:104–108.

Picardo, M., C. Zompeta, M. Grandinetti, F. Ameglio, B. Santucci, A. Gaffioni, and S. Passi. 1996. Paraphenylenediamine, a contact allergen, induces oxidative stress in normal human keratinocytes in culture. *Br. J. Dermatol*. 134:681–685.

Pope, R. W., J. C. Hill, and M. G. Blaskis. 1995. Contact urticaria to the M17 protective mask. *Mill. Med.* 160:536–537.

Rebandel, P., and E. Rudzki. 1995. Occupational allergy to p-phenylenediamine in milk testers. *Contact Dermatitis* 33:138.

Rademaker, M. 1998. Occupational contact dermatitis among New Zealand farmers. 1998. *Aus. J. Dermatol.* 39:164–167.

Rojanapo, W., P. Kupradinum, A. Tepsuwan, S. Chutimatewin, and M. Tanyakaset. 1986. Carcinogenicity of an oxidation product of *p*-phenylenediamine. *Carcinogenesis* 7:1997–2002.

Romaguera, C., F. Grimalt, and J. Vilaplana. 1988. Shoe contact dermatitis. *Contact Dermatitis* 18:178.

Saha, M., and C. R. Srinivas. 1993. Footwear dermatitis possibly due to paraphenylenediamine in socks. *Contact Dermatitis* 28:295.

Sahoo, B., S. Handa, K. Penchallaiah, and N. Kumar. 2000. Contact anaphylaxis due to hair dye. *Contact Dermatitis* 43:244.

Sakai, H., T. Tsukamoto, M. Yamamoto, et al. 2002. Distinction of carcinogens from mutagens by induction of liver cell foci in a model for detection of initiation activity. *Cancer Lett*. 188:33–38.

Santucci, B., A. Cristaudo, C. Cannistraci, A. Amantea, and M. Picardo. 1994. Hypertrophic allergic contact dermatitis from hair dye. *Contact Dermatitis* 31:169–171.

Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP). 2002. *Opinion of the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers Concerning* p-*Phenylenediamine*. Brussels: SCCNFP.

Seidenari, S., L. Mantovani, B. M. Manzini, and M. Pignatti. 1997. Cross-sensitizations between azo dyes and para-amino compound: A study of 236 azo-dye-sensitive subjects. *Contact Dermatitis* 36:91–96.

Sertoli, A., S. Francalanci, M. C. Acciai, and M. Gola. 1999. Epidemiological survey of contact dermatitis in Italy (1984–1993) by GIRDA (Gruppo Italiano Ricerca Dermatiti da Contatto e Ambientali). *Am. J. Contact Dermat*. 10:18–30.

Shah, M., F. M. Lewis, and D. J. Gawrodger. 1997. Patch testing children and adolescents: Five years experience and follow-up. *J. Am. Acad. Dermatol.* 37:964–968.

Shapiro, M., C. Mowad, and W. D. James. 2001. Contact dermatitis due to printer's ink in a milk industry employee: Case report and review of the allergen paraphenylenediamine. *Am. J. Contact Dermat.* 12:109–112.

Sharma, V. K., S. K. Mandal, G. Sethuraman, and N. A. Bakshi. 1999. Paraphenylenediamine-induced lichenoid eruptions *Contact Dermatitis* 41:40–41.

Shigematsu, T., N. Ozawa, and H. Nakayama. 1988. In vitro study of the cross-sensitivity of hair dye using hapten-specific lymphocytes. *Contact Dermatitis* 19:30–35.

Sidbury, R., and F. J. Storrs. 2000. Pruritic eruption at the site of a temporary tattoo. *Am. J. Contact Dermatitis* 11:182–183.

Sieben, S., Y. Kawakubo, T. Al Masaoudi, H. F. Merk, and B. Blomeke. 2002. Delayed-type hypersensitivity reaction to paraphenylenediamine is mediated by 2 different pathways of antigen recognition by specific alphabeta human T-cell clones. *J. Allergy Clin. Immunol*. 109:1005–1011.

Simpson-Dent, S. L., S. H. Hunt, S. C. Davidson, and S. H. Wakelin. 2001. Tattoo dermatitis from primary sensitization to clothing dyes. *Contact Dermatitis* 45:248.

Smith, H. R., S. H. Wakelin, and R. J. Rycroft. 1999. Azo dyes as allergens in carbonless copy paper manufacturing. *Contact Dermatitis* 40:214–215.

Soler-Niedziela, L., X. Shi, J. Nath, and T. Ong. 1991. Studies on three structurally related phenylenediamines with the mouse micronucleus assay system. *Mutat. Res.* 259:43–48.

Søsted, H., T. Agner, K. E. Andersen, and T. Menne. 2002. 55 cases of allergic reactions to hair dye: A descriptive, consumer complaint-based study. *Contact Dermatitis* 47:299–303.

Steiling, W., J. Kreutz, and H. Hofer. 2001. Percutaneous penetration/dermal absorption of hair dyes in vitro. *Toxicol. In Vitro* 15:565–570.

Storrs, F. J., L. E. Rosenthal, R. M. Adams, et al. 1989. Prevalence and relevance of allergic reactions in patients patch tested in North America—1984 to 1985. *J. Am. Acad. Dermatol.* 20:1038–1045.

Stransky, L., and M. Krasteva. 1989. Changing patterns of contact sensitivity in Sofia. *Derm. Beruf. Umwelt*. 37:214–216.

Sutthipisal, N., J. P. McFadden, and E. Cronin. 1993. Sensitization in atopic and non-atopic hairdressers with hand eczema. *Contact Dermatitis* 29:206–209.

Taylor, J. S., H. I. Maibach, A. A. Fisher, and W. F. Bergfeld. 1993. Contact leukoderma associated with the use of hair colors. *Cutis* 52:273–280.

Temesvari, E. 1984. Contact urticaria from paraphenylenediamine. *Contact Dermatitis* 11:125.

Thune, P. 1984. Contact and photocontact allergy to sunscreens. *Photodermatology* 1:5–9.

Tosti, A., M. Pazzaglia, and M. Bertazzoni. 2000. Contact allergy from temporary tattoos. *Arch. Dermatol.* 136:1061–1062.

Tosti, A., M. Pazzaglia, M. Corazza, and A. Virgili. 2000. Allergic contact dermatitis caused by mehindi. *Contact Dermatitis* 42:356.

Uter, W., H. Lessmann, J. Geier, D. Becker, T. Fuchs, and G. Richter. 2002. The spectrum of allergic (cross)-sensitivity in clinical patch testing with 'paraamino' compounds. *Allergy* 57:319–322.

van Zuuren, E. J., and A. P. Lavrijsen. 2002. Allergic reactions and hypopigmentation due to temporary tattooing with henna. *Ned. Tijdschr. Geneeskd*. 146:1332–1335.

Vestey, J. P., P. K. Buxton, and J. A. Savin. 1985. Eyelash curler dermatitis. *Contact Dermatitis* 13:274–275.

Viswanathan, P. N., V. Gupta, and V. Misra. 1986. Studies on the dermal toxicity of *p*-phenylenediamine. *Int. J. Cosmet. Sci.* 7:213–218.

Wakelin, S. H., D. Creamer, R. J. Rycroft, I. R. White, and J. P. McFadden. 1998. Contact dermatitis from paraphenylenediamine used as a skin paint. *Contact Dermatitis* 39:92–93.

Wang, L. H., and S. J. Tsai. 2003. Simultaneous determination of oxidative hair dye *p*-phenylenediamine and its metabolites in human and rabbit biological fluids. *Anal. Biochem.* 312:201–207.

Warbrick, E. V., R. J. Dearman, L.J. Lea, D.A. Basketter, and I. Kimber. 1999. Local lymph node assay responses to paraphenylenediamine: intra and inter laboratory evaluations. *J. Appl. Toxicol.* 19:255–260.

Waters, M. D., H. B. Bergman, and S. Nesnow. 1988. The genetic toxicology of Gene-Tox non-carcinogens. *Mutat. Res.* 205:139–182.

Wolf, R., D. Wolf, H. Matz, and E. Orion. 2003. Cutaneous reactions to temporary tattoos. *Dermatol. Online* 9:3.

Wolfram, L. J., and H. I. Maibach. 1985. Percutaneous penetration of hair dyes. *Arch. Dermatol. Res.* 277:235–241.

Wong, G. A., and C. M. King. 2003. Immediate-type hypersensitivity and allergic contact dermatitis due to para-phenylenediamine in hair dye. *Contact Dermatitis* 48:166.

Xie, Z., R. Hayakawa, M. Sugiura, H. Kojima, H. Konishi, G. Ichihara, and Y. Takeuchi. 2000. Experimental study on skin sensitization potencies and cross-reactivities of hair-dye-related chemicals in guinea pigs. *Contact Dermatitis* 42:270–275.

Yabe, K., K. Saito, T. Murai, M.-A. Hara, and H. Watanabe. 1991. An experimental rhabdomyolysis due to paraphenylenediamine contained in hair dyes: Its effects on serum escaping enzymes (CPK, GOT, and GPT) and histopathological findings in the skeletal muscles. *Res. Pract. Forensic Med.* 34:109–116.

Yagi, H., A. M. el Hendi, A. Diab, and A. A. Elshikh. 1996. Paraphenylenediamine induced optic atrophy following hair dye poisoning. *Hum. Exp. Toxicol*. 15:617–618.

Yamada, K., S. Shirahata, and H. Murakami. 1985. DNA breakage by phenyl compounds. *Agric. Biol. Chem.* 49:1423–1428.

Yokozeki, H., M.-H. Wu, K. Sumi, et al. 2003. Th2 cytokines, IgE and mast cells play a crucial role in the induction of para-phenylenediamine-induced contact hypersensitivity in mice. *Clin. Exp. Immunol.* 132:385–392.

Zhang, Y., T. R. Holford, B. Leaderer, P. Boyle, S. H. Zahm, S. Flynn, G. Tallini, P. H. Owens, and T. Zheng. 2004. Hair-coloring product use and risk of non-hodgkins lymphoma: A population-based case-control study in Connecticut. *Am. J. Epidemiol*. 159:148–154.

Zhao, B., and W. X. Fan. 1991. Facial contact dermatitis. Pathogenetic factors in China. *Int. J. Dermatol.* 30:485–486.

Zheng, T., T. R. Holford, B. Leaderer, Y. Zhang, S. H. Zahm, S. Flynn, G. Tallini, B. Zhang, K. Zhou, P. H. Owens, Q. Lan, N. Rothman, and P. Boyle. 2004. Diet and nutrient intakes and risk of non-hodgkin's lymphoma in Connecticut women. *Am. J. Epidemiol.* 159:454–466.

## PHENYL TRIMETHICONE

In 1986, the CIR Expert Panel found that Phenyl Trimethicone is safe as a cosmetic ingredient in the present practices of use and concentration (Elder 1986). A review of the recent literature uncovered no new studies regarding Phenyl Trimethicone,

but the Panel did consider updated information regarding uses and use concentrations. The Panel determined to not reopen the safety assessment.

Phenyl Trimethicone uses have increased from 169 in 1981 to 279 in 2002, based on industry voluntary reports provided to FDA (Elder 1986; FDA 2002). An industry survey in 2003 indicated that use concentrations range from 0.0075% to 36% (CTFA 2004). The maximum value in that range is higher than the maximum use concentration of 5% reported in 1981 (Elder 1986). Table 17 presents the available use and concentration information for Phenyltrimethicone. The most recent information now represents the present practice of use and concentration.

The Panel considered the increased use concentrations in the context of the reproductive and developmental toxicity data in the original safety assessment. Phenyl Trimethicone was not teratogenic at 500 mg/kg/day in rats and rabbits. For a 70-kg person, this dose corresponds to 35 g/day. At the current maximum use in lipsticks and the amount of lipstick used in a typical day, a dose of Phenyl Trimethicone was estimated to be 10 mg/day. This dose was 3500× lower than the observable effect level.

## REFERENCES


Cosmetic, Toiletry, and Fragrance Association (CTFA). 2004. Concentration of use—phenyl trimethicone. Unpublished data submitted by CTFA on May 10, 2004. (2 pages).[18]

Elder, R. L. 1986. Final report on the safety assessment of Phenyl Trimethicone. *J. Am. Coll. Toxicol*. 5:353–371.

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


## PROPYLENE CARBONATE

A safety assessment of Propylene Carbonate was published in 1987 with the conclusion that it is safe as a cosmetic ingredient in the present practices of use and concentration (Elder 1987). Studies published since the last assessment were reviewed along with updated information concerning frequency of use and use concentrations. The CIR Expert Panel determined to not reopen the safety assessment.

Based on voluntary reports provided by industry to FDA, there were 295 reported uses in 1981 (Elder 1987) and 178 reported uses in 2002 (FDA 2002). Use concentrations from an industry survey (CTFA 2003) ranged from 0.003% to 6%, not very different from the use concentration range reported in 1981 of ≤0.1% to >5% (Elder 1987).

Table 18 presents the available use and concentration information for Propylene Carbonate. The most recent information constitutes present practices of use and concentration.

## REFERENCES


Barry, B. W., S. M. Harrison, and P. H. Dugard. 1985. Vapour and liquid diffusion of model penetrants through human skin; correlation with thermodynamic activity. *J. Pharm. Pharmacol.* 37:226–236.

Bushy Run Research Center. 1989. Propylene Carbonate: Nine-Day Aerosol Inhalation Study on Rats. Unpublished data. Project Report 51–633.[19]

Bushy Run Research Center. 1990. Chronic Dermal Oncogenicity Studies in C3H/HeJ Mice. Unpublished data. Project Report 52–527.[19]

Bushy Run Research Center. 1991. Propylene Carbonate: Fourteen-Week Aerosol Inhalation Study on Rats with Neurotoxicity Evaluation. Unpublished data. Project Report 52–637.[19]

Central Toxicology Laboratory. 2001. Jeffsol Propylene Carbonate-NF: Eye Irritation Study in Rabbits. Unpublished data. Report CTL/FB5863/REG/REPT.[19]

Chemische Werke Huls Ag. 1979. Mutagenitatsontersuchung von Propylencarbonat mit Hilfe des *Salmonella typhimurium*/ Mirosoman-Mutagentats-Tests nach Ames. Unpublished data. Report 41.[19]

Elder, R. L., ed. 1987. Final Report on the Safety Assessment of Propylene Carbonate. *J. Am. Coll. Toxicol.* 6(1):23–51.

Gottschalck, T. E., and G. N. McEwen, Jr., eds. 2004. *International Cosmetic Ingredient Dictionary and Handbook*, 10th ed., Vol. 2. Washington, DC: CTFA.

Kawanami, H., A. Sasaki, K. Matsui, and Y. Ikushima. 2003. A rapid and effective synthesis of propylene carbonate using a supercritical $CO_2$-ionic liquid system. *Chem. Commun.* 7:896–897.

Muzikar, J., T. Van de Goor, B. Gas, and E. Kenndler. 2001. Extension of the application range of UV-absorbing organic solvents in capillary electrophoresis by the use of contactless conductivity detector. *J. Chromatogr. A* 924:147–154.

Papciak, R. J., and V. T. Mallory. 1990. Acute Toxicological evaluation of propylene carbonate. *Acute Toxicity Data* 1:15–16.

Pharmakon Research International, Inc. 1986. Acute Dermal Toxicity Study in Rabbits. Unpublished data. Report PH 422-TX-006-86.[19]

Pharmakon Research International, Inc. 1986. Micronucleus Test OECD. Unpublished data. Report PH 309-TX-004-85.

Pharmakon Research International, Inc. 1988. Developmental Toxicity Study in Rats. Unpublished data. Report PH 328-TX-001-88.[19]

Pharmakon Research International, Inc. 1988. Dose-Range-Finding Developmental Toxicity Study in Rats. Unpublished data. Report PH-32DR-TX-001-87.[19]

Pharmakon Research Interantional, Inc. 1988. Dose-Range-Finding 28-Day Oral Toxicity Study in Rats. Unpublished data. Report PH-436-TX-001-87.[19]

Pharmakon Research International, Inc. 1989. Subchronic 90 Day Oral Toxicity Study in Rats. Unpublished data. Report PH-470-TX-001-88.[19]

Sutou, S. 1996. Achievements by CSGMT MMS: The collaborative study group fo rthe micronucleus test in mammalian Mutagenesis Study Group for the Environmental Mutagen Society of Japan. *Mutat. Res.* 340:151–174.

Ursin, C., C. M. Hansen, J. W. Van Dyk, P. O. Jensen, I. J. Christensen, and J. Ebbehoej. 1995. Permeability of comericial solvents through living human skin. *Am. Ind. Hyg. Assoc. J.* 56:651–660.

Yamada, Y., M. Nakahara, M. Kohno, M. Otsuka, and O. Takaiti. 1989. Metabolic fate of the new anti-ulcer drug enprostil in animals. 4th communication: Effect on hepatic drug metabolizing enzyme system in rats. *Arzneimittelforschung* 39:356–360.


## POLYVINYLPYRROLIDONE/VINYL ACETATE COPOLYMER

In 1983, the CIR Expert Panel concluded that this ingredient is safe as a cosmetic ingredient under the present practices of product and concentration use (Elder 1983). New studies available since that review have been considered by the Expert Panel,

[18] Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

[19] Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

**TABLE 17**
Historical and current cosmetic product uses and concentrations for Phenyl Trimethicone

| Product category | 1981 uses (Elder 1986) | 2002 uses (FDA 2002) | 1986 concentrations (Elder 1986) % | 2003 concentrations (CTFA 2004) % |
|---|---|---|---|---|
| **Baby Care** | 1* | — | >0.1–1* | — |
| **Bath** | | | | |
| Oils, tablets, and salts | 1 | 1 | >0.1–1 | — |
| Other bath | 2 | — | >1–5 | — |
| **Eye Makeup** | | | | |
| Eyeliners | — | 1 | — | 2–6 |
| Eye shadow | 1 | 77 | ≤0.1–5 | 4–13 |
| Eye lotions | — | — | — | 0.008–1 |
| Mascara | 1 | 1 | >0.1–1 | 0.1–0.4 |
| Other eye makeup | 1 | 4 | >0.1–1 | 6–15 |
| **Fragrances** | | | | |
| Colognes and toilet waters | — | — | — | 0.5 |
| Perfumes | — | 1 | — | — |
| Powders | — | 1 | — | — |
| Other fragrances | — | — | — | 0.5 |
| **Noncoloring hair care** | | | | |
| Conditioners | 10 | 8 | ≤0.1–5 | 0.3–2 |
| Sprays | 25 | 23 | ≤0.1–1 | 0.1–18 |
| Straighteners | 1 | — | >1–5 | — |
| Rinses | 1 | — | >0.1–1 | — |
| Shampoos | — | — | — | 1 |
| Tonics, dressings, etc. | 9 | 31 | ≤0.1–5 | 5–11 |
| Wave sets | 2 | — | >0.1–5 | — |
| Other noncoloring hair care | 1 | 7 | >0.1–1 | 0.5–2 |
| **Makeup** | | | | |
| Blushers | 11 | 1 | >1–5 | 2–15 |
| Face powders | 2 | 9 | >0.1–1 | 0.1–8 |
| Foundations | 2 | 17 | >1–5 | 2–22 |
| Leg and body paints | — | — | — | 2 |
| Lipsticks | 2 | 34 | >1–5 | 0.08–36 |
| Makeup bases | 2 | 8 | ≤0.1–5 | — |
| Rouges | — | 2 | — | — |
| Other makeup | — | 13 | — | 0.0075–22 |
| **Nail care** | | | | |
| Creams and lotions | — | — | — | 0.5 |
| Polishes and enamels | 7 | — | >0.1–1 | — |
| **Personal hygiene** | | | | |
| Underarm deodorants | — | 1 | — | — |
| Other personal hygiene | — | 1 | — | — |
| **Shaving** | | | | |
| Aftershave lotions | — | 1 | — | 0.5–2 |
| Preshave lotions | 6 | 1 | >0.1–5 | 2 |
| Other shaving | — | — | — | 0.5 |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | — | 4 | — | 2–4 |
| Face and neck skin care | 8** | 3 | ≤0.1–1** | 4–6 |
| Body and hand skin care | | 4 | | 0.2–18 |
| Moisturizers | 7 | 15 | ≤0.1–5 | 0.8–3 |
| Night skin care | 1 | | ≤0.1 | 2 |
| Other skin care | 1 | | >1–5 | 2 |
| **Suntan** | | | | |
| Suntan gels, creams, liquids and sprays | 6 | 2 | — | 0.5–9 |
| Indoor tanning | 1 | 8 | — | 0.2–5 |
| Other suntan | 1 | | >1–5 | 2 |
| **Total uses/ranges for Phenyl Trimethicone** | **113** | **279** | **≤0.1–5** | **0.0075–36** |

*Product categories within the group not given.

**These categories were combined originally, but are now separate.

**TABLE 18**
Current and historical uses and concentrations of Propylene Carbonate in cosmetics

| Product category | 1981 uses (Elder 1984) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1984) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| **Bath** | | | | |
| Oils, tablets and salts | 1 | 1 | >1–5 | — |
| **Eye makeup** | | | | |
| Eyebrow pencils | 6 | 6 | >1–5 | 0.3 |
| Eyeliners | 17 | 15 | >1–5 | 0.2–0.6 |
| Eye shadow | 42 | 10 | >0.1–5 | 0.4–1 |
| Eye lotions | 1 | — | >1–5 | — |
| Eye makeup remover | — | 3 | — | — |
| Mascara | 34 | 22 | >0.1–5 | 2–4 |
| Other eye makeup | 9 | 12 | >0.1–5 | 0.5 |
| **Fragrances** | | | | |
| Colognes and toilet waters | 5 | — | >1–5 | — |
| Perfumes | 4 | — | >1–5 | — |
| **Noncoloring hair care** | | | | |
| Conditioners | 1 | — | >1–5 | — |
| Tonics, dressings, etc. | — | 1 | — | — |
| **Hair Coloring** | | | | |
| Other hair coloring | 3 | 1 | >1–5 | — |
| **Makeup** | | | | |
| Blushers | 13 | 1 | ≤0.1–>5 | 1–2 |
| Face powders | 1 | — | >1–5 | 0.4 |
| Foundations | 11 | 3 | >0.1–5 | 0.6–2 |
| Rouges | — | — | — | 0.1 |
| Lipsticks | 95 | 35 | ≤0.1–>5 | 0.03–2 |
| Makeup bases | 13 | 4 | >0.1–1 | — |
| Makeup fixatives | 1 | 2 | >1–5 | — |
| Other makeup | 9 | 20 | >0.1–5 | 1 |
| **Nail care** | | | | |
| Creams and lotions | 1 | — | >1–5 | — |
| Polish and enamel | — | — | — | 0.003 |
| Polish and enamel removers | — | 6 | — | 1 |
| Other nail care | — | — | — | 4 |
| **Personal hygiene** | | | | |
| Underarm deodorants | — | 2 | — | 0.2–5 |
| Other personal hygiene | 4 | 26 | ≤0.1–>5 | — |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 9 | 1 | >1–5 | 0.1 |
| Face and neck skin care | 1* | — | >0.1–1* | — |
| Body and hand skin care | | — | | — |
| Moisturizers | 2 | 4 | >1–5 | 0.02–0.2 |
| Night skin care | 4 | 1 | >1–5 | — |
| Paste masks/mud packs | — | 1 | — | 0.3–2 |
| Skin fresheners | 1 | — | >0.1–1 | — |
| **Suntan preparations** | | | | |
| Suntan gels, creams, and liquids | 6 | 1 | >1–5 | 0.08–0.2 |
| Other suntan preparations | 1 | — | >1–5 | — |
| **Total uses/ranges for Propylene Carbonate** | **295** | **178** | **≤0.1–>5** | **0.003–5** |

*These categories were combined originally, but are now separate.

along with the most current information available on use and concentration. The Panel noted that most of the newly available data concern Vinyl Acetate. The Panel determined to not reopen this safety assessment.

As given in the 9th edition of the *International Cosmetic Ingredient Dictionary and Handbook*, the name of this ingredient has been changed to VP/VA Copolymer (Pepe et al. 2002).

Based on voluntary reports provided by industry to FDA, there were 114 reported uses of this ingredient in 1976 (Elder 1983) and 210 reported uses in 2002 (FDA 2002). Use concentrations from an industry survey (CTFA 2003) ranged from 0.3% to 68%, but these data were clarified to note that the product reported to contain 68% is no longer on the market. The actual current use concentration range is 0.3% to 12%, which is in the range of >0.1% to >50% reported in 1976 (Elder 1983).

Table 19 presents the available use and use concentration information. The most current data now represent the present practices of use.

The Panel acknowledged that inhalation of Vinyl Acetate is associated with nasopharyngeal carcinoma. The mechanism of action appears to be an irritant-hyperproliferative type which requires a threshold dose. Two factors suggest that threshold doses could not be achieved from inhalation of cosmetics. First, the VP/VA Copolymer is stable, even under adverse environmental conditions, so that there will be little, if any, Vinyl Acetate actually present, especially since the maximum use concentration is 12%. Second, 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 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, VP/VA Copolymers would not be respirable in formulation.

**TABLE 19**
Historical and current uses and use concentrations for VP/VA Copolymer

| Product category | 1976 uses (Elder 1983) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1983) % | 2003 use concentrations (CTFA 2003) % |
|---|---|---|---|---|
| **Eye makeup** | | | | |
| Eyeliner | — | — | — | 0.3 |
| Eye shadow | — | — | — | 2 |
| Mascara | 2 | 2 | >1–5 | 6–9 |
| Other eye makeup | — | 8 | — | — |
| **Noncoloring hair care** | | | | |
| Hair conditioners | 17 | 12 | >1–50 | 0.3 |
| Hair sprays | 27 | 26 | >0.1–10 | 2–4 |
| Permanent waves | 1 | — | >0.1–1 | — |
| Shampoos | 2 | 1 | >0.1–50 | 7 |
| Tonics, dressings, etc. | 6 | 87 | >0.1–25 | 4–12 |
| Wave sets | 50 | 12 | >0.1–>50 | 7 |
| Other noncoloring hair care | 4 | 52 | >5–25 | 8 |
| **Hair coloring** | | | | |
| Color sprays | — | 1 | — | 0.5 |
| Bleaches | 1 | 2 | >1–5 | — |
| **Makeup** | | | | |
| Foundations | — | — | — | 0.5 |
| Makeup fixatives | 1 | — | >0.1–1 | 4 |
| Other makeup | 1 | 4 | >0.1–1 | 2 |
| **Nail care** | | | | |
| Cuticle softeners | 1 | — | >1–5 | — |
| **Skin care** | | | | |
| Body and hand skin care | — | 1 | — | — |
| Paste masks/mud packs | — | 2 | — | 10 |
| Other skin care preparations | 1 | — | >1–5 | 68* |
| **Total uses/ranges of VP/VA Copolymer** | **114** | **210** | **>0.1–>50** | **0.3–12** |

*This product no longer is marketed, so this use concentration is not included in the total range.

## REFERENCES


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. 1994. Chronic toxicity and oncogenicity inhalation study with vinyl acetate in the rat and mouse. *Fundam. Appl. Toxicol*. 23:215–229.

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., T. R. Tyler, M. B. Vinegar, R. W. Rickard, F. M. Carpanini and T. Cascieri. 1994. Chronic toxicity and oncogenicity study with vinyl acetate in the rat: in utero exposure in drinking water. *Fundam. Appl. Toxicol*. 23:206–214.

Bogdanffy, M. S., and R. Valentine. 2003. Differentiating between local cytotoxicity, mitogenesis, and genotoxicity in carcinogen risk assessments: The case of vinyl acetate. *Toxicol. Lett.* 140–141:83–98.

Bowen, D. 1999. Unpublished information on hair spray particle size provided at the September 9, 1999 CIR Expert Panel meeting.[20]

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2002. Information regarding VA/Crotonates Copolymer. Unpublished data submitted by CTFA on November 19, 2002. (1 page.)[20]

CTFA. 2003. Concentrations of use VA/Crotonates Copolymer. Unpublished data submitted by CTFA on June 12, 2003. (1 page.)[20]

Deese, D. E., and R. E. Joyner. 1969. Vinyl acetate: A study of chronic human exposure. *Am. Indust. Hygiene Assoc. J.* 30:449–457.

Elder, R. L. 1983. Final report on the safety assessment of vinyl polyvinylpyrrolidone/vinyl acetate copolymer. *J. Am. Coll. Toxicol*. 2:141–159.

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 for Research on Cancer (IARC). 1995. Vinyl acetate. *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*. 63:443–466.

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

Kuykendall, J. R., and M. S. Bogdanffy. 1992. Reaction kinetics of DNA-histone crosslinking by vinyl acetate and acetaldehyde. *Carcinogenesis*. 13(11):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. N.Y. Acad. 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, DC: CTFA.

Simon, P., J. G. Filser, and H. M. Bolt. 1985. Metabolism and pharmacokinetics of vinyl acetate. *Arch. Toxicol*. 57(3):191–195.


[20]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

## SAFFLOWER OIL

In 1985 the CIR Expert Panel concluded that this ingredient is safe as a cosmetic ingredient 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 not to reopen this safety assessment.

The terminology for this ingredient in the *International Cosmetic Ingredient Dictionary and Handbook* (Gottshcalck and McEwen 2004) has changed. Safflower Oil is currently Carthamus Tinctorius (Safflower) Seed Oil.

Carthamus Tinctorius (Safflower) Seed Oil was used in 94 products in 1981, based on voluntary reports provided to FDA by industry, and use concentrations ranged from less than 0.1% to greater than 50% (Elder 1985). In 2002 there were 142 uses (FDA 2002) and according to an industry survey the current range of use concentrations is 0.00005% to 84% (CTFA 2004).

Table 20 presents the available use information. The most recent information is now considered to be the present practices of use and concentration.

## REFERENCES


Cheng, J. L., M. Futkuchi, K. Ogawa, et al. 2003. Dose response study of conjugated fatty acid derived from safflower oil on mammary and colon carcinogenesis pretreated with 7,12-dimethylbenz[a]anthracene (DMBA) and 1,2-dimethylhydrazine (DMH) in female Sprague-Dawley rats. *Cancer Lett.* 196:161–168.

Chiang T.-A., P.-F. Wu, and Y.-C. Ko. 1999. Identification of carcinogens in cooking oil fumes. *Environ. Res.* 81:18–22.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2004. Ingredient Use Data—*Carthamus Tincoriums* (Safflower) Seed Oil. Unpublished data submitted by CTFA.[21]

Elder, R. L. Final Report on the Safety Assessment of Safflower Oil. *J. Am. Coll. Toxicol.* 4:171–197.

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

Gottschalk,T. E., and G. N. McEwen, Jr., eds. 2004. *International Cosmetic Ingredient Dictionary and Handbook*, 10th ed. Washington, DC: CTFA.

National Toxicology Program (NTP). 1994. Comparative Toxicology Studies of Corn Oil, Safflower Oil, and Tricaprylin (CAS Nos. 8001-30-7, 800-23-8, and 538-23-8) in male F344/N rats as vehicles for gavage. Final study report. PB 95103958.

Okuno M., T. Tanaka, C. Komaki, et al. 1998. Suppressive effect of low amounts of safflower and perilla oils on diethylnitrosamine-induced hepatocarcinogenesis in male F344 rats. *Nutr. Cancer* 30:186–193.


## SODIUM BORATE AND BORIC ACID

In 1983, the CIR Expert Panel concluded that Sodium Borate and Boric Acid, at concentrations $\leq$5%, are safe as cosmetic ingredients when used as currently recommended, but that cosmetic formulations containing free Sodium Borate or Boric Acid should not be used on infant or injured skin (Elder 1983). Studies available since that safety assessment was completed, along

[21]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

**TABLE 20**
Historical and current cosmetic product uses and concentrations for Carthamus Tinctorius (Safflower) Seed Oil

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2003 concentrations (CTFA 2004) % |
|---|---|---|---|---|
| **Baby care** | | | | |
| Lotions, oils, powders, and creams | — | — | — | 10 |
| **Bath** | | | | |
| Oils, tablets, and salts | 1 | — | >0.1–1 | 7 |
| Other bath | 2 | 1 | >0.1–1 | — |
| **Eye makeup** | | | | |
| Eye makeup remover | 1 | — | >10–25 | 2 |
| Mascara | — | — | — | 1 |
| Other eye makeup | 1 | 5 | >0.1–1 | 6 |
| **Fragrances** | | | | |
| Other fragrances | — | 1 | — | 5 |
| **Noncoloring hair care** | | | | |
| Conditioners | — | 15 | — | — |
| Sprays/aerosol fixatives | 1 | 2 | >5–10 | — |
| Rinses | — | 1 | — | — |
| Shampoos | — | 5 | — | — |
| Tonics, dressings, etc. | — | 5 | — | 0.00005–27 |
| **Hair coloring** | | | | |
| Other hair coloring | — | — | — | 1 |
| **Makeup** | | | | |
| Blushers | — | — | — | 2 |
| Foundations | 6 | 2 | >0.1–5 | 0.02–27 |
| Lipsticks | 4 | 18 | ≤0.1–5 | 0.1–60 |
| Makeup bases | 5 | 3 | — | — |
| Other makeup | 3 | 1 | >1–5 | — |
| **Nail care** | | | | |
| Creams and lotions | — | 1 | — | — |
| Other nail care | — | — | — | 84 |
| **Shaving** | | | | |
| Shaving cream | — | — | — | 0.01 |
| **Skin Care** | | | | |
| Cleansing creams, lotions, etc. | 7 | 3 | ≤0.1–10 | 0.001–5 |
| Face and neck skin care | 15* | 4 | ≤0.1–50* | 0.5–8 |
| Body and hand skin care | | 16 | | 0.3–4 |
| Foot powders and sprays | — | — | — | — |
| Moisturizers | 28 | 17 | ≤0.1– >50 | 0.2–20 |
| Night skin care | 3 | 5 | >1–50 | — |
| Paste masks/mud packs | 1 | 3 | >5–10 | 72 |
| Skin fresheners | 1 | 1 | >0.1–1 | — |
| Wrinkle smoothers** | 1 | — | >25–50 | — |
| Other | 7 | 16 | ≤0.1– >50 | 0.03 |
| **Suntan products** | | | | |
| Suntan gels, creams, liquids and sprays | 7 | 16 | >0.1–>50 | 0.1 |
| Indoor tanning preparations | — | 1 | — | — |
| **Total uses/ranges for Carthamus Tinctorius (Safflower) Oil** | **94** | **142** | **≤0.1–>50** | **0.00005–84** |

*These categories were combined in 1981, but since have been separated.
**No longer a cosmetic product category.

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.

**Sodium Borate** was used in 488 products in 1981, based on voluntary reports provided to FDA by industry; use concentrations ranged from less than 0.1% to greater than 50% (Elder 1983). In 2002 there were 280 uses (FDA 2002) and according to an industry survey the current range of use concentrations is 0.1% to 3% (CTFA 2002).

**Boric Acid** was used in 142 ingredients in 1981, based on voluntary reports provided to FDA by industry, and use concentrations ranged from less than 0.1% to greater than 50% (Elder 1985). In 2002 there were 77 uses (FDA 2002) and according to an industry survey the current range of use concentrations is 0.1% to 2% (CTFA 2002).

Table 21 presents the available usage and use concentration information as a function of cosmetic product category for both ingredients.

Significant among the new studies considered by the CIR Expert Panel are those on the reproductive and developmental toxicity of Boric Acid. Under the auspices of the National Toxicology Program, Fail et al. (1991) reported results of a reproductive assessment by continuous breeding protocol in which Boric Acid administered to rats in their feed was determined to be a reproductive toxicant. The NOAEL was suggested to be 110 mg/kg day$^{-1}$ and the LOAEL was 598 mg/kg day$^{-1}$. Price et al. (1997) reported results of another rat feeding study with a NOEAL of 10 mg/kg day$^{-1}$ and a LOEAL of 13 mg/kg day$^{-1}$ for decreased fetal body weight per litter. Yoshizaki et al. (1999) reported that an oral study using rats resulted in a NOAEL of 50 mg/kg day$^{-1}$ and a LOAEL of 150 mg/kg day$^{-1}$ for reduced sperm counts and the same NOAEL and LOAEL values for reduced implants and viable embryos.

The CIR Expert Panel considered that these findings do not suggest any reason for concern in the context of current use concentrations and the low dermal absorption through intact skin. These findings reinforce the Panel's prior determination that these ingredients should not be used on damaged skin, i.e., skin in which the barrier function has been compromised by disease or injury.

## REFERENCES


Astier, A., F. Baud, and A. Fournier. 1988. Toxicokinetics of boron after an acute poisoning (translated from the French). *J. Pharm. Clin*. 7(special issue II):57–62.

Ban, Y., M. Naya, T. Nishimura, M. Kaneto, K. Kishi, T. Inoue, H. Yoshizaki, and Y. Ooshima. 2001. Collaborative study on rat sperm motion analysis using CellSoft Series 4000 semen analyzer. *J. Toxicol. Sci.* 26:9–24.

Benson, W. H., W. J. Birge, and H. W. Dorough. 1984. Absence of mutagenic activity of sodium borate (borax) and boric acid in the *Salmonella typhimurium* preincubation test. *Environ. Toxicol. Chem*. 3:209–214.

Chapin, R. E., and W. W. Ku. 1994. The reproductive toxicity of boric acid. *Environ. Health Perspect.* 102:87–91.

Chapin, R. E., W. W. Ku, M. A. Kenney, and H. McCoy. 1998. The effects of dietary boric acid on bone strength in rats. *Biol. Trace Elem. Res.* 66:395–399.

Cherrington, J. W., and N. Chernoff. 2002. Periods of vertebral column sensitivity to boric acid treatment in CD-1 mice in utero. *Reprod. Toxicol.* 16:237–243.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2002. Use concentrations of Boric Acid and Sodium Borate as a function of product category–results of industry survey. Unpublished data submitted by CTFA.[22]

Dieter, M. P. 1994. Toxicity and Carcinogenicity Studies of Boric Acid in Male and Female B6C3F1 Mice. *Environ. Health Perspect.*, 102:93–97.

Fail, P. A., J. D. George, J. C. Seely, T. B. Grizzle, and J. J. Heindel. 1991. Reproductive toxicity of boric acid in Swiss (CD-1) mice: Assessment using the continuous breeding protocol. *Fundam. Appl. Toxicol.* 17:225–239.

Fisher, R. S., and J. C. Middleton. 1984. Dermatitis following ingestion of diuretics and boric acid. *J. Am. Acad. Dermatol*. 11:146–147.

Fukuda, R., M. Hirode, I. Mori, F. Chatani, H. Morishima, and H. Mayahara. 2000. Collaborative work to evaluate toxicity on male reproductive organs by repeated dose studies in rats 24). Testicular toxicity of boric acid after 2- and 4-week administration periods. *J. Toxicol. Sci.* 25(special issue):233–239.

Garabrant, D. H., L. Bernstein, J. M. Peters, and T. J. Smith. 1984. Respiratory and eye irritation from boron oxide and boric acid dusts. *J. Occup. Med.* 26:584–586.

Garabrant, D. H., L. Bernstein, J. M. Peters, T. J. Smith, and W. E. Wright. 1985. Respiratory effects of borax dust. *Br. J. Ind. Med*. 42:831–837.

Heindel, J. J., C. J. Price, and B. A. Schwetz. 1994. Developmental toxicity of boric acid in mice, rats, and rabbits. *Environ. Health Perspect*. 102(suppl. 7):107–112.

Hu, X., D. H. Wegman, E. A. Eisen, and S. R. Woskie. 1993. Application of an event marker in the occupational epidemiologic study of acute irritant symptoms. *Epidemiology* 4:266–270.

Hu, X., D. H. Wegman, E. A. Eisen, S. R. Woskie, and R. G. Smith. 1992. Dose related acute irritant symptom responses to occupational exposure to sodium borate dusts. *Br. J. Ind. Med.* 49:706–713.

Ishii, Y., N. Fujizuka, T. Takahashi, K. Shimizu, A. Tuchida, S. Yano, T. Naruse, and T. Chishiro. 1993. A fatal case of acute boric acid poisoning. *J. Toxicol. Clin. Toxicol.* 31:345–352.

Ku, W. W., R. E. Chapin, R. F. Moseman, R. E. Brink, K. D. Pierce, and K. Y. Adams. 1991. Tissue disposition of boron in male Fischer rats. *Toxicol. Appl. Pharmacol.* 111:145–151.

Ku, W. W., R. E. Chapin, R. N. Wine, and B. C. Gladen. 1993a. Testicular toxicity of boric acid (BA): Relationship of dose to lesion development and recovery in the F344 rat. *Reprod. Toxicol.* 7:305–319.

Ku, W. W., L. M. Shih, and R. E. Chapin. 1993. The effects of boric acid (BA) on testicular cells in culture. *Reprod. Toxicol.* 7:321–331.

Kudo, S., H. Tanase, M. Yamasaki, M. Nakao, Y. Miyata, K. Tsuru, and S. Imai. 2000. Collaborative work to evaluate toxicity on male reproductive organs by repeated dose studies in rats 23). A comparative 2- and 4-week repeated oral dose testicular toxicity study of boric acid in rats. *J. Toxicol. Sciences* 25 (special issue):223–232.

Landolph, J. R. 1985. Cytotoxicity and negligible genotoxicity of borax and borax ores to cultured mammalian cells. *Am. J. Indust. Med.* 7:31-44.

Linden, C. H., A. H. Hall, K. W. Kulig, and B. H. Rumack. 1986. Acute ingestions of boric-acid. *J. Toxicol. Clin. Toxicol.* 24:269–280.

Linder, R. E., L. F. Strader, and G. L. Rehnberg. 1990. Effect of acute exposure to boric acid on the male reproductive system of the rat. *J. Toxicol. Environ. Health*. 31:133–146.

Linder, R. E., L. F. Strader, V. L. Slott, and J. D. Suarez. 1992. Endpoints of spermatotoxicity in the rat after short duration exposures to fourteen reproductive toxicants. *Reprod. Toxicol.* 6:491–505.

Miyazaki, T., M. Yashiki, Y. Iwasaki, T. Kojima, H. Ito, and A. Yoshida. 1992. A case of death from boric acid poisoning (translated from Japanese). *Res. Pract. Forensic Med*. 35:173–176.


[22] Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

**TABLE 21**
Historical and current uses and use concentrations for Sodium Borate and Boric Acid

| Product category | 1981 uses (Elder 1983) | 2002 uses (FDA 2002) | 1981 use concentrations (Elder 1983) % | 2002 use concentrations (CTFA 2002) % |
|---|---|---|---|---|
| | | *Sodium Borate* | | |
| **Baby care** | | | | |
| Lotions, oils, powders, creams | 1 | — | 0.1–1 | — |
| **Bath** | | | | |
| Soaps and detergents | 1 | 1 | >0–0.1 | 20[a] |
| Bath oils, tablets, salts | 3 | — | 1–50 | — |
| Bubble baths | 10 | — | 10–50 | — |
| **Eye makeup** | | | | |
| Eyeliner | 14 | 1 | 0.1–5 | — |
| Eye shadow | — | — | — | 0.2 |
| Eye lotion | 2 | — | 0.1–1 | — |
| Eye makeup remover | 5 | 2 | >0–5 | — |
| Mascara | 24 | 12 | 0.1–10 | 0.6 |
| Other eye makeup | 4 | 1 | 0.1–1 | 2 |
| **Fragrances** | | | | |
| Other fragrances | 4 | 1 | >0–1 | — |
| **Noncoloring Hair Care** | | | | |
| Conditioners | 3 | 2 | 0.1–1 | 0.6 |
| Sprays | 1 | — | 1–5 | — |
| Straighteners | 2 | — | 1–5 | — |
| Permanent waves | 16 | 5 | 0.1–10 | — |
| Shampoos | 2 | 1 | 0.1–1 | — |
| Tonics, dressings, etc. | 13 | 7 | >0–5 | — |
| Wave sets | 3 | — | >0–1 | — |
| Other hair care | 3 | 1 | 0.1–10 | — |
| **Hair coloring** | | | | |
| Other hair coloring | 3 | — | 0.1–1 | — |
| **Makeup** | | | | |
| Blushers | 2 | 2 | 0.1–1 | 0.2 |
| Face powders | — | 1 | — | — |
| Foundations | 4 | 3 | 0.1–1 | 0.2–0.5 |
| Lipstick | 1 | — | 0.1–1 | — |
| Makeup bases | 19 | 15 | 0.1–5 | — |
| Other makeup | 1 | — | 0.1–1 | 1 |
| **Nail care** | | | | |
| Cuticle softeners | — | 1 | — | — |
| Nail creams and lotions | 2 | — | 0.1–1 | — |
| **Oral hygiene** | | | | |
| Dentifrices | — | 3 | — | — |
| Mouthwashes and breath fresheners | — | 1 | — | — |
| **Personal hygiene** | | | | |
| Underarm deodorants | 2 | — | >0–1 | — |
| Other personal hygiene | 8 | 6 | 5–>50 | 0.1 |
| **Shaving** | | | | |
| Aftershave lotions | 2 | — | >0–0.1 | — |
| Shaving cream | 4 | 8 | 0.1–5 | — |
| Other shaving | 1 | 1 | 0.1–1 | — |

**TABLE 21**
Historical and current uses and use concentrations for Sodium Borate and Boric Acid *(Continued)*

| Product category | 1981 uses (Elder 1983) | 2002 uses (FDA 2002) | 1981 use concentrations (Elder 1983) % | 2002 use concentrations (CTFA 2002) % |
|---|---|---|---|---|
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 144 | 68 | >0–5 | 0.4–1 |
| Depilatories | 1 | — | 0.1–1 | — |
| Face and neck skin care | 71[b] | 11 | >0–5[b] | — |
| Body and hand skin care | | 32 | | 0.4–0.8 |
| Moisturizers | 47 | 31 | >0–5 | 0.3–1 |
| Night skin care | 37 | 22 | >0–1 | 0.4–0.9 |
| Paste masks/mud packs | 3 | 6 | 1–5 | 0.2–3 |
| Fresheners | 12 | 4 | >0–1 | 0.3 |
| Other skin care | 1 | 23 | >0–>50 | 0.6–0.8 |
| Skin lighteners[c] | 1 | NA[c] | 0.1–1 | NA[c] |
| Hormone products[c] | 2 | NA[c] | 0.1–5 | NA[c] |
| Wrinkle smoothing[c] | 4 | NA[c] | 0.1–5 | NA[c] |
| **Suntan** | | | | |
| Suntan gels, creams, liquids | 5 | 5 | 0.1–1 | 0.4 |
| Other suntan | — | 3 | — | — |
| **Total uses/ranges for Sodium Borate** | **488** | **280** | **>0–>50** | **0.1–3** |
| | | *Boric Acid* | | |
| **Baby Care** | | | | |
| Baby shampoos | 1 | — | 0.1–1 | — |
| **Bath** | | | | |
| Soaps and detergents | 1 | — | 1–5 | |
| Oils, tablets, and salts | 1 | 1 | 0.1–1 | — |
| Bubble baths | — | 1 | — | — |
| **Eye makeup** | | | | |
| Eye lotion | 1 | — | 1–5 | — |
| Eye makeup remover | 3 | 4 | 0.1–5 | — |
| **Fragrances** | | | | |
| Powders | 13 | 7 | 0.1–5 | — |
| Other fragrances | 1 | — | 0.1–1 | — |
| **Noncoloring hair care** | | | | |
| Conditioners | — | 1 | — | 2 |
| Permanent waves | 13 | 5 | 0.1–5 | — |
| Rinses | 1 | — | 1–5 | — |
| Shampoos | 13 | 8 | 0.1–5 | — |
| Tonics, dressings, etc. | 3 | 1 | >0–1 | — |
| Wave sets | 2 | 3 | >0–5 | — |
| Other hair care | 3 | — | 0.1–5 | — |
| **Hair coloring** | | | | |
| Coloring rinses | 14 | — | 1–10 | — |
| Bleaches | — | 3 | — | — |
| Other hair coloring | 3 | — | 0.1–5 | — |
| **Makeup** | | | | |
| Blushers | 2 | — | 0.1–1 | — |
| Face powders | 1 | 1 | 0.1–1 | — |
| Rouges | 1 | — | 0.1–1 | — |
| Makeup fixatives | 2 | 2 | 1–5 | — |

*(Continued on next page)*

**TABLE 21**
Historical and current uses and use concentrations for Sodium Borate and Boric Acid *(Continued)*

| Product category | 1981 uses (Elder 1983) | 2002 uses (FDA 2002) | 1981 use concentrations (Elder 1983) % | 2002 use concentrations (CTFA 2002) % |
|---|---|---|---|---|
| **Oral hygiene** | | | | |
| Mouthwashes and breath fresheners | 5 | — | >0–5 | — |
| **Personal hygiene** | | | | |
| Underarm deodorants | 5 | 2 | 1–10 | — |
| Douches | 5 | 1 | >50 | 10[c] |
| Other personal hygiene | 1 | 2 | 0.1–1 | — |
| **Shaving** | | | | |
| Aftershave lotions | 5 | 5 | >0–5 | 0.4 |
| Preshave lotions | 1 | — | >0–0.1 | — |
| Shaving cream | 6 | 4 | 0.1–5 | 0.1–1 |
| Other shaving | 1 | 1 | 0.1–1 | — |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 4 | 2 | 0.1–5 | — |
| Face and neck skin care | 5[b] | — | 0.1–5[b] | — |
| Body and hand skin care | | 9 | | — |
| Foot powders and sprays | — | 1 | — | — |
| Moisturizers | 4 | 2 | 0.1–5 | 0.5 |
| Night skin care | 1 | 1 | 0.1–1 | — |
| Paste masks/mud packs | 3 | 3 | 0.1–5 | — |
| Skin fresheners | 17 | 6 | >0–5 | — |
| Other skin care | — | 1 | — | — |
| **Total uses/ranges of Boric Acid** | **142** | **77** | **>0–>50** | **0.1–2** |

[a]Diluted to about 0.3% Sodium Borate during use.
[b]These categories were combined in 1981 but are now separate.
[c]No longer considered as cosmetic product categories.
[d]Powder dissolved in water to produce a solution of about 0.1% Boric Acid before use.


Moore, J. A., and an Expert Scientific Committee. 1997. An assessment of boric acid and borax using the IEHR (Institute for Evaluating Health Risks) evaluative process for assessing human developmental and reproductive toxicity of agents. *Reprod. Toxicol*. 11:123–160.

Murray, F. J. 1998. A comparative review of the pharmacokinetics of boric acid in rodents and humans. *Biol. Trace Elem. Res.* 66:331–341.

Nartosky, M. G., J. E. Schmid, J. E., Andrews, and R. J. Kavlock. 1998. Effects of boric acid on axial skeletal development in rats. *Biol. Trace Elem. Res*. 66:373–394.

O'Sullivan, K., and M. Taylor. 1983. Chronic boric acid poisoning in infants. *Arch. Dis. Child.* 58:737–739.

Pahl, M. V., B. D. Culver, P. L. Strong, F. J. Murray, and N. D. Vaziri. 2001. The effect of pregnancy on renal clearance of boron in humans: A study based on normal dietary intake of boron. *Toxicol. Sci.* 60:252–256.

Price, C. J., M. C. Marr, C. B. Myers, J. J. Heindel, and B. A. Schwetz. 1996. Developmental toxicity of boric acid (BORA) in rabbits. *Fundam. Appl. Toxicol*. 34:176–187.

Price, C. J., P. L. Strong, M. C. Marr, C. B. Myers, and F. J. Murray. 1996. Developmental toxicity NOAEL and postnatal recovery in rats fed boric acid during gestation. *J. Am. Coll. Toxicol.* 14:179–193.

Price, C. J., P. L. Strong, F. J. Murray, and M. M. Goldberg. 1997. Blood boron concentrations in pregnant rats fed boric acid throughout gestation. *Reprod. Toxicol*. 11:833–842.

Restuccio, A., M. E. Mortensen, and M. T. Kelley. 1992. Fatal ingestion of boric acid in an adult. *Am. J. Emerg. Med.*10:545–547.

Schillinger, B. M., M. Berstein, L. A. Goldberg, and A. R. Shalita. 1982. Boric acid poisoning. *J. Am. Acad. Dermatol.* 7:667–673.

Schou, J. S., J. A. Jansen, and B. Aggerbeck. 1984. Human pharmacokinetics and safety of boric acid. *Arch. Toxicol. Suppl*. 7:232–235.

Siegel, E. 1986. Boric-acid toxicity. *Pediatr. Clin. N. Am.* 33:363–368.

Siegel, E., and S. Wason. 1986. Boric acid toxicity. *Pediatr. Clin. N. Am.* 33:363–367.

Stüttgen, G., T. Siebel, and B. Aggerbeck. 1982. Absorption of boric acid through human skin depending on the type of vehicle. *Arch. Dermatol. Res.* 272:21–29.

Sylvain, I. C., J. P. Berry, and P. Galle. 1998. Ultrastructural apoptotic lesions induced in rat thymocytes after borax ingestion. *Anticancer Res*. 18:2455–2461.

Treinen, K. A., and R. E. Chapin. 1991. Development of testicular lesions in F344 rats after treatment with boric acid. *Toxicol. Appl. Pharmacol.* 107:325–335.

Vaziri, N. D., F. Oveisi, B. D. Culver, M. V. Pahl, M. E., Andersen, P. L. Strong, and F. J. Murray. 2001. The effect of pregnancy on renal clearance of boron in rats given boric acid orally. *Toxicol. Sci.* 60:257–263.

Wester, R. C., X. Hui, H. I. Maibach, K. Bell, M. J. Schell, D. J. Northington, P. Strong, and B. D. Culver. 1998. In vivo percutaneous absorption of boron as boric acid, borax, and disodium octaborate tetrahydrate in humans: A summary. *Biol. Trace Elem. Res*. 66:101–109.

Wester, R. C., T. Hartway, H. I. Maibach, M. J. Schell, D. J. Northington, B. D. Culver, and P. L. Strong. 1998. In vitro percutaneous absorption of boron

as boric acid, borax, and disodium octaborate tetrahydrate in human skin: A summary. *Biol. Trace Elem. Res*. 66:111–120.

Yoshizaki, H., Y. Izumi, C. Hirayama, A. Fujimoto, H. Kandori, T. Sugitani, and Y. Ooshima. 1999. Availability of sperm examination for male reproductive toxicities in rats treated with boric acid. *J. Toxicol. Sci.* 24:199–208.

## SODIUM DEHYDROACETATE AND DEHYDROACETIC ACID

A safety assessment of Sodium Dehydroacetate and Dehydroacetic Acid was published in 1985 with the conclusion that these ingredients are safe as cosmetic ingredients in the present practices of use and concentration (Elder 1985). Studies available since that safety assessment was completed, along with updated information regarding uses and use concentrations were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

**Sodium Dehydroacetate** was used in 260 products in 1981, based on voluntary reports provided to FDA by industry; use concentrations ranged from less than 0.1% to 1% (Elder 1985). In 2002 there were 325 uses (FDA 2002) and according to an industry survey the current range of use concentrations is 0.00003% to 0.5% (CTFA 2002).

**Dehydroacetic Acid** was used in 139 products in 1981, based on voluntary reports provided to FDA by industry; use concentrations ranged from less than 0.1% to 1% (Elder 1985). In 2002 there were 88 uses (FDA 2002) and according to an industry survey the current range of use concentrations is 0.007% to 0.7% (CTFA 2002).

Table 22 presents the available use and concentration information. The most recent information now constitutes the present practices of use.

## REFERENCES

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2003. Use concentration data on Sodium Dehydroacetate and Dehydroacetic Acid from industry survey. Unpublished data submitted by CTFA, October, 2003. (1 page.)[23]

De Groot, A. C., J. W. Weyland, J. D. Bos, and B. A. Jagtman. 1986. Contact allergy to preservatives I. *Contact Dermatitis* 14:120–122.

Elder, R. L., ed. 1985. Final report on the safety assessment of Sodium Dehydroacetate and Dehydroacetic Acid. *J. Am. Coll. Toxicol.* 4:123–159.

Food and Drug Administration (FDA). 2002. Food additives permitted for direct addition to food for human consumption. *Code of Federal Regulations* 21CFR172.130:30–31.

Fujita, H., and M. Sasaki. 1986. Mutagenicity test of food additives with *Salmonella Typhimurium* TA97a and TA102. *Kenkyu Nenpo-Tokyo-Toritsu Eisei Kenkyusho* 37:447–452.

Gazzaniga, A., M. E. Sangalli, F. Giordano, U. Conte, A. Semenzato, and A. Bettero. 1994. Controlled release of dehydroacetic acid sodium salt for the stability improvement of cosmetic formulations. *Int. J. Cosmet. Sci.* 16:105–112.

Hasegawa, R., Y. Nakaji, Y. Kurokawa, and M. Tobe. 1989. Acute toxicity tests on 113 environmental chemicals. *Sci. Rep. Res. Inst. Tohoku Univ. Ser. C Med*. 36:10–16.

[23] Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

Hayashi, M. M. Kishi, T. Sofuni, and M. Ishidate. 1988. Micronucleus tests in mice on 39 food additives and eight miscellaneous chemicals. *Food Chem. Toxicol*. 26:487–500.

Ishidata, M., T. Sofuni, W. A. Yoshika, M. Hayashi, T. Nohmi, M. Sawada, and A. Matsuoka. 1984. Primary mutagenicity screening of food additives currently used in Japan. *Food Chem. Toxicol*. 22:623–636.

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

Sugihara, N., K. Shimomichi, and K. Furuno. 1997. Cytotoxicity of food preservatives in cultured rat hepatocytes loaded with linolenic acid. *Toxicology*. 120(1):29–36.

Tanaka, S., K. Kawashima, S. Nakaura, S. Djajalaksana, and A. Takanaka. 1988. Studies on the teratogenic potential of sodium dehydroacetate in rats. *Bull. Natl. Inst. Hyg. Sci. (Tokyo)*. 0(106):54–61.

Tomei, F., S. Iavicoli, A. Iavicoli, B. Papaleo, and T.P. Baccolo. 1995. Liver damage in pharmaceutical industry workers. *Arch. Environ. Health*. 50:293–297.

Uchida, O., K. Naito, K. Yasuhara, et al. 1985. Studies on the acute oral toxicity of dehydroacetic-acid sorbic-acid and their combination compound in rats. *Bull. Natl. Inst. Hyg. Sci. (Tokyo)*. 0(103):166–171.

Uchida, O., T. Ochiai, K. Naito, K. Yasuhara, K. Takada, T. Furuya, K. Kobayashi, Y. Ikeda, and M. J. Tobe. 1986. Study on the inhibitory effect of sodium dehydroacetate on the hepatocarcinogenicity of 4 dimethylaminoazobenzene in the rat. *Food Hyg. Soc. Jpn*. 27:466–473.

Yamaguchi, T. 1987. Mutagen formation on photolysis of dehydroacetic acid. *Agric. Biol. Chem*. 51:167–172.

Zeiger, E., B. Anderson, S. Haworth, T. Lawlor, K. Mortelmans, and W. Speck. 1987. Salmonella mutagenicity tests. 3. Results from the testing of 255 chemicals. *Environ. Mutagen*. 9:1–110.

## SODIUM LAURYL SULFOACETATE

A safety assessment on Sodium Lauryl Sulfoacetate was published in 1987 with the conclusion "On the basis of the available data presented in this report, the Expert Panel concludes that Sodium Lauryl Sulfoacetate is safe as a cosmetic ingredient in the present practices of use and concentration" (Elder 1987). Studies available since that safety assessment was completed, along with updated information regarding uses and use concentrations, were considered by the CIR Expert Panel. After reviewing the available data, the Panel determined to not reopen this safety assessment.

Sodium Lauryl Sulfoacetate was used in 93 products in 1981, based on voluntary reports provided to FDA by industry; use concentrations ranged from >0.1% to >50% (Elder 1985). In 2002 there were 68 uses (FDA 2002) and according to an industry survey in 2004 the current range of use concentrations is 0.6% to 21% (CTFA 2004).

Table 23 presents the available use and concentration information. The most recent information now constitutes the present practices of use.

The CIR Expert Panel did note that Stepan Company had submitted robust summaries and test plans on Sodium Lauryl Sulfoacetate as part of EPA's high production volume chemical testing program. This submission argued that the only missing data were reproductive and developmental toxicity data. The company proposed conducting such a study. Though the Panel noted that there are no data in the published literature,

**TABLE 22**
Historical and current uses and use concentrations for Sodium Dehydroacetate and Dehydroacetic Acid

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| | | *Sodium Dehydroacetate* | | |
| **Baby care** | | | | |
| Lotions, oils, powders & creams | — | — | — | 0.6 |
| **Bath** | | | | |
| Soaps and detergents | — | 2 | — | 0.0001 |
| Oils, tablets, and salts | 1 | — | ≤0.1 | — |
| **Eye makeup** | | | | |
| Eyebrow Pencil | — | — | — | 0.2–0.3 |
| Eyeliner | 2 | 4 | ≤0.1–1 | 0.05–0.5 |
| Eye shadow | 56 | 74 | ≤0.1–1 | 0.05–0.3 |
| Eye lotion | — | 3 | — | — |
| Eye makeup remover | — | 1 | — | 0.05 |
| Mascara | 13 | 16 | ≤0.1–1 | 0.001–0.4 |
| Other eye makeup | 4 | 12 | >0.1–1 | 0.0006–0.4 |
| **Fragrances** | | | | |
| Powders | 1 | 3 | >0.1–1 | — |
| Colognes and toilet waters | — | — | — | 0.001–0.5 |
| **Noncoloring hair care** | | | | |
| Conditioners | — | — | — | 0.2 |
| Shampoos | — | 2 | — | 0.2 |
| Tonics, dressings, etc. | 1 | 1 | ≤0.1 | — |
| Other noncoloring hair care | — | 4 | — | — |
| **Hair coloring** | | | | |
| Tints | — | 1 | — | — |
| Other hair coloring | — | 2 | — | — |
| **Makeup** | | | | |
| Blushers | 22 | 15 | ≤0.1–1 | 0.1–0.4 |
| Face powders | 23 | 31 | ≤0.1–1 | 0.05–0.4 |
| Makeup foundations | 8 | 10 | ≤0.1–1 | 0.0001–0.4 |
| Makeup bases | 14 | 6 | >0.1–1 | 0.1 |
| Leg and body paints | — | — | — | 0.1 |
| Lipstick | — | 1 | — | 0.3 |
| Rouges | 2 | — | ≤0.1–1 | — |
| Makeup fixatives | — | 1 | — | — |
| Other makeup | 2 | 4 | >0.1–1 | 0.0003–0.2 |
| **Nail care** | | | | |
| Basecoats and undercoats | — | — | — | 0.02 |
| Nail creams and lotions | — | 3 | — | — |
| Cuticle Softeners | 4 | 2 | >0.1–1 | — |
| Creams and lotions | 2 | — | ≤0.1–1 | — |
| Polish and enamel | — | — | — | 0.2 |
| Other nail care | 1 | — | >0.1–1 | 0.2 |
| **Personal hygiene** | | | | |
| Underarm deodorants | — | 2 | — | — |
| **Shaving** | | | | |
| Shaving cream | 1 | 4 | >0.1–1 | — |
| Other shaving | 1 | 1 | >0.1–1 | — |
| Aftershave lotions | 1 | 1 | ≤0.1 | 0.0003 |

**TABLE 22**
Historical and current uses and use concentrations for Sodium Dehydroacetate and Dehydroacetic Acid *(Continued)*

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) (%) | 2003 concentrations (CTFA 2003) (%) |
|---|---|---|---|---|
| **Skin care** | | | | |
| Skin-cleansing preparations | 23 | 13 | ≤0.1–1 | 0.0003–0.3 |
| Face and neck skin care | 24* | 4 | ≤0.1–1* | 0.008–0.2 |
| Body and hand skin care | | 20 | | 0.00003–0.5 |
| Moisturizers | 27 | 39 | ≤0.1–1 | 0.001–0.3 |
| Night skin care | 7 | 5 | ≤0.1 | 0.003–0.2 |
| Paste masks/mud packs | 4 | 6 | ≤0.1–1 | 0.03–0.2 |
| Fresheners | 2 | 2 | >0.1–1 | — |
| Other skin care | — | 25 | — | 0.00003–0.1 |
| Skin lighteners** | 2 | —** | ≤0.1–1 | —** |
| Wrinkle smoothers** | 1 | —** | >0.1–1 | —** |
| **Suntan** | | | | |
| Suntan gels, creams, and liquids | 5 | 1 | >0.1–1 | 0.2 |
| Indoor tanning preparations | 3 | 2 | ≤0.1–1 | 0.4 |
| Other suntan preparations | 3 | 2 | >0.1–1 | 0.1 |
| **Total uses/ranges for Sodium Dehydroacetate** | **260** | **325** | **≤0.1–1** | **0.00003–0.6** |
| | *Dehydroacetic Acid* | | | |
| **Bath** | | | | |
| Soaps and detergents | — | — | — | 0.03 |
| Oils, tablets and salts | 1 | — | ≤0.1 | — |
| Bubble baths | 2 | 1 | ≤0.1 | — |
| **Eye makeup** | | | | |
| Eyeliner | 1 | — | >0.1–1 | 0.1 |
| Eye shadow | 11 | 4 | ≤0.1–1 | 0.3 |
| Eye lotion | — | — | — | 0.2 |
| Eye makeup remover | 8 | 5 | ≤0.1–1 | 0.1 |
| Mascara | 1 | — | >0.1–1 | 0.2 |
| Other eye makeup | 9 | — | ≤0.1–1 | — |
| **Fragrances** | | | | |
| Colognes and toilet waters | 4 | — | ≤0.1 | — |
| Perfumes | 4 | — | ≤0.1 | — |
| **Noncoloring hair care** | | | | |
| Shampoos | 2 | — | ≤0.1 | 0.02–0.03 |
| Tonics, dressings, etc. | 2 | 1 | ≤0.1–1 | — |
| **Makeup** | | | | |
| Blushers | 5 | 1 | ≤0.1–1 | 0.05–0.2 |
| Face powders | 6 | 3 | ≤0.1–1 | 0.7 |
| Makeup foundations | 13 | 3 | ≤0.1–1 | 0.1 |
| Makeup bases | 1 | — | ≤0.1 | — |
| Rouges | 1 | 1 | >0.1–1 | — |
| Lipstick | 1 | — | ≤0.1 | — |
| Other makeup | 1 | — | ≤0.1 | 0.07 |
| **Nail care** | | | | |
| Cuticle softeners | — | 1 | — | — |
| Polish and enamel | — | 1 | — | — |
| **Personal hygiene** | | | | |
| Other personal hygiene | — | — | — | 0.03 |

*(Continued on next page)*

**TABLE 22**
Historical and current uses and use concentrations for Sodium Dehydroacetate and Dehydroacetic Acid *(Continued)*

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 15 | 8 | ≤0.1–1 | 0.007–0.02 |
| Face and neck skin care | 16* | 11 | ≤0.1–1* | 0.01–0.08 |
| Body and hand skin care | | 9 | | 0.03–0.05 |
| Moisturizers | 10 | 10 | ≤0.1–1 | — |
| Night skin care | 5 | 2 | ≤0.1–1 | 0.03 |
| Paste masks/mud packs | 3 | 6 | ≤0.1–1 | — |
| Skin fresheners | 2 | — | ≤0.1 | — |
| Other skin care | 9 | 16 | ≤0.1–1 | 0.03 |
| Wrinkle smoothers** | 2 | —** | ≤0.1 | —** |
| **Suntan** | | | | |
| Suntan gels, creams, and liquids | 3 | — | >0.1–1 | 0.2 |
| Indoor tanning preparation | — | 5 | — | — |
| Other suntan preparations | 1 | — | >0.1–1 | — |
| **Total Uses/Ranges for Dehydroacetic Acid Totals** | **139** | **88** | **≤0.1–1** | **0.007–0.7** |

*These categories were combined in 1981 but are now separate.
**No longer considered as cosmetic product categories.

which suggest that the reproductive and developmental toxicity potential of Sodium Lauryl Sulfoacetate is an issue, it was agreed that the results of the proposed reproductive and developmental toxicity study would be considered when available.

## REFERENCES

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2004. Use concentration data on sodium lauryl sulfoacetate from industry survey. Unpublished data submitted by CTFA, 2004 (1 page.)[24]

Elder, R. L. 1987. Final report on the safety assessment of sodium lauryl sulfoacetate. *J. Am. Coll. Toxicol.* 6:261–277.

Environmental Protection Agency (EPA). 2004. High Production Volume (HPV) Challenge Program. Robust summaries & test plans: sodium lauryl sulfoacetate (acetic acid, sulfo-, 1-dodecyl ester sodium salt). Internet site accessed August, 2004. http://www.epa.gov/chemrtk/sdmlaurl/c14936tc.html.

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

Gottschalck, T. E., and G. N. McEwen, Jr., eds. 2004. *International Cosmetic Ingredient Dictionary and Handbook*, 10th ed., Washington, DC: CTFA. 1743.

Nikitakis, J. M., and G. N. McEwen, Jr., eds. 1990. *CTFA Compendium of Cosmetic Ingredient Composition—Descriptions I and II*. Washington, DC: CTFA.

NOTOX Safety and Environmental Research BV. 2003. HPV assessment report and test plan for sodium lauryl sulfoacetate (acetic acid, sulfo-, 1-dodecyl ester sodium salt) CAS 1847-58-1. Prepared for: Stepan Company, Northfield, IL. Appendix A. Hambakenwetering: NOTOX, 1–24.[24]

[24]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

## SODIUM SESQUICARBONATE, SODIUM BICARBONATE, AND SODIUM CARBONATE

A safety assessment of Sodium Sesquicarbonate, Sodium Bicarbonate, and Sodium Carbonate was published in 1987 with the conclusion that these ingredients are safe as presently used in cosmetic products (Elder 1987). Studies available since that safety assessment was completed, along with updated information regarding uses and use concentrations, were considered by the CIR Expert Panel. After reviewing the available data, the Panel determined to not reopen this safety assessment.

**Sodium Sesquicarbonate** was used in 111 products in 1981, based on voluntary reports provided to FDA by industry; use concentrations ranged from >1% to 50% (Elder 1985). In 2002 there were 24 uses (FDA 2002) and according to an industry survey in 2004 the current range of use concentrations is 2.0% to 90% (CTFA 2004).

**Sodium Bicarbonate** was used in 45 products in 1981, based on voluntary reports provided to FDA by industry; use concentrations ranged from less than 0.1% to 50% (Elder 1985). In 2002 there were 70 uses (FDA 2002) and according to an industry survey in 2004 the current range of use concentrations is 0.006% to 95% (CTFA 2004).

**Sodium Carbonate** was used in 25 products in 1981, based on voluntary reports provided to FDA by industry; use concentrations ranged from less than 0.1% to 25% (Elder 1985). In 2002 there were 21 uses (FDA 2002) and according to an industry survey in 2004 the current range of use concentrations is 0.000002% to 51% (CTFA 2004).

Table 24 presents the available use and concentration information. The most recent information now constitutes the present practices of use.

**TABLE 23**
Historical and current cosmetic product uses and concentrations for Sodium Lauryl Sulfoacetate

| Product category | 1981 uses (Elder 1987) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1987) % | 2004 concentrations (CTFA 2004) % |
|---|---|---|---|---|
| **Baby care** | | | | |
| Lotions, oils, powders, and creams | — | — | — | 1 |
| **Bath** | | | | |
| Oils, tablets and salts | 1 | 13 | >1–5 | 5–21 |
| Soaps and detergents | — | — | — | 0.6–4 |
| Bubble baths | 85 | 21 | >1–>50 | 6–10 |
| Other bath | — | 27 | — | 6–10 |
| **Fragrances** | | | | |
| Other fragrances | — | 1 | — | 2 |
| **Noncoloring hair care** | | | | |
| Shampoos | — | 1 | — | 1–5 |
| **Hair coloring** | | | | |
| Bleaches | — | 2 | — | — |
| **Nail care** | | | | |
| Other nail care | — | — | — | 4 |
| **Oral hygiene** | | | | |
| Dentifrices | 3 | 1 | >0.1–5 | — |
| Other oral hygiene | — | — | — | 0.7* |
| **Personal hygiene** | | | | |
| Douches | — | — | — | 2 |
| Other personal hygiene | 1 | — | >0.1–1 | 2 |
| **Shaving** | | | | |
| Shaving cream | — | — | — | 2 |
| **Skin care products** | | | | |
| Cleansing creams, lotions, etc. | 2 | 2 | >1–25 | 4 |
| Body and hand skin care | — | — | — | 2 |
| Foot powders and sprays | — | — | — | 3 |
| Other skin care | 1 | — | >5–10 | — |
| **Total uses/ranges for Sodium Lauryl Sulfoacetate** | **93** | **68** | **>0.1–>50** | **0.6–21** |

*A denture cleanser.

## REFERENCES


Akpaffiong, M. J. 1987. Natriuretic and Blood Pressure Effects of Trona in the Rat. *West Afr. J. Pharmacol. Drug Res.* 7:9–14.

Canadian Centre for Occupational Health and Safety. 2004. Sodium Carbonate Chemical Profile. http://www.intox.org Accessed on 11/8/2004.

Clayton, G. D., and F. E. Clayton, eds. 1994. *Patty's Industrial Hygiene and Toxicology*. Vol. 2A, 2B, 2C, 2D, 2E, and 2F. 4th ed., 770.

Cooper, D. J., K. R. Walley, B. R. Wiggs, and J. A. Russell. 1990. Clinical study on bicarbonate. *Ann. Intern. Med.* 112:492–498.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2004. Concentration of Use–Sodium Sesquicarbonate, Sodium Carbonate, and Sodium Bicarbonate. Unpublished data submitted by CTFA 3 pages.[25]

Dean, B. S., and E. P. Krenzeloc. 1987. In vivo effectiveness of oral complexation agents in the management of iron poisoning. *J. Toxicol. Clin. Toxicol*. 25:221–230.

Depasquale, D. A., A. El-Nanarawy, D. Rosen, and T. J. Montville. 1990. Ammonium bicarbonate inhibition of mycotoxigenic fungi and spoliage yeasts. *J. Food Prot.* 53:324–328.

Einhorn, A., L. Horton, L. Altieri, M. Ochsenschlager, and B. Klein. 1989. Serious respiratory consequences of detergent ingestions in children. *Pediatrics* 84(3):472–474.

Emebiri, L. C., and M. I. Nwufo. 1990. Effect of Trona (urao) on the survival and reproduction of Sitophilus zeamais and Tribolium castaneum on stored maize. *Agric. Ecosyst Environ.* 32:69–76.

Gosselin, R. E., H. C. Hodge, R. P. Smith, and M. N. Gleason. 1976. *Clinical toxicology of commercial products*. 4th, ed., II-72. Baltimore: Williams and Wilkins.

Gosselin, R. E., R. P. Smith, and H. C. Hodge. 1984. *Clinical Toxicology of Commercial Products*, 5th ed, 194, II-103. Baltimore: Williams and Wilkins.

Gottschalck, T. E., and G. N. McEwen, Jr., eds. 2004. *International Cosmetic Ingredient Dictionary and Handbook*, 10th ed. 151. Washington, DC: CTFA.

International Programme on Chemical Safety. 2004. Sodium Bicarbonate. Unpublished data submitted by CTFA. 2 pages.[25]

Jackson, E. M. 1996. Familiarity with oral care products: must for the dermatologist. *Cosmet. Dermatol*. 9:43–44.


[25]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

**TABLE 24**
Historical and current uses and use concentrations for Sodium Sesquicarbonate, Sodium Bicarbonate, and Sodium Carbonate

| Product category | 1981 uses (Elder 1987) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1987) (%) | 2004 concentrations (CTFA 2004) (%) |
|---|---|---|---|---|
| | *Sodium Sesquicarbonate* | | | |
| **Bath** | | | | |
| Oils, tablets, and salts | 24 | 16 | >1–50 | 2–90 |
| Soaps and detergents | — | 2 | — | — |
| Bubble baths | 68 | 2 | >5–50 | 18 |
| Capsules | 2 | — | >10–25 | — |
| Other bath | 11 | 2 | >5–50 | 10–35 |
| **Fragrances** | | | | |
| Other fragrances | 1 | 1 | >5–10 | — |
| **Noncoloring hair care** | | | | |
| Straighteners | 1 | — | >50 | — |
| Permanent waves | 2 | — | >1–10 | — |
| **Personal hygiene** | | | | |
| Other personal hygiene | 2 | 1 | >5–10 | — |
| **Skin care** | | | | |
| Foot powders and sprays | — | — | — | 35–59 |
| **Total uses/ranges for Sodium Sesquicarbonate** | **111** | **24** | **>1–50** | **2–90** |
| | *Sodium Bicarbonate* | | | |
| **Baby care** | | | | |
| Lotions, oils, powders, and creams | — | 1 | — | 5 |
| **Bath** | | | | |
| Oils, tablets, and salts | 1 | 7 | <5–10 | 30–64 |
| Soaps and detergents | — | 2 | — | 25–54 |
| Bubble baths | 4 | — | >10–25 | 5–52 |
| Capsules | — | — | — | 49 |
| Other bath | — | — | — | 1–64 |
| **Eye makeup** | | | | |
| Eyebrow pencils | — | — | — | 0.2 |
| Eyeliners | 2 | 1 | ≤0.1–1 | 0.04–0.1 |
| Mascara | — | 6 | — | 0.2 |
| Other eye makeup | | 1 | | |
| **Fragrance** | | | | |
| Powders | 5 | 9 | >0.1–10 | 20 |
| **Noncoloring hair care** | | | | |
| Conditioners | — | — | — | 5 |
| Straighteners | 1 | — | >0.1–1 | — |
| Permanent waves | 5 | 3 | ≤0.1–1 | 10 |
| Shampoos | — | — | — | 0.09 |
| Other noncoloring hair care | 1 | — | >1–5 | — |
| **Hair-coloring products** | | | | |
| Dyes and colors | — | 8 | — | — |
| Bleaches | 1 | — | >25–50 | 0.1–10 |
| **Makeup** | | | | |
| Foundations | — | — | — | 0.09 |
| Lipsticks | — | — | — | 0.03–1 |
| **Nail care** | | | | |
| Other | — | — | — | 39 |

**TABLE 24**
Historical and current uses and use concentrations for Sodium Sesquicarbonate, Sodium Bicarbonate, and Sodium Carbonate
*(Continued)*

| Product category | 1981 uses (Elder 1987) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1987) (%) | 2004 concentrations (CTFA 2004) (%) |
|---|---|---|---|---|
| **Oral hygiene** | | | | |
| Dentifrices | 5 | 10 | >1–50 | 3–95 |
| Mouthwashes and breath fresheners | — | 2 | — | 0.1 |
| Other oral hygiene | — | 1 | — | 0.5 |
| **Personal hygiene** | | | | |
| Underarm deodorants | 2 | — | >1–5 | 0.01–15 |
| Douches | 4 | 2 | ≤0.1–25 | — |
| Feminine deodorants | — | 2 | — | — |
| Other personal hygiene | 4 | 3 | ≤0.1–25 | 0.07–56 |
| **Shaving** | | | | |
| Shaving cream | — | — | — | 0.006 |
| Other shaving | 1 | 1 | ≤0.1 | — |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | — | — | — | 0.04–26 |
| Face and neck skin care | —* | — | —* | 0.01–7 |
| Body and hand skin care | | — | | 10 |
| Foot powders and sprays | — | 4 | — | 25–56 |
| Moisturizers | — | — | — | 0.4 |
| Paste masks/mud packs | 3 | 1 | ≤0.1–50 | 61 |
| Skin fresheners | 2 | 2 | ≤0.1–10 | — |
| Other skin care | 4 | 4 | >10–25 | 2–5*** |
| **Suntan products** | | | | |
| Suntan gels, creams, liquids, and sprays | — | — | — | 0.2 |
| **Total uses/ranges for Sodium Bicarbonate** | **45** | **70** | **≤0.1–50** | **0.006–95** |
| | *Sodium Carbonate* | | | |
| **Bath** | | | | |
| Oils, tablets, and salts | — | 4 | — | 40–51 |
| Soaps and detergents | 2 | 1 | >0.1–1 | 3–32 |
| Bubble baths | 4 | — | >10–25 | 7–39 |
| Other | — | — | — | 0.009–39 |
| **Eye makeup** | | | | |
| Eyebrow pencils | — | — | — | 0.2 |
| Eye shadow | — | — | — | 0.3 |
| Eye lotions | — | — | — | 0.004 |
| Mascara | — | — | — | 0.2 |
| **Fragrances** | | | | |
| Colognes and toilet waters | — | — | — | 0.03 |
| **Noncoloring hair care** | | | | |
| Conditioners | 1 | 2 | >0.1–1 | 0.01 |
| Straighteners | 1 | — | >1–5 | — |
| Permanent waves | 1 | 1 | >1–5 | — |
| Shampoos | 2 | 1 | >0.1–1 | 0.08 |
| Tonics, dressings, etc. | — | — | — | 0.000002–0.01 |
| Wave sets | — | — | — | 1 |

*(Continued on next page)*

**TABLE 24**
Historical and current uses and use concentrations for Sodium Sesquicarbonate, Sodium Bicarbonate, and Sodium Carbonate *(Continued)*

| Product category | 1981 uses (Elder 1987) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1987) (%) | 2004 concentrations (CTFA 2004) (%) |
|---|---|---|---|---|
| **Hair coloring** | | | | |
| Dyes and colors | 1 | 2 | >1–5 | 0.1–0.6 |
| Rinses | — | — | — | 0.02 |
| Bleaches | 2 | — | >0.1–10 | 25 |
| Other hair coloring | — | — | — | 1 |
| **Makeup** | | | | |
| Blushers | — | — | — | 0.03 |
| Foundations | 1 | 1 | ≤0.1 | 0.3 |
| Lipsticks | — | 3 | — | — |
| **Nail care** | | | | |
| Other nail care | — | — | — | 0.6 |
| **Oral hygiene** | | | | |
| Dentifrices | — | — | — | 2 |
| Other oral hygiene | — | — | — | 22*** |
| **Personal hygiene** | | | | |
| Underarm deodorants | — | — | — | 0.002 |
| Douches | 1 | | >5–10 | — |
| Other | 3 | 2 | >1–5 | — |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 2 | 1 | ≤0.1 | 0.02–0.2 |
| Face and neck skin care | —* | — | —* | 0.008 |
| Body and hand skin care | | 1 | | — |
| Moisturizers | 2 | 2 | ≤0.1 | — |
| Skin fresheners | 1 | — | ≤0.1 | — |
| Hormone preparations** | 1 | N/A** | ≤0.1 | N/A** |
| **Total uses/ranges for Sodium Carbonate** | **25** | **21** | **≤0.1–25** | **0.000002–51** |

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


JEFO. 2004a. Sodium Bicarbonate Powder "Cow Brand". http://www.jefo.ca Accessed on 11/8/2004.

JEFO. 2004b. Sodium Sesquicarbonate (Arm & Hammer). http://www.jefo.ca. Accessed on 11/8/2004.

Kuu, W. Y., R. Chilamkurti, and C. Chen. 1998. Effect of relative humidity and temperature on moisture sorption and stability of sodium bicarbonate powder. *Int. J. Pharmacol*. 166:167–175.

Lewis, R. J. ed. 1996. *Sax's Dangerous Properties of Industrial Materials*, 9th ed., 2952. New York: John Wiley and Sons.

Mallinkrodt Baker, Inc. 2004. Sodium bicarbonate. http://www.chem.tamu.edu Access 11/8/2004.

Mallinkrodt Baker, Inc. 2004. Sodium carbonate anhydrous. http://www.jtbaker.com 11/8/2004.

Marvola, M., Nykanen, S., and M. Nokelainen. 1991. Bioavailability of erythromcin acistrate from hard gelatin capsules containing sodium bicarbonate. *Pharm. Res*. 8:1056–1058.

Miller, H. C. 1993. Cardiac arrest after intravenous pentamidine in an infant. *Pediatr. Infect. Dis. J*. 12:694–696.

National Institute for Occupational Safety and Health (NIOSH). 2004. Sodium sesquicarbonate dihydrate. http://www.cdc.gov. Accessed on 11/8/2004.

Orica. 2004. Chemical Fact Sheet–Sodium Carbonate. http://www.orica.com. Accessed on 11/8/2004.

Sander, J. E., S. I. Savage, and G. N. Rowland. 1998. Sodium sesquicarbonate toxicity in broiler chickens. *Avian Dis.* 42:215–218.

Sodipo, O. A. 1993. How safe is the consumption of Trona? *Am. J. Public Health* 83:1181.

Solvay Chemicals. 2004a. Dense Soda Ash—Properties. http://www.sodaash.com. Accessed on 11/8/2004.

Solvay Chemicals. 2004b. Trona—Sodium Sesquicarbonate. http://www.solvaychemicals.us. Accessed on 11/8/2004.

United States Department of Energy. 2004. Soda Ash. http://www.oit.doe.gov. 6 pages.

Uzogara, S. G., Morton, I. D., Daniel, J. W., and Emery, J. M. 1990. Use of kanwa-cooked cowpea (Vigna unguiculata) in infant food formulation: effect on protein utilization and digestibility. *J. Trop. Pediatr*. 36:207–208.

Walker, J. A., Sherman, R. A., and R. P. Cody. 1990. Effect of oral base on enteral aluminum absorption. *Arch. Intern. Med*. 150:2037–2039.

## STEARYL ALCOHOL, OLEYL ALCOHOL, AND OCTYLDODECANOL

A safety assessment of Stearyl Alcohol, Oleyl Alcohol, and Octyldodecanol was published in 1985 with the conclusion "safe as currently used in cosmetic products" (Elder 1985). New studies, along with the updated information in Table 25 regarding uses and used concentrations, were considered by the CIR Expert Panel. The Panel determined not to reopen this safety assessment.

**Stearyl Alcohol** was used in 425 cosmetic products in 1981, based on voluntary reports provided to FDA by industry with concentrations ranging from ≤0.1% to 50% (Elder 1985). In 2002, Stearyl Alcohol was reportedly used in 1063 cosmetic products (FDA 2002). Concentration of use data from an industry survey in 2003 indicated that Stearyl Alcohol was used in a range from 0.002% to 56% (CTFA 2003).

The Panel noted that the Hannuksela (1988) report reviewed the previous literature which included a report of positive patch test reactions to Stearyl Alcohol as high as 44%. Although this information raised some concern, Hannuksela (1988) did report current data with a frequency of 11 positive tests out of over 1000 patch tests performed; a low frequency consistent with current experience.

**Oleyl Alcohol** was used in 1018 cosmetic products in 1981, with concentrations ranging from ≤0.1% to >50% (Elder 1985). In 2002, Oleyl Alcohol was used in 343 cosmetic products (FDA 2002). Concentration of use data from a 2003 survey indicated that Oleyl Alcohol was used in a range from 0.0002% to 18% (CTFA 2003).

Although Tosti et al. (1996) reported a high proportion of 34 patients as positive to Oleyl Alcohol in a patch test, the Panel indicated that such reactions are not seen in their experience.

**Octyldodecanol** was used in 371 cosmetic products in 1981, with concentrations ranging from ≤0.1% to >50% (Elder 1985). In 2002, Octyldodecanol was used in 814 cosmetic products (FDA 2002). Concentration use data from 2003 indicted that Octyldodecanol was used in a range from 0.006% to 85% (CTFA 2003).

Table 25 presents the available use information for Stearyl Alcohol, Oleyl Alcohol, and Octyldodecanol. The most current information now represents the present practices of use.

## REFERENCES


Abdullah, A., S. Walker, C. Y. Tan, and I. S. Foulds. 1997. Sensitization to oleth-3-phosphate and oleth-5 in hair wax. *Contact Dermatitis* 37:188.

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

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2003. Ingredient Use Data. Unpublished data submitted by CTFA.[26]

Dawn, G., and A. Forsyth. 2003. Genital swelling caused by octyldodecanol contact dermatitis. *Clin. Exp. Dermatol.* 28:228–229.


[26]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036–4702, USA.


de Berker, D., P. Marren, S. M. Powell, and T. J. Ryan. 1992. Contact sensitivity to the stearyl alcohol in Efudix cream (5-fluorouracil). *Contact Dermatitis* 26:138.

Elder, R. L. 1985. Final report on the Safety Assessment of Stearyl Alcohol, Oleyl Alcohol and Octyl Dodecanol. *J. Am. Coll. Toxicol.* 4:1–29.

Filippi, U., M. Gibellini, G. Guasoni, et al. 1982. Proposal for the pharmacopeia; octyl dodecanol. *Boll. Chim. Farm.* 121:425–427.

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

Guidetti, M. S., C. Vincenzi, L. Guerra, and A. Tosti. 1994. Contact dermatitis due to oleyl alcohol. *Contact Dermatitis* 31:260–261.

Hannuksela, M. 1988. Skin contact allergy to emulsifiers. *Int. J. Cosmet. Sci.* 10:9–14.

Koch, P. 1995. Occupational allergic contact dermatitis from oleyl alcohol and monoethanolamine in a metalworking fluid. *Contact Dermatitis* 33:273.

Komamura, H., T. Doi, S. Inui, and K. Yoshikawa. 1997. A case of contact dermatitis due to impurities of cetyl alcohol. *Contact Dermatitis* 36:44–46.

Lashmar, U. T., J. Hadgraft, and N. Thomas. 1989. Topical application of penetration enhancers to the skin of nude mice: A histopathological study. *J. Pharm. Pharmacol.* 41:118–122.

Lee, B. J., J. S. Choe, and C. K. Kim. 1998. Preparation and characterization of melatonin-loaded stearyl alcohol microspheres. *J. Microencapsul.* 15:775–787.

McNeil, J. D., M. W. Whitehouse, M. A. Quin, L. G. Cleland, and B. Vernon-Roberts. 1985. Oleyl alcohol is a potent inflammogen in both the rat paw and the rabbit knee. *Aust. N. Z. J. Med.* 15:191.

Murota, K., T. Kawada, N. Matsui, M. Sakakibara, N. Takahashi, and T. Fushiki. 2000. Oleyl alcohol inhibits intestinal long-chain fatty acid absorption in rats. *J. Nutr. Sci. Vitaminol.* 46:302–308.

Niven, R. W., and P. R. Byron. 1990. Solute absorption from the airways of the isolated rat lung. II. Effect of surfactants on absorption of fluorescein. *Pharm. Res.* 7:8–13.

Olsen, O., M. Ainsworth, O. B. Schaffalitzky de Muckadell, and P. Cantor. 1989. Effects of oleic acid and oleyl alcohol on cholecystokinin and secretin in plasma pancreatobiliary secretion. *Scand. J. Gastroenterol.* 24:529–532.

Petersen, F., O. Olsen, L.V. Jepsen, and J. Christiansen. 1992. Fat and gastric acid secretion. *Digestion* 52:43–46.

Sato, A., K. Obata, Y. Ikeda, et al. 1996. Evaluation of human skin irritation by carboxylic acids, alcohols, esters, and aldehydes, with nitrocellulose-replica method and closed patch testing. *Contact Dermatitis* 34:12–16.

Takada Y., K. Kageyama, R. Yamada, Y. Onoyama, T. Nakajima, M. Hosono, and N. Miwa. 2001. Correlation of DNA synthesis-inhibiting activity and the extent of alcohols of graded chain-length upon hyperthermia. *Oncol. Rep.* 8:547–551.

Tan, B. B., A. L. Noble, M. E. Roberts, J. T. Lear, and J. S. English. 1997. Allergic contact dermatitis from oleyl alcohol in lipstick cross-reacting with ricinoleic acid in castor oil and lanolin. *Contact Dermatitis* 37:41–42.

Tosti, A., C. Vincenzi, L. Guerra, and E. Andrisano. 1996. Contact dermatitis from fatty alcohols. *Contact Dermatitis* 35:287–289.

Wakabayashi, T., M. Horiuchi, K. Adachi, and T. Koyama. 1984. Induction of megamitochondria in rat hepatocytes by 1-octadecanol. *J. Electron Microsc. (Tokyo)* 33:236–238.

Yesudian, P. D., and C. M. King. 2001. Allergic contact dermatitis from stearyl alcohol in Efudix cream. *Contact Dermatitis* 45:313–314.


## TOLUENE

A safety assessment of Toluene was published in 1987 with the conclusion that Toluene "is safe for cosmetic use at the present practices of use and concentration" despite limited skin exposure data (Elder 1987). Since then a large number of studies

**TABLE 25**
Historical and current cosmetic product uses and concentrations for Stearyl Alcohol, Oleyl Alcohol, and Octyldodecanol

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| | | *Stearyl Alcohol* | | |
| **Baby care** | | | | |
| Lotions, oils, powders, and creams | 2 | 9 | >0.1–1 | 0.6–2 |
| Other baby care | — | 1 | — | 2 |
| **Bath** | | | | |
| Soaps and detergents | — | 1 | — | 0.06 |
| Bubble baths | — | — | — | 2 |
| Other bath | — | 1 | — | 1–6 |
| **Eye makeup** | | | | |
| Eyebrow pencils | 1 | — | >1–5 | 3 |
| Eyeliners | — | 3 | — | — |
| Eye shadow | 24 | 6 | ≤0.1–1 | 8 |
| Eye lotions | — | 5 | — | 0.4–0.5 |
| Eye makeup remover | — | — | — | 0.9 |
| Mascara | 2 | 5 | >0.1–1 | 0.2 - 2 |
| Other eye makeup | 2 | 9 | ≤0.1–1 | 5 |
| **Fragrances** | | | | |
| Perfumes | — | — | — | 2 |
| Powders | — | 1 | — | — |
| Sachets | 26 | 1 | >0.1–25 | 1 |
| Other fragrances | — | 8 | — | 2 |
| **Noncoloring hair care** | | | | |
| Conditioners | 46 | 174 | ≤0.1–10 | 0.02–8 |
| Straighteners | 2 | 7 | >0.1–1, >5–10 | 2 |
| Permanent waves | 5 | 4 | ≤0.1–1 | 3 |
| Rinses | 21 | 4 | ≤0.1–5 | 3–5 |
| Shampoos | 1 | 23 | >0.1–1 | 0.1–5 |
| Tonics, dressings, etc. | — | 9 | — | 1–5 |
| Other noncoloring hair care | — | 3 | — | 1–5 |
| **Hair coloring** | | | | |
| Dyes and colors | 1 | 259 | >0.1–1 | — |
| Tints | — | — | — | 4 |
| Rinses | — | — | — | 2–5 |
| Lighteners with color | — | 1 | — | — |
| Bleaches | 5 | 25 | >0.1–5 | — |
| Other hair coloring | 2 | 1 | >1–5 | 2 |
| **Makeup** | | | | |
| Blushers | 15 | — | ≤0.1–1 | 2 |
| Foundations | 8 | 32 | >0.1–1 | 0.8–3 |
| Leg and body paints | 3 | — | >0.1–1 | — |
| Lipsticks | 3 | 2 | ≤0.1–1 | 0.2–3 |
| Makeup bases | 63 | 12 | ≤0.1–5 | 0.6 |
| Rouges | 1 | 1 | ≤0.1 | — |
| Makeup fixatives | 1 | 2 | ≤0.1 | — |
| Other makeup | 2 | 6 | ≤0.1–1 | 0.5–5 |
| **Nail care** | | | | |
| Cuticle softeners | 2 | 1 | >0.1–1 | 2 |

**TABLE 25**
Historical and current cosmetic product uses and concentrations for Stearyl Alcohol, Oleyl Alcohol, and Octyldodecanol
*(Continued)*

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| Creams and lotions | 1 | 2 | >1–5 | 1 |
| Other nail care | — | 1 | — | 6 |
| **Personal hygiene** | | | | |
| Underarm deodorants | 3 | 8 | >25–50 | 13–25 |
| Douches | — | — | — | 0.1 |
| Other personal hygiene | 10 | 66 | >1–5, >10–25 | — |
| **Shaving** | | | | |
| Aftershave lotions | — | 5 | — | 0.2–3 |
| Beard softeners | 1 | — | >5–10 | — |
| Preshave lotions | — | — | — | 1 |
| Shaving cream | 6 | 7 | >0.1–5 | 0.2–3 |
| Other shaving | 2 | — | ≤0.1–1 | 2 |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 39 | 52 | ≤0.1–10 | 0.5–8 |
| Depilatories | 6 | 1 | >1–5 | 1 |
| Face and neck skin care | 36* | 19 | ≤0.1–10* | 1–8 |
| Body and hand skin care | | 96 | | 0.002–9 |
| Foot powders and sprays | — | 3 | — | 2–17 |
| Moisturizers | 50 | 106 | ≤0.1–10 | 0.002–56 |
| Night skin care | 12 | 14 | ≤0.1–5 | 0.002–3 |
| Paste masks/mud packs | 2 | 11 | >0.1–5 | 0.8–6 |
| Skin fresheners | 1 | 2 | >0.1–1 | — |
| Other skin care | 9 | 31 | ≤0.1–10 | 0.02–12 |
| Skin lighteners** | 6 | NA** | >0.1–10 | NA** |
| **Suntan products** | | | | |
| Suntan gels, creams, liquids, and sprays | 2 | 3 | >0.1–1, >5–10 | 1–4 |
| Indoor tanning preparations | 1 | 19 | >1–5 | 2–3 |
| Other | — | 1 | — | 0.3 |
| **Total uses/ranges for Stearyl Alcohol** | **425** | **1063** | **≤0.1–50** | **0.002–56** |
| | | *Oleyl Alcohol* | | |
| **Bath** | | | | |
| Oils, tablets, and salts | 17 | 1 | ≤0.1–25 | — |
| Soaps and detergents | — | 2 | — | 0.0003 |
| Bubble baths | 1 | — | >1–5 | — |
| Capsules | 1 | — | >5–10 | 1–5 |
| Other bath | 3 | — | >1–5 | — |
| **Eye makeup** | | | | |
| Eyebrow pencils | 1 | — | >5–10 | — |
| Eyeliners | 15 | 5 | >1–25 | 0.4–0.5 |
| Eye shadow | 124 | 5 | ≤0.1–25 | 1 |
| Mascara | 26 | 2 | >1–5 | — |
| Other eye makeup | 8 | 2 | >0.1–25 | — |
| **Fragrances** | | | | |
| Colognes and toilet waters | 2 | — | >0.1–1 | — |
| Perfumes | 5 | 1 | ≤0.1, >1–5, >10–25 | 5 |
| Sachets | 2 | 1 | >1–5 | — |
| Other fragrances | 9 | 1 | >0.1–5 | 1–5 |

*(Continued on next page)*

**TABLE 25**
Historical and current cosmetic product uses and concentrations for Stearyl Alcohol, Oleyl Alcohol, and Octyldodecanol
*(Continued)*

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| **Noncoloring hair care** | | | | |
| Conditioners | 9 | 26 | >0.1–5 | 0.3–3 |
| Sprays/aerosol fixatives | — | 3 | — | — |
| Straighteners | 4 | 9 | >1–5 | 1 |
| Permanent waves | — | — | — | 3 |
| Rinses | — | — | — | 18 |
| Tonics, dressings, etc. | 4 | 6 | >0.1–5 | 0.3–4 |
| Other noncoloring hair care | 1 | 2 | >1–5 | — |
| **Hair coloring** | | | | |
| Dyes and colors | 63 | 143 | >1–5, >10–25 | 6–8 |
| Tints | 13 | — | >10–25 | — |
| Bleaches | 2 | 2 | >1–5 | — |
| Other hair coloring | — | 1 | — | — |
| **Makeup** | | | | |
| Blushers | 13 | 2 | >1–>50 | 1–10 |
| Face powders | 1 | — | >1–5 | — |
| Foundations | 5 | 5 | >0.1–5 | 0.5–5 |
| Lipsticks | 633 | 82 | ≤0.1–> 50 | — |
| Makeup bases | 2 | — | >1–5, >10–25 | — |
| Rouges | 3 | — | >1–5, >10–25 | — |
| Other makeup | 10 | 5 | >5–25 | — |
| **Nail care** | | | | |
| Basecoats and undercoats | — | 1 | — | — |
| Nail polish and enamel removers | 1 | — | >1–5 | — |
| **Personal hygiene** | | | | |
| Underarm deodorants | 2 | — | >1–5 | 0.0005 |
| Feminine deodorants | 1 | 1 | >25–50 | 0.1 |
| Other personal hygiene | 2 | 2 | >0.1–5 | — |
| **Shaving products** | | | | |
| Aftershave lotions | 2 | 2 | >1–5 | 0.05 |
| Preshave lotions | 1 | 1 | >0.1–1 | — |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 2 | 1 | >1–5 | — |
| Face and neck skin care | 6* | 2 | ≤0.1–10* | 0.0002–3 |
| Body and hand skin care | | 6 | | 0.05 |
| Foot powders and sprays | — | — | — | 2 |
| Moisturizers | 8 | 9 | ≤0.1–25 | 4 |
| Night skin care | 2 | 1 | >1–25 | 3 |
| Paste masks/mud packs | 2 | 2 | ≤0.1–5 | — |
| Skin fresheners | 2 | 6 | ≤0.1–1 | — |
| Other skin care | 4 | — | ≤0.1–25 | 3 |
| Hormone preparations** | 1 | NA** | >10–25 | NA** |
| **Suntan products** | | | | |
| Suntan gels, creams, liquids and sprays | 5 | 3 | >0.1–10 | — |
| **Total uses/ranges for Oleyl Alcohol** | **1018** | **343** | **≤0.1–>50** | **0.0002–18** |

**TABLE 25**
Historical and current cosmetic product uses and concentrations for Stearyl Alcohol, Oleyl Alcohol, and Octyldodecanol *(Continued)*

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| | | *Octyldodecanol* | | |
| **Bath** | | | | |
| Oils, tablets, and salts | 4 | 8 | >5–10 | 1–30 |
| Soaps and detergents | 1 | — | ≤0.1 | — |
| **Eye makeup** | | | | |
| Eyebrow pencils | 1 | 10 | >5–10 | 4 |
| Eyeliners | 14 | 202 | >0.1–10 | 3–7 |
| Eye shadow | 82 | 17 | >1–25 | 0.1–15 |
| Eye lotions | 1 | — | >25–50 | — |
| Eye makeup remover | 3 | 3 | >1–5, >10–25 | 5 |
| Mascara | 1 | — | >1–5 | 1–3 |
| Other eye makeup | 4 | 20 | >5–25 | 0.1 |
| **Fragrances** | | | | |
| Perfumes | 3 | — | >25–50 | — |
| Powders | 4 | — | >0.1–1 | 0.3 |
| Sachets | 6 | — | >25–50 | — |
| Other fragrances | 1 | 1 | >5–10 | — |
| **Noncoloring hair care** | | | | |
| Conditioners | 3 | 11 | >0.1–5 | 3–15 |
| Sprays/aerosol fixatives | 2 | 2 | >0.1–5 | — |
| Straighteners | — | — | — | 0.5 |
| Rinses | 2 | 3 | >0.1–1 | 4–6 |
| Tonics, dressings, etc. | — | — | — | 0.5–20 |
| Other noncoloring hair care | — | — | — | 3 |
| **Hair coloring** | | | | |
| Dyes and colors | 41 | 84 | >5–25 | 10 |
| Rinses | — | — | — | 1 |
| Color sprays | — | 1 | — | — |
| Other hair coloring | — | 1 | — | — |
| **Makeup** | | | | |
| Blushers | 6 | 9 | >1–25 | 15–23 |
| Face powders | 6 | 6 | >0.1–10 | 8 |
| Foundations | — | 20 | — | 5–16 |
| Lipsticks | 112 | 182 | >0.1–>50 | 3–82 |
| Makeup bases | 1 | 1 | >0.1–1 | — |
| Rouges | 1 | 2 | >10–25 | 10–20 |
| Makeup fixatives | 1 | — | >5–10 | — |
| Other | 2 | 23 | >1–10 | 3–17 |
| **Nail care** | | | | |
| Polishes and enamels | — | — | — | 2 |
| Other nail care | — | — | — | 0.06 |
| **Personal hygiene** | | | | |
| Underarm deodorants | 1 | 3 | >10–25 | 2–17 |
| Douches | — | — | — | 0.4 |
| Other personal hygiene | 1 | 2 | >1–5 | 1 |

*Continued on next page*

**TABLE 25**
Historical and current cosmetic product uses and concentrations for Stearyl Alcohol, Oleyl Alcohol, and Octyldodecanol
*(Continued)*

| Product category | 1981 uses (Elder 1985) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1985) % | 2003 concentrations (CTFA 2003) % |
|---|---|---|---|---|
| **Shaving products** | | | | |
| Aftershave lotions | — | 2 | — | 0.03–0.07 |
| Preshave lotions | 1 | 3 | >0.1–1 | — |
| Shaving cream | 1 | 1 | >0.1–1 | 0.4 |
| Other | — | 3 | — | — |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 9 | 22 | ≤0.1, >1–10 | 0.03–17 |
| Face and neck skin care | 23* | 19 | >0.1–50* | 0.03–85 |
| Body and hand skin care | | 59 | | 0.006–6 |
| Moisturizers | 14 | 35 | ≤0.1–25 | 2–3 |
| Night skin care | 3 | 15 | >1–5, >10–25 | 1 |
| Paste masks/mud packs | — | 7 | — | |
| Other skin care | 7 | 24 | >1–25 | 0.03–14 |
| Wrinkle smoothers** | 1 | NA** | >1–5 | NA** |
| Skin lighteners** | 4 | NA** | >0.1–5 | NA** |
| **Suntan** | | | | |
| Suntan gels, creams, liquids, and sprays | 3 | 9 | >5–25 | 3–59 |
| Other suntan | 1 | 4 | >1–5 | |
| **Total uses/ranges for Octyldodecanol** | **371** | **814** | **≤ 0.1–>50** | **0.006–85** |

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

have appeared in the scientific literature. These studies, along with updated information regarding uses and use concentrations, were considered by the CIR Expert Panel. Based on its consideration of the available data, the Panel decided to not reopen this safety assessment.

Toluene was used in 555 cosmetic products in 1981, based on voluntary reports provided to FDA by industry with concentrations ranging from >10%–50% (Elder 1987). In 2002, toluene was reportedly used in 59 cosmetic products (FDA 2002). Concentration of use data from an industry survey in 2003 indicated that Toluene was used in a range from 20% to 26% (CTFA 2004).

Table 26 provides the available data on usage and use concentration as a function of cosmetic product category. The most current information now represents the present practices of use.

Many of the newly available studies reported findings consistent with the data in the original safety assessment.

New findings of adverse effects included the following effects: Toluene was ototoxic for guinea pigs; interferes with performance and learning in neurotoxicity and behavior studies in animals; increased numbers of litters with low birth weights pups and adversely affected brain development; in cultured embryos exposed to Toluene, yolk sac diameter, crown-rump length, somite number, and protein concentration were significantly

**TABLE 26**
Historical and current cosmetic product uses and concentrations for Toluene

| Product category | 1984 uses (Elder 1987) | 2002 uses (FDA 2002) | 1984 concentrations (Elder 1987) % | 2003 concentrations (CTFA 2004) % |
|---|---|---|---|---|
| **Nail care** | | | | |
| Basecoats and undercoats | 32 | 21 | >10–50 | — |
| Polishes and enamels | 501 | 23 | >10-50 | 20–25 |
| Polish and enamel removers | — | 2 | — | — |
| Other nail care | 22 | 13 | >10–50 | 26 |
| **Total uses/ranges for Toluene** | **555** | **59** | **>10–50** | **20–26** |

reduced. A National Toxicology Program study concluded that there was no evidence of carcinogenic activity for Toluene in F344/N rats and $B6C3F_1$ mice.

The new adverse effects noted above appeared only at high exposures. They were found only when animals were exposed to Toluene vapor at a level of $10^2$ to $10^3$ ppm. Such exposures, however, were not attainable in an exposure study of human subjects using nail polish—those values ranged from 1–4 ppm.

The Panel recognized that other data indicate adverse effects in the brain of Toluene abusers and in children born to mothers who inhaled Toluene during pregnancy. Again, the nature of these studies suggests high exposures and are not relevant to the use of Toluene in cosmetic products.

## REFERENCES


Aakhus, A. M., A. Smit-Kielland, A. Ripel, and N. O. Solum. 1991. Effects of toluene on platelet membrane glycoprotein Ib and actin-binding protein. *Biochem. Pharmacol.* 42:805–811.

Angerer, J., and A. Krämer. 1997. Occupational chronic exposure to organic solvents XVI. Ambient and biological monitoring of workers exposed to toluene. *Int. Arch. Occup. Environ. Health*. 69:91–96.

Arito, H., H. Tsuruta, and M. Oguri. 1988. Changes in sleep and wakefulness following single and repeated exposures to toluene vapor in rats. *Arch. Toxicol.* 62:76–80.

Arnold, G. L., R. S. Kirby, S. Lagendoerfer, and L. Wilkins-Haug. 1994. Toluene embryopathy: Clinical delineation and developmental follow-up. *Pediatrics* 93:216–220.

Aydin, K., S. Sencer, T. Demir, K. Ogel, et al. 2002. Cranial MR findings in chronic toluene abuse by inhalation. *Am. J. Neuroradiol*. 23:1173–1179.

Bælum, J. 1990. Toluene in alveolar air during controlled exposure to constant and to varying concentrations. *Int. Arch. Occup. Environ. Health* 62:59–64.

Bælum, J., G. R. Lundqvist, L. Mølhave, and N. T. Andersen. 1990. Human response to varying concentrations of toluene. *Int. Arch. Occup. Environ. Health* 62:65–71.

Bælum, J., L. Mølhave, S. H. Hansen, and M. Døssing. 1993. Hepatic metabolism of toluene after gastrointestinal uptake in humans. *Scand. J. Work Environ. Health* 19:55–62.

Battle, D. C., S. Sabatinin, and N. A. Kurtzman. 1988. On the mechanism of toluene-induced renal tubular acidosis. *Nephron*. 49:210–218.

Benignus, V. A., K. E. Muller, C. N. Barton, and J. A. Bittikofer. 1981. Toluene levels in blood and brain of rats during and after respiratory exposure. *Toxicol. Appl. Pharmacol*. 61:326.

Beyer, C. E., D. Stafford, M. G. LeSage, J. R. Glowa, and J. D. Stektee. 2001. Repeated exposure to inhaled toluene includes behavioral and neurochemical cross-sensitization to cocaine in rats. *Psychopharmacology* 154:198–204.

Bjornaes, S., and L. U. Naalsund. 1988. Biochemical changes in different brain areas after toluene inhalation. *Toxicology* 49:367–374.

Bosch, X., J. M. Campistol, J. Montoliu, and R. Evert. 1988. Myelofibrosis and focal segmental glomerulosclerosis associated with toluene poisoning. *Human Toxicol*. 7:357–361.

Bosch, X., J. M. Campistol, J. Montoliu, and F. Cervantes. 1989. Toluene-associated myelofibrosis. *Blut.* 58:219–220.

Brown, R. H. 1988a. Determination of benzene, toluene, and xylene in industrial air by charcoal tube, solvent desorption and gas chomatography. *IARC Sci. Publ*. 85:225–233.

Brown, R. H. 1988b. Determination of benzene, toluene, and xylene in industrial air by porous polymer adsorption tube, thermal desorption and gas chromatography. *IARC Sci. Publ*. 85:235–242.

Brown-Woodman, P. D. C., W. S. Webster, K. Picker, and F. Huq. 1994. In vitro assessment of individual and interactive effects of aromatic hydrocarbons on embryonic development of the rat. *Repro. Toxicol.* 8:121–135.

Brugnone, F., M. Gubbi, K. Ayyad, and C. Giuliari. 1995. Blood toluene as a biological index of environmental toluene exposure in the "normal" population and in occupationally exposed workers immediately after exposure and 16 hours later. *Int. Arch. Occup. Environ. Health* 66:421–425.

Bushnell, P. J., K. L. Kelly, and K. M. Crofton. 1994. Effects of toluene inhalation on detection of auditory signals in rats. *Neurotoxicol. Teratol*. 16:149–160.

Cambell, L., D. M. Marsh, and H. K. Wilson. 1987. Towards a biological monitoring strategy for toluene. *Ann. Occup. Hyg*. 31:121–133.

Campo, P., R. Lataye, B. Cossec, and V. Placidi. 1997. Toluene-induced hearing loss: A mid-frequency location of the cochlear lesions. *Neurotoxicol. and Teratol.* 19:129–140.

Cavalleri, A., F. Gobba, E. Nicali, and V. Fiocchi. 2000. Dose-related color vision impairment in toluene-exposed workers. *Arch. Environ. Health* 6:399–404.

Chan, M. H., and H. H. Chen. 2003. Toluene exposure increases aminophylline-induced seizure susceptibility in mice. *Toxicol. Appl. Pharmacol*. 193:303–308.

Chao, T. C., D. S. Lo, J. Koh, and T. C. Ting. 1993. Glue sniffing deaths in Singapore-volatile aromatic hydrocarbons in post-mortem blood by headspace gas chromatography. *Med. Sci. Law*. 33:253–260.

Chen, H. H., and Y. F. Lee. 2002. Neonatal toluene exposure selectively alters sensitivity to different chemoconvulsant drugs in juvenile rats. *Pharmacol. Biochem. Behav.* 73:921–927.

Chen, M. L., S. H. Chen, G. R. Guo, and I. F. Mao. 2002. Relationship between environmental exposure to toluene, xylene and ethylbenzene and the expired breath concentrations for gasoline service workers. *J. Environ. Monit.* 4:652–656.

Cintra, A., B. Andbjer, U. B. Finnman, and M. Hajman. 1996. Subacute toluene exposure increases DA dysfunction in the 6-OH dopamine lesioned nigrostriatal dopaminergic system of the rat. *Neurosci. Lett.* 217:61–65.

Cintra, A., B. Andbjer, U. B. Finnman, and M. Hajman. 1999. Subchronic toluene exposure in low concentrations produces signs of reduced dysfunction in the 6 hydroxydopamine lesioned nigrostriatal dopaminergic system of the rat. *Neurosci. Lett.* 274:5–8.

Cho, S. I., A. Damokush, L. M. Ryan, and D. Chen. 2001. Effects of exposure to organic solvents on menstrual cycle length. *J. Occup. Environ. Med.* 43:567–575.

Chouanière, D., P. Wild, J. M. Fontana, and M. Hery. 2002. Neurobehavioral disturbances arising from occupational toluene exposure. *Am. J. Ind. Med.* 41:77–88.

Coelho, L., A. Amorim, and E. M. Alvarez-Leite. 1997. Determination of *o*-cresol by gas chromatography and comparison with hippuric acid levels in urine samples of individuals exposed to toluene. *J. Toxicol. Environ. Health* 50:401–407.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 1993. Respiratory measurements during fingernail polishing. Unpublished data submitted by CTFA.[27]

CTFA. 2004. Toluene use concentrations—results of a 2003 industry survey. Unpublished data submitted by CTFA.[27]

Cruz, S. L., T. Mirshahi, B. Thomas, and R. L. Balster. 1998. Effects of the abused solvent toluene on recombinant *N*-methyl-D-aspartate and non-*N*-methyl-D-aspartate receptors expressed in *Xenopus* oocytes. *J. Pharmacol. Exp. Ther.* 286:334–340.

Dalgaard, M., A. Hussaini, K. S. Houguard, and U. Hass. 2001. Developmental toxicity of toluene in male rats: Effects on semen quality, testis morphology, and apoptotic neurodegeneration. *Arch. Toxicol*. 75:103–109.

Da Silva, V. A., L. R. Malheiros, and F. M. R. Bueno. 1990. Effects of toluene exposure during gestation on neurobehavioral development of rats and hamsters. *Brazilian J. Med. Biol. Res*. 23:533–537.

Da Silva, V. A., L. R. Malheiros, F. J. Paumgartten, and M. Sa-Rego. 1990. Developmental toxicity of in utero exposure to toluene on malnourished and well nourished rats. *Toxicology* 64:155–168.


[27] Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

Da Silva, V. A., L. R. Malheiros, L. H. Fijueredo, and M. M. Sa-Rego. 1991. Neurobehavioral development of rats exposed to toluene through maternal milk. *Brazilian J. Med. Biol. Res*. 24:1239–1243.

Davies, M. B., S. J. M. Weatherby, N. Haq, and S. J. Ellis. 2000. A multiple-sclerosis-like syndrome associated with glue-sniffing. *J. R. Soc. Med*. 93:313–314.

Davis, R. R., W. J. Murphy, J. E. Snawder, and C. A. Striley. 2002. Susceptibility to the ototoxic properties of toluene is species specific. *Hear. Res*. 166:24–32.

Dees, C., M. Askari, and D. Henley. 1996. Carcinogenic potential of benzene and toluene when evaluated using cyclin-dependent kinase activation and p53-DNA binding. *Environ. Health Perspect*. 104:1289–1292.

De Gandarias, J. M., E. Echevarria, J. Irazusa, and E. Casis. 1993. Lys- and Leu-aminopeptidase activity after acute toluene exposure in the rat brain. *Toxicol. Indust. Health* 9:511–517.

Deleu, D., and Y. Hanssens. 2000. Cerebellar dysfunction in chronic toluene abuse: Beneficial response to amantadine hydrochloride. *Clin. Toxicol*. 38:37–41.

Deschamps, D., C. Géraud, and S. Dally. 2001. Cognitive functions in workers exposed to toluene: Evaluation at least 48 hours after removal from exposure. *Int. Arch. Occup. Environ. Health*. 74:285–288.

Duydu, Y., S. Suzen, N. Erdem, and H. Uysal. 1999. Validation of hippuric acid as a biomarker of toluene exposure. *Bull. Environ. Contam. Toxicol*. 63:1–8.

Echeverria, D., L. Fine, G. Langolf, and A. Schork. 1989. Acute neurobehavioural effects of toluene. *Br. J. Ind. Med*. 46:483–495.

Edelfors, S., and A. Ravn-Jonsen. 1987. Calcium uptake in brain synaptosomes from rats exposed to daily toluene for up to 80 weeks. *Pharmacol. Toxicol*. 61:305–307.

Edelfors, S., and A. Ravn-Jonsen. 1989. The effect of toluene exposure for up to 18 months (78 weeks) on the ($Ca^{2+}/Mg^{2+}$) ATPase and fluidity of synaptosomal membranes isolated from rat brain. *Pharmacol. Toxicol*. 65:140–142.

Edelfors, S., U. Hass, and K. S. Hougaard. 2002. Changes in markers of oxidative stress and membrane properties in synaptosomes from rats exposed prenatally to toluene. *Pharmacol. Toxicol*. 90:26–31.

Edling, C., B. Hellman, B. Arvidson, and G. Johansson. 1997. Positron emission tomography studies of healthy volunteers—no effects on the dopamine terminals and synthesis after short term exposure to toluene. *Hum. Exp. Toxicol*. 16:171–176.

Einav, S., Y. Amitai, J. Reichman, and D. Geber. 1997. Bradycardia in toluene poisoning. *Clin. Toxicol*. 35:295–298.

Eller, N., B. Netterstrøm, and P. Laursen. 1999. Risk of chronic effects on the central nervous system at low toluene exposure. *Occup. Med*. 49:389–395.

Filley, C. M., R. K. Heaton, and N. L. Rosenberg. 1990. White matter dementia in chronic toluene abuse. *Neurology* 40:532–534.

Foo, S. C., J. Jeyaratnam, and D. Koh. 1990. Chronic neurobehavioural effects of toluene. *Br. J. Ind. Med.* 47:480–484.

Foo, S. C., W. O. Phoon, and J. Lee. 1988. Neurobehavioural symptoms among workers occupationally exposed to toluene. *Asia-Pacific J. Pub. Health*. 2:192–197.

Forkman, B. A., T. Ljungberg, A. C. Johnson, and P. Nylen. 1991. Long-term effects of toluene inhalation on rat behavior. *Neurotoxicol. Teratol*. 13:475–481.

Funada, M., M. Sato, Y. Makino, and K. Wada. 2002. Evaluation of rearing effect of toluene by the conditioned place preference procedure in mice. *Brain Res. Protocols* 10:47–54.

Furman, G. M., D. M. Silverman, and R. A. Schatz. 1991. The effect of toluene on rat lung benzo[a]pyrene metabolism and microsomal membrane lipids. *Toxicology* 68:75–87.

Furman, G. M., D. M. Silverman, and R.A. Schatz. 1998. Inhibition of rat lung mixed-function oxidase activity following repeated low-level toluene inhalation: possible role of toluene metabolites. *J. Toxicol. Environ. Health* 54:633–645.

Fuxe, K., et al. 1987. Effects of subacute treatment with toluene on cerebrocortical $\alpha$- and $\beta$-adrenergic receptors in the rat. Evidence for an increased number and a reduced affinity of $\beta$-adrenergic receptors. *Acta Physiol. Scand.* 130:307–311.

Gartze, J., and D. Burck. 1997. Occupational health monitoring using solid phase extraction of urine. *J. Pharmaceut. Biomed. Analysis* 15:851–854.

Gerasimov, M. R., W. K. Schiffer, D. Marstellar, R. Ferrier, et al. 2002. Toluene inhalation produces regionally specific changes in extracellular dopamine. *Drug Alcohol Depend.* 65:243–251.

Ghosh, T. K., R. L. Copeland, Jr, J. C. Gear, and S. N. Pradhan. 1989. Effects of toluene exposure on the spontaneous cortical activity in rats. *Pharmacol. Biochem. Behav.* 32:987–992.

Ghosh, T. K., R. L. Copeland, Jr., and S. N. Pradhan. 1990. Sensitivity of EEG in young rats to toluene exposure. *Pharmacol. Biochem. Behav*. 36:778–785.

Ghosh, T. K., and S. N. Pradhan. 1987. Effects of toluene inhalation on fixed-ratio liquid-reinforced behavior in rats. *Drug Dev. Res*. 11:123–130.

Golubtsova, N. N., L. A. Lyubovtseva, and A. O. Loit. 2000. Effect of toluene on bioamine-containing structures in the spleen. *Bull. Exp. Biol. Med.* 130:1162–1165.

Goodwin, T. M. 1988. Toluene abuse and renal tubular acidosis in pregnancy. *Obstet. Gynecol.* 71:715–718.

Gospe, S. M., Jr., and M. A. S. Al-Bayati. 1994. Comparison of oral and inhalation exposures to toluene. *J. Am. Coll. Toxicol.* 13:21–32.

Gospe, S. M., Jr., and M. J. Calaban. 1988. Central nervous system distribution of inhaled toluene. *Fundam. Appl. Toxicol.* 11:540–545.

Gospe, S. M., Jr., D. B. Saeed, S. S. Zhou, and F. J. Zeman. 1994. The effects of high-dose toluene on embryonic development in the rat. *Pedia. Res.* 36:811–815.

Gospe, S. M., Jr., and S. S. Zhou. 1998. Toluene abuse embryopathy: Longitudinal neurodevelopmental effects of prenatal exposure to toluene in rats. *Reprod. Toxicol.* 12:119–126.

Gospe, S. M., Jr., and S. S. Zhou. 2000. Prenatal exposure to toluene results in abnormal neurogenesis and migration in rat somatosensory cortex. *Pediatr. Res.* 47:362–368.

Gospe, S. M., Jr., S. S. Zhou, D. B. Saeed, and F. J. Zeman. 1996. Development of a rat model of toluene abuse embryopathy. *Pediatr. Res.* 40:82–87.

Gottschalck, T., and G. N. McEwen, Jr. 2004. *International cosmetic ingredient dictionary and handbook*. Washington, DC: CTFA.

Guzelian, P., S. Mills, and H. J. Fallon. 1988. Liver structure and function in print workers exposed to toluene. *J. Occup. Med.* 30:791–796.

Hammer, D., N. Mayer, and E. H. Pfeiffer. 1998. Sister chromatid exchanges in rotogravure printing plant workers. *Int. Arch. Occup. Health* 71:138–142.

Hammer, K. D. 2002. Metabolite ratio of toluene-exposed rotogravure printing plant workers reflects individual mutagenic risk by sister chromatid exchanges. *Mutat. Res.* 519:171–177.

Hanioka, H., M. Hamamura, K. Kakino, H. Ugata, et al. 1995. Dog liver microsomal P450 enzyme-mediated Toluene biotransformation. *Xenobiotica* 25:1207–1217.

Hansson, E., G. Von Euler, K. Fuxe, and T. Hansson. 1988. Toluene induces changes in the morphology of astroglia and neurons in striatal primary cell cultures. *Toxicology* 49:155–163.

Harabuchi, I., R. Kishi, T. Ikeda, H. Kiyosawa, et al. 1993. Circadian variations of acute toxicity and blood and brain concentrations of inhaled toluene in rats. *Br. J. Ind. Med.* 50:280–286.

Hass, U., S. P. Lund, K. S. Hougaard, and L. Simonsen. 1999. Developmental neurotoxicity after toluene inhalation exposure in rats. *Neurotoxicol. Teratol.* 21:349–357.

Hersh. J. H. 1989. Toluene embryopathy: Two new cases. *J. Med. Genet*. 26:333–337.

Hjelm, E. W., A. Lof, A. Sato, A. Colmsjo, et al. 1994. Dietary and ethanol induced alterations of the toxikokinetics of toluene in humans. *Occup. Environ. Med.* 51:487–491.

Hori, H., S. I. Shimatsu, K. Arashidani, J. Hori, et al. 1999. Effect of simultaneous exposure to methanol and toluene vapor on their metabolites in rats. *J. Occup. Health* 41:149–153.

Hougaard, K. S., U. Hass, S. P. Lund, and L. Simonsen. 1999. Effects of prenatal exposure to toluene on postnatal development and behavior in rats. *Neurotoxicol. Teratol.* 21:241–250.

Hougaard, K. S., Å. M. Hansen, U. Hass, and S. P. Lund. 2003. Toluene depresses plasma corticosterone in pregnant rats. *Pharmacol. Toxicol.* 92:148–152.

Huang, J., N Asaeda, Y. Takeuchi, E. Shibata, et al. 1992. Dose dependent effects of chronic exposure to toluene on neuronal and glial cell marker proteins in the central nervous system of rats. *Br. J. Ind. Med.* 49:282–286.

Huang, J., K. Kato, E. Shibata, N. Hisanaga, et al. 1990. Effects of subacute toluene exposure on neuronal and glial marker proteins in rat brain. *Toxicology* 61:109–117.

Hunnewell, J., and N. R. Miller. 1998. Bilateral internuclear ophthalmoplegia related to chronic toluene abuse. *J. Neuro-Opthalmol*. 18:277–280.

Hussain, T. F., P. A. Heidenreich, and N. Benowitz. 1996. Recurrent non-Q wave myocardial infarction associated with toluene abuse. *Am. Heart J.* 3:615–616.

Hsieh, G. C., R. P. Sharma, and R. D. R. Parker. 1989. Immunotoxicological evaluation of toluene exposure via drinking water in mice. *Environ. Res.* 49:93–103.

Hsieh, G. C., R. P. Sharma, R. D. R. Parker, and R. A. Coulombe, Jr. 1990. Evaluation of toluene exposure via drinking water on levels of regional brain biogenic monoamines and their metabolites in CD-1 mice. *Ecotoxicol. Environ. Safety*. 20:175–184.

Iizumi, H., K. Fukui, H. Utsumi, Y. Kawashima, et al. 1995. Effect of chronic toluene exposure on tyrosine hydroxylase-positive nerve elements in the rat forebrain: An immunohistochemical study combined with semiquantitative morphometric analysis. *NeuroReport* 7:81–84.

Ikeda, M., and H. Tsukagoshi. 1990. Encephalopathy due to toluene sniffing. *Eur. Neurol.* 30:347–349.

Ikeuchi, Y., J. Hirai, Y. Okada, T. Mio, et al. 1993. Excitatory and inhibitory effects of toluene on neural activity in guinea pig hippocampal slices. *Neurosci. Lett*. 158:63–66.

Inoue, O., E. Kanno, S. Kudo, M. Kakizaki, et al. 1998. High-pressure liquid chromatographic determination of toluene in urine as a marker of occupational exposure to toluene. *Int. Arch. Occup. Environ. Health*. 71:302–308.

Inoue, O., K. Seiji, H. Nakastsuka, T. Watanabe, et al. 1989. Strain difference in free *p*-cresol excretion in urine of rats exposed to toluene at sub-narcotic concentrations. *Bull. Environ. Contam. Toxicol*. 43:74–79.

International Agency for Research on Cancer (IARC). 1999. Toluene. *IARC Monogr. Eval. Carcinog. Risks. Hum.* 71:829–864.

Jang, J. Y., S. K. Kang, and H. K. Chung. 1993. Biological exposure indices of organic solvents for Korean workers. *Int. Arch. Occup. Environ. Health*. 65:S219–S222.

Jensen, B., E. Olsen, and P. Wolkoff. 1996. Toluene in rotogravure printed brochures: High speed emission testing and comparison with exposure data. *Appl. Occup. Environ. Hygiene* 11:1055–1063.

Johnson, A. C., and B. Canlon. 1994. Progressive hair cell loss induced by toluene exposure. *Hear. Res*. 75:201–208.

Johnson, A. C., L. Juntunene, P. Nylén, E. Borg, et al. 1988. Effect of interaction between noise and toluene on auditory function in the rat. *Acta Otolaryngol*. 105:56–63.

Johnson, A. C., P. Nylén, E. Borg, and G. Höglund. 1990. Sequence of exposure to noise and toluene can determine loss of auditory sensitivity in the rat. *Acta Otolaryngol*. 109:34–40.

Jone, C. M., and A. H. B. Wu. 1988. An unusual case of toluene-induced metabolic acidosis. *Clin. Chem*. 34:2596–2599.

Jones, H. E., and R. E. Balster. 1997. Neurobehavioral consequences of intermittent prenatal exposure to high concentrations of toluene. *Neurotoxicol. Teratol.* 19:305–313.

Kamijima, M., Y. Nakazawa, M. Yamakawa, E. Shibata, et al. 1994. Metabolic acidosis and renal tubular injury due to pure toluene inhalation. *Arch. Environ. Health* 49:410–413.

Kamijo, K., K. Soma, I. Hasegawa, and T. Ohwada. 1998. Fatal bilateral adrenal hemorrhage following acute toluene poisoning: A case report. *J. Toxicol. Clin. Toxicol.* 36:365–368.

Kamran, S., and R. Bakshi. 1998. MRI in chronic toluene abuse: Low signal in the cerebral cortex on T2 weighted images. *Neuroradiology* 40:519–521.

Kao, K. C., Y. H. Tsai, M. C. Lin, C. C. Huang, et al. 2000. Hypokalemic muscular paralysis causing acute respiratory failure due to rhabdomylolysis with renal tubular acidosis in a chronic glue sniffer. *Clin. Toxicol*. 38:679–681.

Kawai, T., K. Mizunuma, Y. Okada, S. Huriguchi, et al. 1996. Toluene itself as the best urinary marker of toluene exposure. *Int. Arch. Occup. Environ. Health*. 68:289–297.

Kawai, T., K. Mizunuma, T. Yasugi, S. Horiguchi, et al. 1994. Toluene in blood as a marker of choice for low-level exposure to toluene. *Int. Arch. Occup. Environ. Health* 66:309–315.

Kawamoto, T., K. Matsuno, Y. K. Odama, K. Murata, et al. 1994. ALDH2 polymorphism and biological monitoring of toluene. *Arch. Environ. Health* 49:332–336.

Kawamoto, T. M., Koga, K. Murata, S. Matsuda, et al. 1995. Effects of ALDH2, CYP1A1 and CYP2E1 genetic polymorphisms and smoking and drinking habits on toluene metabolism in humans. *Toxicol. Appl. Pharmacol.* 133:295–304.

Kehr, J., and U. Ungerstedt. 1974. Fast HPLC estimation of gamma-aminobutyric acid in microdialysis perfusates: Effects of nipecotic and 3-mercaptopropionic acids. *J. Neurochem*. 51:1308–1310.

Kim, N. Y., and S. W. Park. 2000. The comparison of toluene determination between headspace-solid phase microextration and headspace methods in glue-sniffer's blood and urine samples. *J. Forensic Sci*. 45:702–707.

Kim, S. K., and Y. C. Kim. 1996. Effect of a single administration of benzene, toluene or m-xylene on carboxyhaemoglobin elevation and metabolism in rats. *J. Appl. Toxicol*. 16:437–444.

Kiyokawa, M., A. Mizota, M. Takasoh, and E. Adachi-Usami. 1999. Pattern visual evoked cortical potentials in patients with toxic optic neuropathy caused by toluene abuse. *Jpn. J. Ophthalmol*. 43:438–442.

Klimisch, H. J., J. Hellwig, and A. Hofmann. 1992. Studies on the prenatal toxicity of toluene in rabbits following inhalation exposure and proposal of a pregnancy guidance value. *Arch. Toxicol*. 66:373–381.

Knisely, J. S., D. C. Rees, and R. L. Balster. 1990. Discriminative stimulus properties of toluene in the rat. *Neurotoxicol. Teratol.* 12:129–133.

Korbo, L., O. Ladefoged, H. R. Lam, G. Ustergaard, et al. 1996. Neuronal loss in hippocampus in rats exposed to toluene. *NeuroToxicology* 17:359–366.

Korpela, M., and H. Tähti. 1988. The effect of in vitro and in vivo toluene exposure on rat erythrocyte and synaptosome membrane integral enzymes. *Pharmacol. Toxicol.* 63:30–32.

Ladefoged, O., V. Kjær, and J. J. Larsen. 1990. Effect of toluene on ethanol preference in rats. *Pharmacol. Toxicol.* 67:302–306.

Ladefoged, O., P. Strange, A. Moller, H. R. Lam, et al. 1991. Irreversible effect in rats of toluene (inhalation) exposure for six months. *Pharmacol. Toxicol.* 68:384–390.

Larsen, F., and H. L. Leira. 1988. Organic brain syndrome and long-term exposure to toluene: A clinical, psychiatric study of vocationally active printing workers.*J. Occup. Med.* 30:875–878.

Lataye, R., and P. Campo. 1997. Combined effects of a simultaneous exposure to noise and toluene on hearing function. *Neurotoxicol. Teratol.* 19:373–382.

Lataye, R., P. Campo, and G. Loquet. 1999. Toluene ototoxicity in rats: Assessment of the frequency of hearing deficit by electrocochleography. *Neurotoxicol. Teratol.* 21:267–276.

Lavoie, F. W., M. C. Dolan, D. F. Danzl, and R. L. Barber. 1987. Recurrent resuscitation and 'no code' orders in a 27-year old spray paint abuser.*Ann. Emerg. Med*. 16:1266–1273.

LeBel, C. P., and R. A. Schatz. 1988. Toluene-induced alterations in rat synaptosomal membrane composition and function. *J. Biochem. Toxicol*. 3:279–293.

LeBel, C. P., and R. A. Schatz. 1989. Effect of toluene on rat synaptosomal phospholipid methylation and membrane fluidity. *Biochem. Pharmacol.* 38:4005–4011.

Lee, Y. L., M. C. Pai, J. H. Chen, and Y. L. Guo. 2003. Central neurological abnormalities and multiple chemical sensitivity caused by chronic toluene exposure. *J. Occup. Med.* 53:479–482.

Li, H. S., A. C. Johnson, E. Borg, and G. Höglund. 1992. Auditory degeneration after exposure to toluene in two genotypes of mice. *Arch. Toxicol*. 66:382–386.

Lindemann, R. 1991. Congenital renal tubular dysfunction associated with maternal sniffing of organic solvents. *Acta. Pædiatr. Scand*. 80:882–884.

Little, C. H., G. M. Georgiou, M. J. Shelton, F. Simpson, et al. 1999. Clinical and immunological responses in subjects sensitive to solvents. *Arch. Environ. Health* 54:6–14.

Little, A. R., Z. Gong, U. Singh, H. El-Fawal, et al. 1998. Decreases in brain glial fibrillary acidic protein (GFAP) are associated with increased serum corticosterone following inhalation exposure to Toluene. *NeuroToxicology* 19:739–748.

Liu, S. J., K. Seiji, T. Watanabe, Z. Chen, et al. 1992. Toluene vapor exposure and urinary excretion of hippuric acid among workers in China. *Am. J. Indust. Med.* 22:313–323.

Liu, Y., and L. D. Fechter. 1997. Toluene disrupts outer hair cell morphometry and intracellular calcium homeostasis in cochlear cells of guinea pigs.*Toxicol. Appl. Pharmacol.* 142:270–277.

Löf, A., E. W. Hjelm, A. Colmsjo, B. O. Lundmark, et al. 1993. Toxicokinetics of toluene and urinary excretion of hippuric acid after human exposure to $^2H_8$-toluene. *Br. J. Indust. Med.* 50:55–59.

Löf, A., M. Wallén, and E. W. Hjelm. 1990. Influence of paracetamol and acetylsalicylic acid on the toxicokinetics of toluene. *Pharmacol. Toxicol.* 66:138–141.

Lorenzana-Jimenez, M., and M. Salas. 1990. Behavioral effects of chronic toluene exposure in the developing rat. *Neurotoxicol. Teratol.* 12:353–357.

Luderer, U., M. S. Morgan, C. A. Brodkin, D. A. Kalman, et al. 1999. Reproductive endocrine effects of acute exposure to toluene in men and women. *Occup. Environ. Med*. 56:657–666.

Ma, W., K. M. Shaffer, J. J. Papcrazio, T. J. O'Shaughnessy, et al. 2002. Toluene inhibits muscarininc receptor-mediated cytosolic $Ca^{2+}$ responses in neural precursor cells. *NeuroToxicology* 23:61–68.

Matsuoka, M., J. Matsumura, H. Igisu, H. Hori, et al. 1997. Effects of single exposure to toluene vapor on the expression of immediate early genes and GFAP gene in the mouse brain. *Arch. Toxicol*. 71:722–723.

Mattia, C. J., S. F. Ali, and S. C. Bondy. 1993. Toluene-induced oxidative stress in several brain regions and other organs. *Mol. Chem. Neuropathol*. 18:313–328.

Mattia, C. J., C. P. LeBel, and S. C. Bondy. 1991. Effects of toluene and its metabolites on cerebral reactive oxygen species generation. *Biochem. Pharmacol.* 42:879–882.

Mattsson, J. L., S. J. Gorzinski, R. R. Albee, and M. A. Zimmer. 1990. Evoked potential changes from 13 weeks of simulated toluene abuse in rats. *Pharmacol. Biochem. Behavior* 36:683–689.

McWilliams, M., G. D. Chen and L. D. Fechter. 2000. Low-level toluene disrupts auditory function in guinea pigs. *Toxicol. Appl. Pharmacol.* 167:18–29.

Mehta, C. S., P. N. Sun, A. Zikarge, M. Mumtaz, et al. 1998. Acute toxicity of toluene in male and female rats: A single oral dose exposure 2 week study. *Toxic Subst. Mech*. 17:43–55.

Meulenbelt, J., G. de Groot, and T. J.F. Savelkoul. 1990. Two cases of acute toluene intoxication. *Br. J. Ind. Med.* 47:417–420.

Meulenberg, C. J. W., and H. P. M. Vijverberg. 2003. Selective inhibition of $\gamma$-aminobutyric acid type A receptors in human IMR-32 cells by low concentrations of toluene. *Toxicology* 190:243–248.

Miyagawa, M., T. Honma, and M. Sato. 1995. Effects of subchronic exposure to toluene on working and reference memory in rats. *Neurotoxicol. Teratol.* 17:657–664.

Miyagi, Y., R. Shima, K. Ishido, T. Yasutake, et al. 1999. Tremor induced by toluene misuse successfully treated by a Vim thalamotomy. *J. Neurol. Neurosurg. Psychiatry* 66:794–796.

Mollenhauer, H. H., D. J. Morre, D. Pikaard, and D. E. Clark. 1990. An ultrastructural evaluation of toluene toxicity using cultured mammalian cells. *J. Submicrosc. Cytol. Pathol*. 22:523–527.

Monster, A. C., S. Kězić, I. V. de Gevel, and F. A. de Wolff. 1993. Evaluation of biological monitoring parameters for occupational exposure to toluene. *Int. Arch. Occup. Environ. Health*. 65:S159–S162.

Mørck, H. I., P. Winkel, and F. Gyntelberg. 1988. Health effects of toluene exposure. *Dan. Med. Bull*. 35:196–200.

Morøn, L., J. Pascual, M. P. Portillo, L. Casis, et al. 2004. Toluene alters appetite, NPY, and galanin immunostaining in the rat hypothalamus. *Neurotoxicol. Teratol.* 26:195–200.

Murata, M., M. Tsujikawa, and S. Kawanishi. 1999. Oxidative DNA damage by minor metabolites of toluene may lead to carcinogenesis and reproductive dysfunction. *Biochem. Biophy. Res. Commun.* 261:478–483.

Muttray, A., V. Wolters, D. Jung, and J. Konietzko. 1999. Effects of high doses of toluene on color vision. *Neurotoxicol. Teratol.* 21:41–45.

Nakai, N., M. Murata, M. Nagahama, T. Hirase, et al. 2003. Oxidative DNA damage induced by toluene is involved in its male reproductive toxicity. *Free Radic. Res.* 37:69–76.

Nakajima, T., R. S. Wang, E. Elovaara, F. J. Gonzalez, et al. 1997. Toluene metabolism by cDNA-expressed human hepatic cytochrome P450. *Biochem. Pharmacol.* 53:271–277.

Nakajima, T., R. W. Wang, E. Elovaara, S. S. Park, et al. 1992. A comparative study on the contribution of cytochrome P450 isozymes to metabolism of benzene, toluene, and trichloroethylene in rat liver. *Biochem. Pharmacol.* 43:251–257.

Nakajima, T., R. S. Wang, E. Elovaara, S. S. Park, et al. 1993. Cytochrome P450-related differences between rats and mice in the metabolism of benzene, toluene and trichloroethylene in liver microsomes. *Biochem. Pharmacol.* 45:1079–1085.

Nakajima, T., R. S. Wang, Y. Katakura, R. Kishi, et al. 1992. Sex-, age- and pregnancy- induced changes in metabolism of toluene and trichloroethylene in rat liver in relation to the regulation of cytochrome P450IIE1 and P450IIC11 content. *J. Pharmacol. Exp. Therapeut*. 261:869–874.

National Toxicology Program. 1990. Toxicology and carcinogenesis studies of toluene (CAS No. 108-88-3) in F344/N rats and B6C3F1 mice (inhalation studies). PB90256371.

Neghab, M., and N. H. Stacey. 1997. Toluene-induced elevation of serum bile acids: relationship to bile acid transport. *J. Toxicol. Environ. Health* 52:249–268.

Ng, T. P., S. C. Foo, and T. Yoong. 1992. Risk of spontaneous abortion in workers exposed to toluene. *Br. J. Ind. Med*. 49:804–808.

Nielsen, B. S., H. R. Lam, and O. Ladefoged. 2003. Developmental neurotoxicity of toluene in rats as measured by L-ornithine decarboxylase in the cerebellum. *Pharmacol. Toxicol.* 92:51–54.

Nise, G., R. Attewell, S. Skerfving, and P. Ørbæk. 1989. Elimination of toluene from venous blood and adipose tissue after occupational exposure. *Br. J. Ind. Med*. 46:407–411.

Nise, G., and P. Ørbæk. 1988. Toluene in venous blood during and after work in rotogravure printing. *Int. Arch. Occup. Environ. Health* 60:31–35.

Norström, Å., B. Andersson, L. Aringer, J. O. Levin, et al. 1988. Determination of specific mercapturic acids in human urine after experimental exposure to toluene or o-xylene. In: *Methods for detecting DNA damaging agents in humans: Applications in cancer epidemiology and prevention*, H. Bartsch, K. Hemminki, and I. K. O'Neill, 232–234. IARC Scientific Publications No. 89. Lyon, France.

Nylén, P., B. Larsby, A. C. Johnson, B. Eriksson, et al. 1991. Vestibular-oculomotor, opto-oculomotor and visual function in the rat after long-term inhalation exposure to toluene. *Acta. Otolaryngol*. 111:36–43.

Ogata, M., H. Michitsuji, and Y. Fujiki. 1999. Estimating amounts of toluene inhaled by workers with protective mask using biological indicators of toluene. *Toxicol. Lett*. 108:233–239.

Ogata, M., and T. Taguchi. 1987. Quantitation of urinary metabolites of toluene, xylene, styrene, ethylbenzne and phenol by automated high performance liquid chromatography. *Int. Arch. Occup. Environ. Health* 59:263–272.

Ong, C. N., S. C. Foo, and B. L. Lee. 1994. Effect of fasting on toluene metabolism: A study of hippuric acid and *o*-cresol excretion. *Appl. Occup. Environ. Hyg*. 9:622–625.

Ono, A., K. Kawashima, K. Sekita, A. Hirose, et al. 1999. Toluene inhalation induced epididymal sperm dysfunction in rats. *Toxicology* 139:193–205.

Ono, A., K. Sekita, K. Ohno, A. Hirose, et al. 1995. Reproductive and developmental toxicity studies of toluene I. Teratogenicity study of inhalation exposure in pregnant rats. *J. Toxicol. Sci.* 20:109–134.

Ono, A., K. Sekita, Y. Ugawa, A. Hirose, et al. 1996. Reproductive and developmental toxicity studies of toluene II. Effects of inhalation exposure on fertility in rats. *J. Environ. Pathol. Toxicol. Oncol.* 15:9–20.

Ørbæk, P., and G. Nise. 1989. Neurasthenic complaints and psychometric function of toluene-exposed rotogravure printers. *Am. J. Ind. Med.* 16:67–77.

Páez-Martinez, N., S. L. Cruz, and C. López-Rubalcava. 2003. Comparative study of the effects of toluene, benzene, 1,1,1,-trichloroethane, diethyl ether, and flurothyl on anxiety and nociception in mice. *Toxicol. Appl. Pharmacol.* 193:9–16.

Paraf, F., J. Lewis, and S. Jothy. 1993. Acute fatty liver of pregnancy after exposure to toluene. *J. Clin. Gastroenterol*. 17:163-165.

Park, S. W., N. Kim, Y. Yang, B. Seo, et al. 1998. Toluene distribution of glue sniffers' biological fluid samples in Korea. *J. Forensic Sci*. 43:888–890.

Pearson, M. A., H. E. Hoyme, L. H. Seaver, and M. E. Rimsza. Toluene embryopathy: Delineation of the phenotype and comparison with fetal alcohol syndrome. *Pediatrics* 93:211–215.

Pelclová, D., M. Cerná, A. Pasturková, V. Vrbiková, et al. 2000. Study of the genotoxicity of toluene. *Arch. Environ. Health* 55:268–273.

Pelclová, D., P. Rössner and J. Picková. 1990. Chromosome aberrations in rotogravure printing plant workers. *Mutat. Res.* 245:299–303.

Pellizari, E. D., R. A. Zweidinger, and L. S. Sheldon. 1988. Determination of benzene, toluene, and xylene in breath samples by gas chromatography/mass spectrometry. *IARC Sci. Publ*. 85:267–279.

Pierce, C. H., Y. Chen, R. L. Dills, and D. A. Kalman. 2002. Toluene metabolites as biological indicators of exposure. *Toxicol. Lett.* 129:65–76.

Pierce, C. H., R..L. Dills, T. A. Lewandowski, and M. S. Morgan. 1997. Estimation of background exposure to toluene using a physiologically-based kinetic model. *J. Occup. Health* 39:130–137.

Pierce, C. H., T. A. Lewandowski, R. L. Dills, and M. S. Morgan. 1999. A comparison of $^{1}H_{8}$- and $^{2}H_{8}$-toluene toxicokinetics in men. *Xenobiotica* 29:93–108.

Plenge-Bönig, A. and W. Karmaus. 1999. Exposure to toluene in the printing industry is associated with subfecundity in women but not in men. *Occup. Environ. Med*. 56:443–448.

Popp, W., C. Vahrenholz, S. Yaman, C. Müller, et al. 1992. Investigations of the frequency of DNA strand breakage and cross-linking and of sister chromatid exchange frequency in the lymphocytes of female workers exposed to benzene and toluene. *Carcinogenesis* 13:57–61.

Pryor, G. T. 1990. Persisting neurotoxic consequences of solvent abuse: A developing animal model for toluene-induced neurotoxicity. *NIDA Res. Monogr*. 101:156–166.

Pryor, G. T. 1991. A toluene-induced motor syndrome in rats resembling that seen in some human solvent abusers. *Neurotoxicol. Teratol.* 13:387–400.

Rahill, A. A., B. Weiss, P. E. Morrow, and M. W. Frampton. 1996. Human performance during exposure to toluene. *Aviat. Space Environ. Med.* 67:640–647.

Raikhlin–Eisenkraft, B., E. Hoffer, Y. Baum, and Y. Bentur. 2001. Determination of urinary hippuric acid in toluene abuse. *Clin. Toxicol.* 39:73–76.

Roberts, L. G., A. C. Bevans, and C. A. Schreiner. 2003. Developmental and reproductive toxicity evaluation of toluene vapor in the rat I. Reproductive toxicity. *Reprod. Toxicol.* 17:649–658.

Rogers, W. R., C. S. Miller, and L. Bunegin. 1999. A rat model of neurobehavioral sensitization to toluene. *Toxicol. Indust. Health* 15:356–369.

Rosenberg, N. L., B. K. Kleinschmidt-DeMasters, and K. A. Davis. 1988. Toluene abuse causes diffuse central nervous system white matter changes. *Ann. Neurol*. 23:611–614.

Rosenberg, N. L., M. C. Spitz, C. M. Filley, J. N. Dreisbach, and K. A. Davis. 1988. Central nervous system effects of chronic toluene abuse-clinical, brainstem evoked response and Magnetic Resonance Imaging studies. *Neurotoxicol. Teratol.* 10:489–495.

Richer, C. L., S. Chakrabarti, M. Senecal-Querillon, M. A. Duhr, et al. 1993. Cytogenetic effects of low-level exposure to toluene, xylene, and their mixture on human blood lymphocytes. *Int. Arch. Occup. Environ. Health* 64:581–585.

Riegel, A. C., and E. D. French. 1999. An electrophysiological analysis of rat ventral tegmental dopamine neuronal activity during acute toluene exposure. *Pharmacol. Toxicol.* 85:37–43.

Rudel, L. L., and M. D. Morris. 1973. Determination of cholesterol using *o*-phthalaldehyde. *J. Lipid Res.* 14:364.

Ryghseter, T., J. Jenssen, and T. Syversen. 1992. Acute toxicity of toluene determined using glioma cells contained in sealed rolling bottles with controlled vapour concentration. *Toxic. In Vitro* 6:605–607.

Ryu, Y. H., J. D. Lee, P. H. Yoon, P. Jeon, et al. 1998. Cerebral perfusion impairment in a patient with toluene abuse.*J. Nucl. Med.* 39:632–633.

Schäper, M., P. Demes, E. Kiesswetter, M. Zupanic, et al. 2004. Color vision and occupational toluene exposure: Results of repeated examinations. *Toxicol. Lett*. 151:193–202.

Shibata, K., Y. Yoshita, and H. Matsumoto. 1994. Extensive chemical burns from toluene. *Am. J. Emerg. Med.* 12:353–355.

Shimamoto, A., E. Tanaka, D. Mizuno, and S. Misawa. 1999. Age- and sex-related changes in toluene metabolism by rat hepatic microsomes in vitro. *Res. Commun. Mol. Pathol. Pharmacol*. 104:265–276.

Slomianka, L., S. Edelfors, A. Ravn-Junsen, J. Rungby, et al. 1990. The effect of low-level toluene exposure on the developing hippocampal region of the rat: Histological evidence and volumetric findings. *Toxicology* 62:189–202.

Smith-Kielland, A., Å. Ripel, and G. Gadeholt. 1989. Effects of toluene on protein synthesis and the interaction with ethanol in hepatocytes isolated from fed and fasted rats. *Pharmacol. Toxicol.* 64:83–87.

Soulage, C., D. Perrin, P. Berenguer, and J. M. Pequignot. 2004. Sub-chronic exposure to toluene at 40 ppm alters the monoamine biosynthesis rate in discrete brain areas. *Toxicology* 196:21–30.

Stengård, K. 1994. Effect of toluene inhalation on extracellular striatal acetylcholine release studied with microdialysis. *Pharmacol. Toxicol.* 75:115–118.

Stengård, K. 1995. Tail pinch increases acetylcholine release in rat striatum even after toluene exposure. *Pharmacol. Biochem. Behav.* 52:261–264.

Stengård, K., G. Höglund, and U. Ungerstedt. 1994. Extracellular dopamine levels within the striatum increase during inhalation exposure to toluene: A microdialysis study in awake, freely moving rats.*Toxicol. Lett.* 71:245–255.

Stengård, K., R. Tham, W. T. O'Connor, G. Höglund, et al. 1993. Acute toluene exposure increases extracellular GABA in the cerebellum of rat: A microdialysis study. *Pharmacol. Toxicol.* 73:315–318.

Suleiman, S. A. 1987. Petroleum hydrocarbon toxicity in vitro: Effect of n-alkanes, benzene and toluene on pulmonary alveolar macrophages and lysosomal enzymes of the lung. *Arch. Toxicol*. 59:402–407.

Sullivan, M. J., and R. B. Conolly. 1988. Comparison of blood toluene levels after inhalation and oral administration. *Environ. Res.* 45:64–70.

Sullivan, M. J., K. E. Rarey, and R. B. Conolly. 1989. Ototoxicity of toluene in rats. *Neurotoxicol. Teratol.* 10:525–530.

Svensson, B. G., G. Nise, V. Englander, R. Attewell, et al. 1990. Deaths and tumours among rotogravure printers exposed to toluene. *Br. J. Ind. Med.* 47:372–379.

Svensson, B. G., G. Nise, E. M. Erfurth, A. Nilsson, et al. 1992. Hormone status in occupational toluene exposure. *Am. J. Ind. Med.* 22:99–107.

Svensson, B. G., G. Nise, E. M. Erfurth, and H. Olsson. 1992. Neuroendocrine effects in printing workers exposed to toluene. *Br. J. Ind. Med.* 49:402–408.

Takahashi, S., K. Tanabe, C. Maseda, J. Shiono, et al. 1988. Increased plasma free fatty acid and triglyceride levels after single administration of toluene in rabbits. *J. Toxicol. Environ. Health* 25:87–95.

Tap, Ö., S. Solmaz, S. Polat, U. U. Mete, et al. The effect of toluene on the rat ovary: An ultrastructural study. *J. Submicrosc. Cytol. Pathol*. 28:553–558.

Tardif, R., G. Truchon, and J. Brodeur. 1998. Comparison of hippuric acid and *o*-cresol in urine and unchanged toluene in alveolar air for the biological

monitoring of exposure to toluene in human volunteers. *Appl. Occup. Environ. Hyg*. 13:127–132.

Taskinen, H., A. Antilla, M. L. Lindbohm, M. Sallmen, et al. 1989. Spontaneous abortions and congenital malformations among the wives of men occupationally exposed to organic solvents. *Scand. J. Work. Environ. Health.* 15:345–352.

Tassaneeyakul, W., D. J. Birkett, J. W. Edwards, M. E. Veronese, et al. 1996. Human cytochrome P450 isoform specificity in the regioselective metabolism of toluene and *o*-, *M*-, and *p*-xylene. *J. Pharmacol. Exp. Therapeut.* 276:101–108.

Thiel, R., and I. Chahoud. 1997. Postnatal development and behaviour of Wistar rats after prenatal toluene exposure. *Arch. Toxicol*. 71:258–265.

Thrall, K. D., K. K. Weitz, and A. D. Woodstock. 2002. Use of real-time breath analysis and physiologically based pharmacokinetic modeling to evaluate dermal absorption of aqueous toluene in human volunteers. *Toxicol. Sci.* 68:280–287.

Toyonaga, N., E. Adachi-Usami, and H. Yamazaki. 1989. Clinical and electrophysiological findings in three patients with toluene dependency. *Doc. Ophthalmol*.73:201–207.

Truchon, G., R. Tardiff, and J. Brodeur. 1996. Gas chromatographic determination of urinary *o*-cresol for the monitoring of toluene exposure. *J. Anal. Toxicol.* 20:309–312.

Ukai, H., T. Watanabe, H. Nakatsuka, T. Satoh, et al. 1993. Dose-dependent increase in subjective symptoms among toluene-exposed workers. *Environ. Res.* 60:274–289.

Unger, E., A. Alexander, T. Fritz, N. Rosenberg, et al. 1994. Toluene abuse: Physical basis for hypointensity of the basal ganglia on T2-weighted MR images. *Radiology* 193:473–746.

Urban, P., and E. Lukáš. 1990. Visual evoked potentials in rotogravure printers exposed to toluene. *Br. J. Indust. Med.* 47:819–823.

Verma, Y., and S. V.S. Rana. 2003. Gender differences in the metabolism of benzene, toluene and trichloroethylene in rat with special reference to certain biochemical parameters. *J. Environ. Biol*. 24:135–140.

Von Euler, G., K. Fuxe, T. Hansson, and P. Eneroth. 1989. Persistent effects of neonatal toluene exposure on regional brain catecholamine levels and turnover in the adult male rat. *Toxicology* 54:1–16.

Von Euler, G., K. Fuxe, T. Hansson, and J.Å. Gustafsson. 1988a. Effects of toluene treatment in vivo and in vitro on the binding characteristics of [$^3$H]neurotensin in rat striatal membranes. *Toxicology* 49:149–154.

Von Euler, G., K. Fuxe, T. Hannsson, and S. O. Ogren,. 1988b. Effects of chronic toluene exposure on central monoamine and peptide receptors and their interactions in the adult male rat. *Toxicology.* 52:103–126.

Von Euler, G., E. Hansson, and K. Fuxe. 1989. Toluene treatment in vitro and calcium regulated protein phosphorylation in primary astroglial cell cultures from the rat striatum. *Toxicol. In Vitro* 3:235–240.

Von Euler, G., S. O. Ogren, S. C. Bondy, and M. McKee. 1991. Subacute exposure to low concentrations of toluene affects dopamine-mediated locomotor activity in the rat. *Toxicology* 67:333–349.

Von Euler, G., S.O Ogren, P. Eneroth, and K. Fuxe. 1994. Persistent effects of 80 ppm toluene on dopamine-regulated locomotor activity and prolactin secretion in the male rat. *NeuroToxicology* 15:621–624.

Von Euler, G., S. O. Ogren, X. M. Li, and K. Fuxe et al. 1993. Persistent effects of subchronic toluene exposure on spatial learning and memory, dopamine-mediated locomotor activity and dopamine $D_2$ agonist binding in the rat. *Toxicology* 77:223–232.

Von Euler, M., T. M. Pham, M. Hillefors, and B. Bjelke. 2000. Inhalation of low concentrations of toluene induces persistent effects on a learning retention task, beam-walk performance, and cerebrocortical size in the rat. *Exp. Neurol.* 163:1–8.

Vrca, A., D. Bozicevic, V. Karacic, and R. Fuchs. 1995. Visual evoked potentials in individuals exposed to long-term low concentrations of toluene. *Arch. Toxicol*. 69:337–340.

Vrca, A., V. Karacic, D. Bozicevic, and V. Bosikov. 1996. Brainstem auditory evoked potentials in individuals exposed to long-term low concentrations of toluene. *Am. J. Ind. Med.* 30:62–66.

Wada, H. 1989. Single toluene exposure and changes of response latency in shock avoidance performance. *Neurotoxicol. Teratol.* 11:265–272.

Wada, H.. 1999. Toluene and temporal discrimination in rats: Effects on accuracy, discriminability, and time estimation. *Neurotoxicol. Teratol.* 21:709–718.

Wada, H., T. Hosokawa, and K. Saito. 1988. Repeated toluene exposure and changes of response latency in shock avoidance learning. *Neurotoxicol. Teratol.* 10:387–391.

Wang, G., G. Maranelli, L. Perbellini, and G. Guglielmi. 1993. Reference values for blood toluene in the occupationally nonexposed general population. *Int. Arch. Occup. Environ. Health* 65:201–203.

Wang, R. S., T. Nakajima, S. S. Park, and H. V. Gelboin. 1993. Monoclonal antibody-directed assessment of toluene induction of rat hepatic cytochrome P450 isozymes. *Biochem. Pharmacol.* 46:413–419.

Washington, W. J., A. Wilson, C. Lyons, and D. Dennie. 1989. Lack of toluene-induced dominant lethals in rats. *Ohio J. Sci*. 89:2–4.

Wiebelt, H. and N. Becker. 1999. Mortality in a cohort of toluene exposed *employees (Rotogravure printing plant workers). J Occup. Environ. Med.* 41:1134–1139.

Wiley, J. L., A. S. Bale, and R. L. Balster. 2003. Evaluation of toluene dependence and cross-sensitization to diazepam. *Life Sci*. 72:3023–3033.

Wilkins-Haug, L., and P. A. Gabow. 1991. Toluene abuse during pregnancy: Obstetric complications and perinatal outcomes. *Obstet. Gynecol*. 77:504–509.

Wood, R. W., and V. A. Colotla. 1990. Biphasic changes in mouse motor activity during exposure to toluene. *Fundam. Appl. Toxicol.* 14:6–14.

Wood, R. W., and C. Cox. 1995. A repeated measures approach too the detection of the acute behavioral effects of toluene at low concentrations. *Fundam. Appl. Toxicol*. 25:293–301.

Xiong, L., J. D. Matthes, J. Li, and J. R. Jinkins. 1993. MR imaging of "spray heads": Toluene abuse via aerosol paint inhalation. *Am. J. Neuroradiol*. 14:1195–1199.

Yamada, K. 1993. Influence of lacquer thinner and some organic solvents on reproductive and accessory reproductive organs in the male rat. *Biol. Pharm. Bull*. 16:425–427.

Yamaguchi, H., Y. Kidachi, and K. Ryoyama. 2002. Toluene at environmentally relevant low levels disrupts differentiation of astrocyte precursor cells. Arch. *Environ. Health* 57:232–238.

Yelian, F. D., and W. R. Dukelow. 1992. Cellular toxicity of toluene on mouse gamete cells and preimplantation embryos. *Arch. Toxicol*. 66:443–445.

Zavalic, M., Z. Mandic, R. Turk, A. Bogandi-Sare, et al. 1998a. Assessment of color vision impairment in male workers exposed to toluene generally above occupational exposure limits. *Occup. Med*. 48:175–180.

Zavalic, M., Z. Mandic, R. Turk, A. Bogandi-Sare, et al. 1998b. Qualitative color vision impairment in toluene-exposed workers. *Int. Arch. Occup. Environ. Health*. 71:194–200.

## TOLUENESULFONAMIDE/FORMALDEHYDE RESIN

A safety assessment of Toluenesulfonamide/Formaldehyde Resin (including Toluenesulfonamide/Formaldehyde Resin-80) was published in 1986 with the conclusion that these ingredients were safe as cosmetic ingredients in the present practices of use and concentration (Elder 1986). Studies available since that time, along with updated information regarding uses and use concentrations, were considered by the CIR Expert Panel. Based on its consideration of the available data, the Panel decided to not reopen this safety assessment.

The terminology for this ingredient in the *International Cosmetic Ingredient Dictionary and Handbook* has changed—Tosylamide/Formaldehyde Resin is the current terminology (Gottschalck and McEwen 2004).

**TABLE 27**
Historical and current cosmetic product uses and concentrations for Tosylamide/Formaldehyde Resin

| Product category | 1981 uses (Elder 1986) | 2002 uses (FDA 2002) | 1981 use concentrations (Elder 1986) % | 2003 use concentrations (CTFA 2004) % |
|---|---|---|---|---|
| | | *Tosylamide/Formaldehyde Resin* | | |
| **Nail care products** | | | | |
| Basecoats and undercoats | 31 | — | 1–10 | 8–11 |
| Nail polishes and enamels | 172 | 29 | ≤0.1–25 | 7–13 |
| Other | 8 | — | 1–10 | 7–8 |
| **Total uses/ranges for Tosylamide/Formaldehyde Resin** | **211** | **29** | **≤0.1–25** | **7–13** |
| | | *Tosylamide/Formaldehyde Resin-80* | | |
| **Nail care products** | | | | |
| Basecoats and undercoats (44) | 5 | — | 1–10 | — |
| Nail polishes and enamels (767) | 344 | — | ≤0.1–25 | — |
| Other (50) | 7 | — | ≤0.1–25 | — |
| **Total uses/ranges for Tosylamide/Formaldehyde Resin-80** | **356** | **29** | **≤0.1–25** | — |

**Tosylamide/Formaldehyde Resin** was used in 211 cosmetic products in 1981, based on voluntary reports provided to FDA by industry with concentrations ranging from ≤0.1%–25% (Elder 1986). In 2002, stearyl alcohol was reportedly used in 29 cosmetic products (FDA 2002). Concentration of use data from an industry survey in 2003 indicated that Toluene was used in a range from 7%–13% (CTFA 2004).

**Tosylamide/Formaldehyde Resin-80** was used in 356 cosmetic products in 1981, based on voluntary reports provided to FDA by industry with concentrations ranging from ≤0.1%–25% (Elder 1986). In 2002, there were no reports of use (FDA 2002), nor did an industry survey in 2003 indicated any current use concentrations (CTFA 2004).

Table 27 provides the available data on usage and use concentration as a function of cosmetic product category. The most current information now represents the present practices of use and concentration.

Case reports of allergic reaction to nail care products containing Tosylamide/Formaldehyde Resin were consistent with the data in the original safety assessment.

## REFERENCES


Berne, B., A. Boström, A. F. Grahfén, and M. Tammela. 1996. Adverse effects of cosmetics and toiletries reported to the Swedish Medical Products Agency 1989–1994. *Contact Dermatitis* 34:359–362.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2004. Survey of Tosylamide/Formaldehyde Resin usage. Unpublished data submitted by CTFA.[28] 1 page.

de Groot, A., D. P. Bruynzeel, J. D. Bos, et al. 1988. The allergens in cosmetics. *Arch Dermatol*. 124:1525–1529.

De Wit, F. S., A. C. de Groot, J. W. Weyland, and J. D. Bos 1988. An outbreak of contact dermatitis from toluenesulfnamide Formaldehyde resin in a nail hardener. *Contact Dermatitis*. 18:280–283.

Duarte, I., R. Lazzarinin, and C. M. Kobata 2003. Contact dermatitis in adolescents. *Am. J. Contact Dermatitis* 14:200–204.

Elder, R. L. 1986. Final report on the safety assessment of Toluenesulfonamide/Formaldehyde Resin. *J. Am. Coll. Toxicol.* 5:471–490.

Giorgini, S., C. Brusi, S. Francalanci, et al. 1994. Prevention of allergic contact dermatitis from nail vanishes and hardeners. *Contact Dermatitis* 31:325–326.

Gottschalck, T., and G. N. McEwen, Jr. 2004.*International cosmetic ingredient dictionary and handbook*. Washington, DC: CTFA.

Guin, J. D., K. Baas, and P. Nelson-Adesokan. 1998. Contact sensitization to cyanoacrylate adhesive as a cause of severe onychodystorphy. *Int. J. Dermatol.* 37:31–36.

Hausen, B. M., M. Milbrodt, and W. A. Koenig. 1995. The allergens of nail polish. (I). Allergenic constituents of common nail polish and toluenesulfonamide-Formaldehyde resin (TS-F-R). *Contact Dermatitis* 33:157–164.

Lazarov, A. 1999. Perianal contact dermatitis caused by nail lacquer allergy. *Am. J. Contact Dermatitis* 10:43–44.

Staines, K. S., D. H. Felix and A. Forsyth. 1998. Desquamative gingivitis, sole manifestation of tosylamide/formaldehyde resin allergy. *Contact Dermatitis* 39:90.

Vilaplana, J., and C. Romaguera. 2000. Contact dermatitis from tosylamide/formaldehyde resin with photosensitivity. *Contact Dermatitis* 42:311–312.


[28] Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

## TRAGACANTH GUM

A safety assessment of Tragacanth Gum was published in 1987 with the conclusion that these ingredients were safe as cosmetic ingredients in the present practices of use and concentration (Elder 1987). Studies available since that time, along with updated information regarding uses and use concentrations, were considered by the CIR Expert Panel. Based on its consideration of the available data, the Panel decided to not reopen this safety assessment.

**TABLE 28**
Historical and current cosmetic product uses and concentrations for Astragalus Gummifer Gum

| Product category | 1981 uses (Elder 1987) | 2002 uses (FDA 2002) | 1981 concentrations (Elder 1987) % | 2004 concentrations (CTFA 2004) % |
|---|---|---|---|---|
| **Eye makeup** | | | | |
| Eye shadow | 3 | — | ≤0.1 | — |
| **Noncoloring hair care** | | | | |
| Conditioners | — | 1 | ≤0.1 | — |
| Tonics, dressings, etc. | 1 | 2 | >0.1–1 | ≤0.01 |
| Wave Sets | — | 1 | | — |
| **Hair coloring** | | | | |
| Hair Bleaches | 2 | 1 | >1–5 | ≤3 |
| **Makeup** | | | | |
| Blushers | 2 | — | >1–5 | — |
| Face Powders | 6 | — | ≤0.1–1 | — |
| Foundations | 1 | — | >0.1–1 | — |
| Rouges | 1 | — | >0.1–1 | — |
| **Oral hygiene** | | | | |
| Dentrifices | 2 | 2 | >0.1–5 | — |
| **Shaving** | | | | |
| Aftershave lotions | 1 | — | >0.1–1 | — |
| Preshave lotions | 1 | — | >0.1–1 | — |
| **Skin care** | | | | |
| Cleansing creams, lotions, etc. | 1 | | >0.1–1 | — |
| Face and neck skin care | | — | | — |
| Body and hand skin care | 2* | — | >0.1–1* | — |
| Moisturizers | 1 | — | >0.1–1 | — |
| Paste masks/mud packs | 5 | 1 | >0.1–10 | — |
| **Total uses/ranges for Astragalus Gummifer Gum** | **29** | 8 | **≤0.1–10** | **≤0.01%–≤3** |

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

The terminology for this ingredient in the *International Cosmetic Ingredient Dictionary and Handbook* has changed—Astragalus Gummifer Gum is the current terminology (Gottschalck and McEwen 2004).

Astragalus Gummifer Gum was used in 29 cosmetic products in 1981, based on voluntary reports provided to FDA by industry with concentrations ranging from ≤0.1% to 10% (Elder 1987). In 2002, stearyl alcohol was reportedly used in 8 cosmetic products (FDA 2002). Concentration of use data from an industry survey in 2004 indicated that Astragalus Gummifer Gum was used at concentrations from ≤0.01% to ≤3% (CTFA 2004).

Table 28 provides the available data on usage and use concentration as a function of cosmetic product category. The most current information now represents the present practices of use and concentration.

In the original safety assessment, this ingredient was described as derived from various Astragalus species, principally *Astragalus gummifer*. More recent information suggests that *Astragalus microcephalus* may be another source of this gum. The Panel suggested that the *International Cosmetic Ingredient Dictionary and Handbook* should be updated to include specific mention of Astragalus Microcephalus Gum, and a new name adopted, if needed.

The Panel noted that pesticide impurities may form part of the composition of this plant-derived ingredient and has advised industry that the total (polychlorinated biphenyl) PCB/pesticide contamination should be limited to not more than 40 ppm, with not more than 10 ppm for any specific residue. The following limitations for other impurities were also recommended: arsenic (3 mg/kg max), heavy metals (0.002% max), and lead (5 mg/kg max).

## REFERENCES

Anderson, D. M. W., and M. M. E. Bridgeman. 1985. The composition of the proteinaceous polysaccharides exuded by Astragalus microcephalus, A. Gummifer and A. Kurdicus—the sources of Turkish gum tragacanth. *Phytochemistry* 24:2301–2304.

Anderson, D. M., P. Ashby, A. Busuttil, S. A. Kempson, and M. E. Lawson. 1984. Transmission electron microscopy of heart and liver tissues from rats fed with gums arabic and tragacanth. *Toxicol. Lett.* 21:83–89.

Anderson, D. M., A. Busuttil, S. A. Kempson, and D. W. Penman. 1986. Transmission electron microscopy of jejunum, ileum, and caecum tissues from rats fed with gums arabic, karaya and tragacanth. *Toxicology* 41:75–82.

Anderson, D. M., J. F. Howlett, and C. G. McNab. 1985. The amino acid composition of the proteinaceous component of gum tragacanth (Asiatic Astragalus spp.). *Food Addit. Contam.* 2:231–235.

Andrikopoulos, N. K., A. C. Kaliora, A. N. Assimopoulou, and V. P. Papapeorgiou. 2003. Biological activity of some naturally occurring resins, gums and pigments against in vitro LDL oxidation. *Phytother. Res.* 17:501–507.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2004. Use concentration data on Astragalus Gummifer Gum from industry survey. Unpublished data submitted by CTFA, 2004 (1 page).[29]

De la Rosa, M. C., M. R. Medina, and C. Vivar. 1995. Microbiological quality of pharmaceutical raw materials. *Pharm. Acta Helv.* 70:227–232.

De Paermentier, F., P. Heuschling, B. Knoops, P. Janssens De Varebeke, G. Pauwels, C. Laszlo de Kaszon-Jakabfalva, and P. Vanden Bosch De Aguilar. 1989. Suloctidil increases the rat brain cortex microvascular regeneration after a lesion. *Life Sci.* 44:41–47.

Eastwood, M. A., W. G. Brydon, and D. M. Anderson. 1984. The effects of dietary gum tragacanth in man. *Toxicol. Lett.* 21:73–82.

Elder, R. L. 1987. Final report on the safety assessment of tragacanth gum. *J. Am. Coll. Toxicol.* 6:1–22.

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

Gottschalck, T. E., and G. N. McEwen, Jr., eds. 2004. *International Cosmetic Ingredient Dictionary and Handbook,* 10th ed., 151. Washington, DC: CTFA.

Hagiwara, A., P. Boonyaphiphat, M. Kawabe, H. Naito, T. Shirai, and N. Ito. 1992. Lack of carcinogenicity of tragacanth gum in B6C3F1 mice. *Food Chem. Toxicol*. 30:673–679.

Hagiwara, A., H. Tanaka, D. Tiwawech, T. Shirai, and N. Ito. 1991. Oral toxicity study of tragacanth gum in B6C3F1 mice: Development of squamous-cell hyperplasia in the forestomach and its reversibility. *J. Toxicol. Environ. Health*. 34:207–218.

Hashimoto, R., M. Inouye, and Y. Murata. 1999. Hypoplastic lung observed in rat with chemical-induced congenital diaphragmatic hernia: A preliminary report. *Environ. Med*. 43:66–68.

Johnston, D., M. R. Gray, C. S. Reed, F. W. Bonner, and N. H. Anderson. 1990. Comparative evaluation of five common suspending agents used in drug safety studies. *Drug Dev. Ind. Pharm.* 16:1893–1909.

Joint FAO/WHO Expert Committee on Food Additives (JECFA). 1986a. *Evaluation of certain food additives: Twenty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives*, 37–38. WHO technical report series 733. Geneva: WHO.

JECFA. 1986b. *Toxicological monograph on tragacanth gum*, 1–21, WHO food additive series 20. Geneva: WHO.

JECFA. 2004. Compendium of Food Additive Specifications. Specifications for food additives. Internet site accessed July, 2004. http://apps3.fao.org/jecfa/additive_specs/docs/0/additive-0453.htm.

Kitchin, K. T., and J. L. Brown. 1987. Biochemical effects of two promoters of hepatocarcinogenesis in rats. *Food Chem. Toxicol.* 25:603–607.

Kitchin, K. T., and J. L. Brown. 1989. Biochemical studies of promoters of carcinogenesis in rat liver. *Teratog. Carcinog. Mutagen.* 9:273–285.

Kitchin, K. T., J. L. Brown, and A. P. Kulkarni. 1991. Ornithine decarboxylase induction and DNA damage as a predictive assay for potential carcinogenicity. *Prog. Clin. Biol. Res.* 369:137–144.

Kitchin, K. T., J. L. Brown, and A. P. Kulkarni. 1993. Predicting rodent carcinogenicity of Ames test false positives by in vivo biochemical parameters. *Mutat. Res.* 290:155–164.

Kitchin, K. T., J. L. Brown, and A. P. Kulkarni. 1994. Complementarity of genotoxic and nongenotoxic predictors of rodent carcinogenicity. *Teratogen. Carcinogen. Mutagen.* 13:83–100.

Kuroda, K., Y. S. Yoo, and T. Ishibashi. 1989. Rec-assay of natural food additives. Part 2. *Seikatsu Eisei* 33:15–23.

[29] Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

Lagier, F., A. Cartier, J. Somer, J. Dolovich, and J.-L. Malo. 1990. Occupational asthma caused by guar gum. *J. Allergy Clin. Immunol.* 85:785–790.

Lammers, J. H. C. M., and B. M. Kulig. 1997. Multivariate time of peak effects assessment for use in selecting time of testing in acute neurotoxicity studies. *Neurotoxicology* 18:1079–1084.

Manson, J. M., F. J. Guerriero, T. Brown, and J. San Sebastian. 1986. Lack of in vivo mutagenicity and testicular toxicity of triamterene in mice. *Fundam. Appl. Toxicol.* 7:533–546.

National Academy of Sciences (NAS). (1996) *Food chemicals codex*, 4th ed., 424. Washington, DC: National Academy Press.

Paulson, J. D., J. W. Oldham, R. F. Preston, and D. Newman. 1985. Lack of genotoxicity of the cancer chemopreventive agent *N*-(4-hydroxyphenyl)retinamide. *Fundam. Appl. Toxicol.* 5:144–150.

Strobel, S., A. Ferguson, and D. M. Anderson. 1986. Immunogenicity, immunological cross reactivity and non-specific irritant properties of the exudate gums, arabic, karaya and tragacanth. *Food Addit. Contam.* 3:47–56.

Taylor, S. L., and S. L. Hefle. 2001. Ingredient and labeling issues associated with allergenic foods. *Allergy*. 56:64–69.

Verbeken, D., S. Dierckx, and K. Dewettinck. 2003. Exudate gums: Occurrence, production, and applications. *Appl. Microbiol. Biotechnol*. 63:10–21.

Yamaguchi, T. 1992. Inhibitory activity of heat treated vegetables and indigestible polysaccharides on mutagenicity. *Mutat. Res.* 284:205–213.

## VINYL ACETATE/CROTONIC ACID COPOLYMER

A safety assessment of the Vinyl Acetate/Crotonic Acid Copolymer in 1983 concluded that this ingredient is considered safe as a cosmetic ingredient under present practices of product and concentration use (Elder 1983). 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.

The terminology for this ingredient in the *International Cosmetic Ingredient Dictionary and Handbook* has changed—VA/Crotonates Copolymer is the current terminology (Gottschalck and McEwen 2004).

VA/Crotonates Copolymer was used in 55 cosmetic products in 1976, based on voluntary reports provided to FDA by industry with concentrations ranging from >0.01% to 25% (Elder 1986). In 2002, VA/Crotonates Copolymer was used in 38 cosmetic products (FDA 2002). Concentration of use data from an industry survey in 2003 indicated that this ingredient was used at concentrations from 0.05% to 11% (CTFA 2003).

Table 29 presents the available use information for VA/Crotonates Copolymer. The most recent information now constitutes the present practice of use and concentration.

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. Therefore,

**TABLE 29**
Historical and current cosmetic product uses and concentrations for VA/Crotonates Copolymer

| Product category | 1976 uses (Elder 1983) | 2002 uses (FDA 2002) | 1976 use concentrations (Elder 1983, 1976) (%) | 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 | >.01–25 | 2–11 |
| Hair straighteners | — | 1 | — | — |
| Tonics, dressings, and other hair-grooming aids | 2 | 10 | >1–5 | 0.05–4 |
| Wave sets | 9 | 3 | >1–5 | 2 |
| Other hair preparations (noncoloring) | 10 | 9 | >1–10 | 2–3 |
| Hair dyes and colors (all types requiring caution statement and patch testing) | — | — | — | 5 |
| Moisturizing creams, lotions, and powders | — | — | — | 2 |
| **Total uses/ranges for VA/Crotonates Copolymer** | **55** | **38** | **>0.01–25** | **0.05–11** |

the Panel was not concerned about inhalation as a route of absorption.

Although there were reports associating vinyl acetate with nasopharyngeal carcinoma in rat inhalation studies, the amount of residual vinyl acetate monomer in VA/Crotonates Copolymer was below the no observed effect level. Additionally, studies show that the reported carcinogenicity of vinyl acetate in rats is through a nongenotoxic mechanism. Occupational studies in which workers were exposure 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. These data support the CIR Expert Panel's confidence that vinyl acetate is not a concern in the safety of VA/Crotonates Copolymer.

## 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 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.[30]

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2002a. Information regarding VA/Crotonates Copolymer. Unpublished data submitted by CTFA on October 31, 2002. (1 page.)[30]

CTFA. 2002b. Concentrations of use VA/Crotonates Copolymer. Unpublished data submitted by CTFA on November 1, 2002. (1 page.)[30]

Deese, D. E., and R. E. Joyner. 1969. Vinyl acetate: A study of chronic human exposure. *Am. Ind. Hyg. Assoc. J.* 30:449–457.

Elder, R. L. 1983. Final report on the safety assessment of vinyl acetate/crotonic acid copolymer. *J. Am. Coll. Toxicol*. 2:125–140.

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

Gottschalck, T., and G. N. McEwen. 2004. *International Cosmetic Ingredient Dictionary and Handbook*, 10th ed. Washington, DC: CTFA.

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, P. A. and D. O'Brien. 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.

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. N.Y. Acad. 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.


[30]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

**TABLE 30**
Historical and current cosmetic product uses and concentrations for Zinc Phenolsulfonate

| Product category | 1986 uses (CIR 1986) | 2002 uses (FDA 2002) | 1981 concentrations (CIR 1986) (%) | 2004 concentrations (CTFA 2004) (%) |
|---|---|---|---|---|
| **Fragrances** | | | | |
| Powders | 5 | 1 | >0.1–5 | — |
| **Personal hygiene** | | | | |
| Underarm deodorants | 40 | 15 | >0.1–5 | 4 |
| **Shaving** | | | | |
| Aftershave lotions | 4 | 2 | >0.1–5 | — |
| Shaving cream | 3 | — | — | — |
| **Skin care** | | | | |
| Skin cleansing creams, lotions, liquids, and pads | 2 | | >0.1–5 | — |
| Body and hand skin care preparations | — | 2 | — | — |
| Foot powders and sprays | — | 1 | — | 3 |
| Moisturizers | 1 | 1 | ≤0.1 | — |
| Paste masks/mud packs | 1 | — | >1–5 | — |
| Skin fresheners | 9 | — | ≤0.1–5 | — |
| Other | 2 | 1 | 1–5 | — |
| **Total uses/ranges for Zinc Phenolsulfonate** | **67** | **23** | **≤0.1–5** | **3–4** |

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.

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.

## ZINC PHENOLSULFONATE

A safety assessment of Zinc Phenolsulfonate published in 1986 concluded that this ingredient is considered safe as a cosmetic ingredient under present practices of product and concentration use (Elder 1986). 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.

Zinc Phenolsulfonate was used in 67 cosmetic products in 1981, based on voluntary reports provided to FDA by industry with concentrations ranging from ≤0.1 to 5% (Elder 1986). In 2002, Zinc Phenolsulfonate was used in 23 cosmetic products (FDA 2002). Concentration of use data from an industry survey in 2004 indicated that this ingredient was used at concentrations from 3 to 4% (CTFA 2004).

Table 30 presents the available use information for Zinc Phenolsulfonate. The most recent information now constitutes the present practice of use and concentration.

## REFERENCES

Cosmetic, Toiletry, and Fragrance Assocation (CTFA). 2004. Concentration of use data for Zinc Phenolsulfonate. Unpublished data submitted by CTFA. 1 page.[31]

Elder, R. L. 1986. Final report on the safety assessment of Zinc Phenolsulfonate. *J. Am. Coll. Toxicol.* 5:373–390.

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

Gottschalck, T. E., and G. N. McEwen, Jr., eds. 2004. *International Cosmetic Ingredient Dictionary and Handbook*, 10th ed., vol. 3. Washington, DC: CTFA.

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.

[31] Available from the Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036, USA.