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Annual Review of Cosmetic Ingredient Safety Assessments: 2007-2010

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This Annual Review of Cosmetic Ingredient Safety Assessments updates and affirms the findings of the Cosmetic Ingredient Review (CIR) Expert Panel's assessment of almost 30 compounds used in cosmetic ingredients. The review also summarizes new findings from epidemiology studies of hair dyes.

The CIR Expert Panel's re-review process is intended to uncover any new data since the last safety assessment. In some cases, newly available data are largely redundant compared with the data available in the original safety assessment. In other cases, new data present new safety issues. If after considering the newly available information, the CIR Expert Panel decides to not reopen a safety assessment, this finding, along with any background material, is summarized and announced publicly. To assure that the scientific community is aware of any new information and the decision not to reopen, this Annual Review of Cosmetic Ingredient Safety Assessments is prepared.

A list of reference sources is provided after each ingredient re-review summary that updates the available published literature and includes any unpublished data made available since the original safety assessment.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 CIR Expert Panel has assessed the safety of over 2100 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*.

The ingredients the CIR Expert Panel reconsidered during the 2007-2010 period and did not reopen are:

Acetamide MEA
5-Bromo-5-nitro-1,3-dioxane
Butyl benzyl phthalate
t-Butyl hydroquinone (TBHQ)
Chlorhexidine, chlorhexidine dihydrochloride, chlorhexidine digluconate, chlorhexidine diacetate
2-Chloro-*p*-phenylenediamine and 2-chloro-*p*-phenylenediamine sulfate
2,4-Diaminophenol and 2,4-diaminophenol dihydrochloride
Diisopropylamine
Disperse blue 1
Disperse violet 1
Ethyl hexanediol
HC Blue No. 2
HC Red No. 3
HC Yellow No. 2
Hydroxybenzomorpholine
Isopropyl isostearate
Lauramine oxide and stearamine oxide
Methenamine
1-Naphthol
Phenoxyethanol
Phenyl methyl pyrazolone
N-Phenyl-*p*-phenylenediamine
Polyoxymethylene urea
Polyquaternium-7
Quaternium-22
Shellac
Sodium and potassium bromate
Stearpyrium chloride and lapyrium chloride

Among these are several cosmetic ingredients used in hair dye products (2-chloro-*p*-phenylenediamine and 2-chloro-*p*-phenylenediamine sulfate, 2,4-diaminophenol and 2,4-diaminophenol dihydrochloride, disperse blue 1, disperse violet 1, HC Blue No. 2, HC Red No. 3, HC Yellow No. 2, 1-naphthol, phenyl methyl pyrazolone, and *N*-phenyl-*p*-phenylenediamine).

Hair Dye Epidemiology

As part of its continuing assessment of cosmetic ingredient safety, the CIR Expert Panel reviews all epidemiology studies

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on hair dyes. While the safety of individual hair dye ingredients are not addressed in epidemiology studies that seek to determine links, if any, between hair dye use and disease, such studies do provide broad information. The CIR Expert Panel has developed an approach in which a given hair dye ingredient is categorized into groupings that are relevant to the epidemiology data; for example, permanent or oxidative versus semipermanent or nonoxidative.

The epidemiology studies reviewed by the Expert Panel are summarized on the CIR Web site (http://www.cir-safety.org/findings.shtml); only a summary of these data are provided in a safety assessment of a specific hair dye ingredient.

Summaries of these studies the Panel reviewed during 2007-2010 are presented by the outcome studied.

Bladder Cancer

Bolt and Golka[1] reviewed the published literature on bladder cancer risk and personal use of hair dyes (17 publications) or occupation as a hairdresser and/or barber (23 publications) and concluded that, based on these studies, there seems to be no relevant bladder cancer risk from the use of oxidative hair dyes currently available. The authors could not rule out a bladder cancer risk in hairdressers who worked with oxidative hair dyes available decades ago.

Kelsh et al[2] conducted meta-analyses of primary epidemiology studies of hair dye use and bladder cancer and performed their own meta-analysis that examined regular use of hair dye, including permanent hair dye, gender, duration of use, lifetime extent of use, and use of dark hair dye. No association was found between any use of hair dye and bladder cancer among women, men, or both sexes. No statistically significant differences were found for permanent hair dye; duration of any use; duration of permanent hair dye use or lifetime application of any hair dye, permanent hair dye, or dark color hair dye.

Lymphoma and Leukemia

Chiu et al[3] evaluated non-Hodgkin lymphoma subtypes defined according to the presence or absence of t(14:18) translocation from samples taken from a case–control study conducted in Nebraska during 1983-1986. Exposures in 65 t(14:18)-positive cases and 107 t(14:18)-negative cases were compared with those among 1432 controls. Among women, hair dye use was not associated with either t(14;18)-positive or t(14:18)-negative subtypes. (There were too few cases for meaningful analysis of hair dye use among men.) The use of permanent hair dye was associated with a 40% higher risk of the t(14:18)-negative subtype (odds ratio [OR] of 1.4). Hair dye use was not associated with follicular lymphoma or diffuse large B-cell lymphoma in either sex.

Morton et al[4] conducted a US population-based case–control study of non-Hodgkin lymphoma. In 1321 cases and 1057 controls, hair dye use included when hair dye use first occurred, use of permanent versus semipermanent dyes, frequency of use, color (black, brown, red, blonde) and intensity of dye used (light vs dark), and total lifetime use. Blood samples obtained from 773 cases and 668 controls and buccal cell samples from 399 cases and 314 controls were used to extract DNA for analyzing *NAT1* and *NAT2* genotypes and *NAT2* acetylation phenotype.

The authors reported no evidence of increased non-Hodgkin lymphoma risk among women, who began hair dye use in or after 1980, or in men. For women whose year of first use was prior to 1980, the odds ratio (OR) for any permanent hair dye use was 1.3 (95% confidence interval [CI] 0.9-1.9); for permanent dark hair dye use was 1.3 (95% CI 0.9-2.0); and for intense tone (ie, black, dark brown, and dark blonde) permanent hair dye use was 1.6 (95% CI 0.9-2.7). For women whose year of first use was 1980 or later, the ORs, for each of the 3 groups listed above, were 0.9 (95% CI 0.6-1.4), 1.2 (95% CI 0.7-1.7), and 0.6 (95% CI 0.4-1.1), respectively.

The risk did not increase consistently with frequency of use, duration of use, or total lifetime use. Women with the *NAT2* slow acetylator phenotype or who had no copies of the *NAT1*10* allele and used intense tone permanent hair dyes before 1980 did not have an increased risk of non-Hodgkin lymphoma (OR 1.5; 95% CI 0.6-3.6 and OR 1.5; 95% CI 0.7-3.3, respectively), but women with the *NAT2* rapid/intermediate acetylator phenotype or those carrying 1 or 2 copies of the *NAT1*10* allele did have an increased risk (OR 3.3; 95% CI 1.3-8.6 and OR 2.5; 95% CI 0.9-7.6, respectively).

Zhang et al[5] concluded that there was an increased risk of non-Hodgkin lymphoma in women who started using hair dyes before 1980, but not in women who started use after 1980. They performed an evaluation of pooled data from 4 previous studies in which information on sex, duration of use, number of applications, dates of use, and type and color of the hair dye used was available and in which non-Hodgkin lymphoma was classified by histologic type. A total of 4461 cases and 5799 controls were included. In the analysis of non-Hodgkin lymphoma subtypes, there was an increased risk of follicular lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma mainly in users who began use before 1980, but no increased risk of diffuse large B-cell lymphoma, marginal-zone lymphoma, or T cell lymphoma. For women who began use after 1980, an increased risk of follicular lymphoma only was suggested for users of dark hair dyes. Other comparisons failed to show the differences between risks of dark versus light hair dyes and permanent versus semipermanent hair dyes. In the analysis of subtypes, similar failures to show differences were present in the data.

Koutros et al[6] found no association between hair dye use and myeloma risk, semipermanent hair dye use, permanent dye use, or dark permanent hair dye use. The authors also reported no significant association of myeloma with use of hair dyes before age 30 years, use begun before 1980, >240 lifetime uses, or use of dark permanent dyes for $\geq$28 years. They conducted a population-based case–control study of 175 cases of multiple myeloma with 679 matched controls. Information on type and color of hair-coloring product, age at first use, age when the use

was stopped, duration of use, and frequency of use per year were obtained from interviews.

Reproductive and Developmental Outcomes

Axmon and Rylander[7] conducted a cohort study of Swedish women, who had attended vocational schools for hairdressers (3137), and their sisters (3952) based on data obtained from Swedish national registries. Low-birth-weight (less than 2500 g), small for gestational age, and large for gestational age data were gathered from Swedish birth registries of infants born to the hairdressers (6223 infants) and their sisters (8388 infants). The authors reported no association between occupation as a hairdresser and increased risk of low-birth-weight or small for gestational age parameters. Among the infants born to the hairdressers' sisters, the distribution of birth weights were wider than that among the infants born to the hairdressers. For "large for gestational age" data, there was a reduced risk of women who had actually worked as hairdressers during at least 1 pregnancy. The infants born to these women also had a significantly lower mean birth weight (3387 g vs 3419 g; $P = .033$).

Gallicchio et al[8] conducted a study of cosmetologists to determine whether they are at increased risk of poor pregnancy outcomes compared with women of the same age who are not cosmetologists. Participants were self-selected through mass mailing of questionnaires. Respondents to the survey had to be between 21 and 55 years of age and not have had a hysterectomy or oophorectomy. A cohort of 350 cosmetologists and 397 women in other occupations who self-reported that they met the inclusion criteria and had 5 or fewer singleton pregnancies were included. Outcome measures were miscarriage, stillbirth, and occurrence of maternal health conditions during pregnancy (preeclampsia, high blood pressure, and diabetes), hospitalization or physician-ordered bed rest during pregnancy, preterm labor, and premature delivery (before 37 weeks at delivery). The authors reported no statistically significant associations between occupation as a cosmetologist and any pregnancy outcomes after adjustment for age, race, education, and smoking and alcohol use at the time of pregnancy.

Halliday-Bell et al[9] identified all singleton births to hairdressers (10 662) and cosmetologists (2490) from the 1990-2004 Finnish Medical Birth Registry. Singleton births to teachers (18 594) were used as the control population. Data were obtained from the confidential registry on the parameters of sex distribution, low-birth-weight, small for gestational age, preterm delivery, and perinatal death. In comparing occupation as a hairdresser to that of a teacher, the authors reported a higher incidence of low-birth-weight, small for gestational age, preterm delivery, and perinatal death, but no difference in sex distribution. In comparing occupation as a cosmetologist to that of a teacher, the authors reported a higher incidence of small for gestational age and perinatal death but no difference in sex distribution, incidence of low birth weight, or preterm delivery. The authors concluded that occupation as a hairdresser or cosmetologist may reduce fetal growth and that occupation as a hairdresser may also increase the incidence of preterm delivery and perinatal death.

Herdt-Losavio et al[10] conducted a retrospective cohort study of cosmetologists (15 003) compared with realtors (4246) or compared with the general population (12 171) using birth records in New York State from 1997 to 2003. From the birth records, the authors obtained information on low-birth-weight, small for gestational age, and preterm birth. The incidence of low–birth-weight (1500-2499 g) was higher for cosmetologists compared with realtors but not when compared with the general population. For nonwhite cosmetologists, the incidence of low-birth-weight was higher compared with realtors and the general population. No statistically significant differences were reported for any comparison of small for gestational age or preterm births.

Baste et al[11] conducted a cross-sectional study among women in Hordaland county in Norway. Among 10 512 women providing information by self-report, 221 were hairdressers. An association between occupation as a hairdresser and increased risk of infertility (OR 1.3; 95% CI 1.08-1.55) or spontaneous abortion (OR 1.31; 95% CI 1.07-1.60) were found. These associations were found primarily among those individuals who reported that they were never smokers.

Other Outcomes

Mendelsohn et al[12] examined personal hair dye use and cancer risk in a prospective cohort of 73 366 Chinese women (29 076 hair dye users and 44 290 nonusers). Cancer diagnoses were ascertained through the Shanghai Cancer Registry in 1536 nonusers and 901 hair dye users. Self-administered questionnaires followed by interviews were used to gather data on use of hair dyes over the past 3 years, with follow-up questions about frequency of use over the past year and years of use for those individuals who answered "yes" to the initial question about recent hair dye use; the authors noted that hair dye color was not determined, but that most hair dye use would be expected to be dark hair dyes. The authors reported no significant association with hair dye use and overall cancer or for several common cancers, including breast cancer, lung cancer, stomach cancer, bladder cancer, hematopoietic cancer, including subtypes of non-Hodgkin lymphoma, multiple myeloma, and leukemia. The authors cautioned that the study is limited by small numbers of certain cancer types.

Exposure Assessment

Ambrosone et al[13] evaluated DNA adducts in breast ductal epithelial cells isolated from breast milk obtained from 64 women. A questionnaire was used to determine prior hair dye use, meat intake, and tobacco exposure. The following were reported:

- 2-Amino-6-phenylimidazo[4,5-*b*]pyridine (PhIP)-DNA adducts (30 participants, mean detectable level of 4.7 $\pm$ 1.7 adducts/107 nucleotides),

- Benzo[*a*]pyrene-7,8-diol-9,10-epoxide (BPDE)-adducts (13 participants, mean detectable level of 1.7 ± 0.7 adducts/10 nucleotides), and
- 4-Amino biphenyl (4-ABP)-DNA adducts (18 participants, mean detectable level of 4.7 ± 2.2 adducts/107 nucleotides).

No association was reported between PhIP-DNA adducts or BPDE-DNA adducts and either meat consumption or tobacco exposure. The authors did not present PhIP-DNA or BPDE-DNA adduct data as a function of hair dye exposure. The authors reported that the presence of 4-ABP-DNA adducts were associated with use of hair dyes in the previous year but the association was not statistically significant. Among the hair dye users, the OR for use 6 to 12 months prior to sample collection was 5.42 (95% CI 0.49-59.74) and for 0 to 6 months, the OR was 11.17 (95% CI 1.14-109.19).

For temporary hair dye users, the OR was 9.47 (95% CI 0.46-195.04) and for permanent hair dye users the OR was 8.20 (95% CI 0.94-71.83). Use of light hair dye colors had an OR of 18.12 (95% CI 1.45-226.83), medium colors had an OR of 5.61 (95% CI 0.35-90.35), and dark colors had an OR of 2.57 (95% CI 0.10-64.31).

The authors reported that rapid *NAT1* and *NAT2* genotypes were associated with an increase in PhIP-DNA adducts and 4-ABP-DNA adducts, compared with slow acetylator genotypes, and that the level of 4-ABP-DNA adducts was higher for rapid *NAT2* genotypes compared to rapid *NAT1* genotypes.

The authors did not provide data on BPDE-DNA adducts as a function of *NAT* genotype. The authors also did not present data on 4-APB-DNA adducts as a function of meat consumption or tobacco exposure. The authors acknowledged that the small sample size resulted in wide CIs and limited the statistical power of the results.

Hueber-Becker et al[14] monitored the exposure of hairdressers to oxidative hair dyes under controlled conditions to determine whether the process of oxidative hair dye use produces measurable external and/or systemic exposure, and, if so, which parts of the process are responsible. [14C]-*p*-Phenylenediamine dihydrochloride was combined with a commercial product containing *p*-phenylenediamine dihydrochloride (4%), resorcinol (2%), and *m*-aminophenol (2%) in the dye component and a cream formulation developer with hydrogen peroxide (6%). In addition to the task of hair dye preparation and dyeing, the study monitored exposure during shampooing, rinsing, and conditioning and during hair cutting and drying. Six artificial human training heads with implanted human hair were used in a given day. One hairdresser performed the hair dye preparation and dyeing, a second hairdresser did the shampooing, and so on, and a third hairdresser did the cutting and drying—on all 6 heads. This process was repeated 6 times, involving a total of 18 hairdressers and 36 artificial human heads. Other than the mixing bowl, hair wash, and hair, recoveries were all less than 0.5% and most <0.1%.

Urinary excretion of radioactivity in the 18 hairdressers determined over 3 intervals (0-12 hours, 12-24 hours, and 24-48 hours) resulted in excretion values (all values below the limit of detection were given the value of the limit of detection) of <8.8 ± 4.4; <6.8 ± 4.6, and <9.7 ± 6.0 mg [14C] *p*-phenylenediamine dihydrochloride equivalent. Excretion values per working day (including 6 complete procedures) was <25.3 ± 5.2 mg [14C] *p*-phenylenediamine dihydrochloride equivalent. For a 71-kg individual, the exposure was calculated to be <0.36 mg/kg per day. The authors expressed uncertainty as to the source of this low level of measured systemic exposure. The authors noted that detectable air levels of radioactivity were found during the preparation and dyeing phase and the hair-cutting phase but not in the washing phase. In those individuals exposed to detectable air levels, urinary excretion was not elevated compared to individuals exposed to air samples with no detectable radioactivity.

International Agency for Research on Cancer

In 2008, International Agency for Research on Cancer (IARC) issued new working group observations on bladder cancer and hematological cancers.[15] The working group considered 82 studies involving personal use of hair dyes and 85 studies of occupational exposures. They concluded that the data are insufficient (quality, consistency, or statistical power) to conclude the presence or absence of a causal link between personal use of hair dyes and cancer. They also reviewed animal studies and cited major limitations (qualitative and quantitative) that preclude concluding that hair dyes have carcinogenic effects in animals. Occupational exposure as a hairdresser, barber, or beautician was also assessed. The working group noted that such occupations may involve exposure to hair dyes, but that any risk cannot be attributed to hair dye exposure, but is linked to all exposures that individuals may experience in these occupations. With that caveat, the working group did find that exposures experienced in these occupations are probably carcinogenic.

Discussion

In considering these data on many different end points, 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 end points based on lack of strength of the associations and inconsistency of findings. The Panel stated that use of direct hair dyes, while 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.

Author's Note

All unpublished sources cited in these re-reviews are available from the Director, Cosmetic Ingredient Reivew, 1101 17th St., NW Suite 412 Washington, D.C. 20036 USA

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References

1. Bolt HM, Golka K. The debate on carcinogenicity of permanent hair dyes: new insights. *Crit Rev Toxicol*. 2007;37(6):521-536.
2. Kelsh MA, Alexander DD, Kalmes RM, Buffler PA. Personal use of hair dyes and risk of bladder cancer: a meta-analysis of epidemiologic data. *Cancer Causes Control*. 2008;19(6):549-558.
3. Chiu BC-H, Dave BJ, Blair A, et al. Cigarette smoking, familial hematopoietic cancer, hair dye use, and risk of t(14;18)-defined subtypes of non-Hodgkin's lymphoma. *Am J Epidemiol*. 2011; 165(6):652-659.
4. Morton LM, Bernstein L, Wang SS, et al. Hair dye use, genetic variation in N-acetyltransferase 1 (NAT1) and 2 (NAT2), and risk of non-Hodgkin lymphoma. *Carcinogenesis*. 2007;28(8): 1759-1764.
5. Zhang Y, de Sanjose S, Bracci PM, et al. Personal use of hair dye and the risk of certain subtypes of non-Hodgkin lymphoma. *Am J Epidemiol*. 2008;167(11):1321-1331.
6. Koutros S, Baris D, Bell E, et al. Use of hair colouring products and risk of multiple myeloma among US women. *Occup Environ Med*. 2009;66(1):68-70.
7. Axmon A, Rylander L. Birth weight and fetal growth in infants born to female hairdressers and their sisters. *Occup Environ Med*. 2009;66(3):198-204.
8. Gallicchio L, Miller S, Greene T, Zacur H, Flaws J. Cosmetologists and reproductive outcomes. *Obstet Gynecol*. 2009;113(5): 1018-1026.
9. Halliday-Bell JA, Gissler M, Jaakkola JJK. Work as a hairdresser and cosmetologist and adverse pregnancy outcomes. *Occup Med (Lond)*. 2009;59(3):180-184.
10. Herdt-Losavio ML, Lin S, Druschel CM, Hwang S-A, Mauer MP, Carlson GA. The risk of having a low birth weight or preterm infant among cosmetologists in New York State. *Matern Child Health J*. 2009;13(1):90-97.
11. Baste V, Moen BE, Riise T, Hollund BE, Øyen N. Infertility and spontaneous abortion among female hairdressers: the Hordaland Health Study. *J Occup Environ Med*. 2008;50(12): 1371-1377.
12. Mendelsohn JB, Li QZ, Ji BT, et al. Personal use of hair dye and cancer risk in a prospective cohort of Chinese women. *Cancer Sci*. 2009;100(6):1088-1091.
13. Ambrosone CB, Abrams SM, Gorlewska-Roberts K, Kadlubar FF. Hair dye use, meat intake, and tobacco exposure and presence of carcinogen-DNA adducts in exfoliated breast ductal epithelial cells. *Arch Biochem Biophys*. 2007;464(2): 169-175.
14. Hueber-Becker F, Nohynek GJ, Dufour EK. Occupational exposure of hairdressers to [14C]-para-phenylenediamine-containing oxidative hair dyes: a mass balance study. *Food Chem Toxicol*. 2007;45(1):160-169.
15. Baan R, Straif K, Grosse Y, et al. WHO international agency for research on cancer monograph working group: carcinogenicity of some amines, organic dyes, and related exposures. *Lancet Oncol*. 2009;9(4):322-323.

Acetamide MEA

Conclusion

In a 1993 safety assessment of acetamide monoethanolamine (MEA), the Cosmetic Ingredient Review (CIR) Expert Panel stated that acetamide MEA is considered safe up to a concentration of 7.5% in leave-on products and at the current practices of use in rinse-off products.[1] The Expert Panel reviewed updated information regarding product types and concentrations of use. No new information on acetamide MEA was found, and the Panel did not reopen this safety assessment. The Panel confirmed that acetamide MEA is safe as a cosmetic ingredient at concentrations not to exceed 7.5% in leave-on products and is safe in rinse-off products in the practices of use and concentration as given in Table 1.

Discussion

The CIR Expert Panel noted that a safety assessment of MEA had been performed,[2] with the conclusion that MEA should be used only in rinse-off products at concentrations up to 5%. The Panel contrasted that conclusion with that of acetamide MEA for which leave-on use is considered safe up to a concentration of 7.5%. Because acetamide MEA is a stable ingredient on the skin, however, the Panel determined that the restriction to rinse-off products of MEA would not be applicable to acetamide MEA. The Panel agreed that the available skin sensitization studies at 7.5% supported leave-on use of acetamide MEA up to that concentration.

The Panel considered the possibility that the available data could support the safety of chemically similar ingredients.

Table 1 Historical and Current Cosmetic Product Uses and Concentrations for Acetamide MEA

Product Category	1992 Uses[1]	2007 Uses[3]	1992 Concentrations,[1] %	2008 Concentrations,[4] %
Bath products				
Soaps and detergents	–	2	–	–
Other	3	–	–	–
Noncoloring hair care products				
Conditioners	60	69	25	0.01-3
Sprays/aerosol fixatives	–	11	–	–
Rinses	–	2	–	0.5
Shampoos	14	21	5	0.0001
Tonics, dressings, etc	12	16	10	0.03-0.3
Wave sets	7	2	5	–
Other[a]	3	9	–	0.2-5
Nail care products				
Other	–	1	–	–
Personal hygiene products				
Underarm deodorants	–	9	–	0.7
Skin care products				
Skin cleansing creams, lotions, liquids, and pads	–	4	–	0.06
Face and neck creams, lotions, powder, and sprays	–[b]	–	–[b]	0.2-3
Body and hand creams, lotions, powder, and sprays		7		–
Moisturizers	3	1	–	–
Night creams, lotions, powder, and sprays	–	3	–	–
Skin fresheners	–	1	–	–
Total uses/ranges for acetamide MEA	102	159	5-25	0.0001-5

[a] 0.2% in a leave-on conditioner; 0.7% in an oil treatment; 3% in a hair mask; and 5% in a nonaerosol hair spray.
[b] This category was combined when the original safety assessment was performed and is now 2 separate categories.

Because skin sensitization and skin penetration data are not available for these chemically similar ingredients, however, the decision was made that the safety test data in the original safety assessment support the safety of acetamide MEA only.

References

1. Elder RL. Final report on the safety assessment of Acetamide MEA. *J Am Coll Toxicol*. 1993;12(3):225-236.
2. Elder RL. Final report on safety assessment of triethanolamine, diethanolamine, and monoethanolamine. *J Am Coll Toxicol*. 1983;2(7):183-235.
3. Food and Drug Administration. 2007. Frequency of use of cosmetic ingredients. FDA Database.
4. CTFA. 2008. Use concentration survey results. Acetamide MEA. 1 pages.

5-Bromo-5-Nitro-1,3-Dioxane

Conclusion

In its 1990 safety assessment of 5-bromo-5-nitro-1,3-dioxane,[1] the Cosmetic Ingredient Review (CIR) Expert Panel stated that this ingredient 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. The CIR Expert Panel considered newly available studies[2,3] and reviewed current usage,[4] including use concentrations.[5] The Expert Panel confirmed the safety of 5-bromo-5-nitro-1,3-dioxane at concentrations $\leq$0.1%, except under circumstances where its action with amines or amides can result in the formation of nitrosamines or nitrosamides and did not reopen this safety assessment.

Discussion

Current and historical usage and use concentration data are presented in Table 1. In 1988, it was reported by industry (to the US Food and Drug Administration [FDA] voluntary product reporting program) that 5-bromo-5-nitro-1,3-dioxane was used in 46 product formulations[1] at concentrations up to and including 1%. Currently, its use in 34 product formulations in specific product

Table 1. Historical and Current Cosmetic Product Uses and Concentrations for 5-Bromo-5-Nitro-1,3-Dioxane

Product Category	1988 Uses (Total Number of Products in Category)[1]	2007 Uses (Total Number of Products in Category)[4]	1988 Use Concentration Ranges[1] (%)	2007 Use Concentrations[5] (%)
Baby products				
Shampoos	–	1 (38)	–	–
Bath products	19 (1008)		≤0.1 and >0.1-1	
OILS, tablets, and salts	–	1 (207)		–
Bubble baths	–	1 (256)		–
Noncoloring hair care products	24 (1315)		≤0.1 and >0.1-1	
Conditioners	–	6 (715)	–	–
Rinses	–	1 (46)	–	–
Shampoos	–	16 (1022)	–	0.04
Hair coloring products				
Dyes and colors	–	1 (1600)	–	–
Other	–	4 (73)	–	–
Skin care products	3 (2004)			
Personal hygiene products				
Soaps and detergents	–	2 (594)	–	–
Feminine hygiene products				
Other	–	1 (390)	–	–
Totals	46	38	≤0.1 and >0.1-1	0.04

categories[4,5] is reported to FDA and an industry survey produced 1 use concentration, 0.04%.

The CIR Expert Panel noted that safety concerns about 1,4-dioxane, which may be an impurity in some cosmetic ingredient preparations, do not exist for 5-bromo-5-nitro-1,3-dioxane because 1,4-dioxane is not an impurity, nor is it a breakdown product.

References

1. Elder RL (ed). Final report on the safety assessment of 5-bromo-5-nitro-1,3-dioxane. *J Am Coll Toxicol*. 1990;9(2):279-288.
2. European Commission. http://ec.europa.eu/enterprise/cosmetics/index_en.htm. 2007. Accessed October 1, 2006.
3. Gruvberger B, Bruzo M. Contact allergy to commercially available preservative containing in humans and guinea pigs. *Dermatosen im Beru und Umwelt*. 1997;45:272-27we4.
4. Food and Drug Administration. Frequency of use of cosmetic ingredients. FDA Database. Unpublished study submitted by CTFA; 2007.
5. CTFA. Use concentration survey results. Unpublished study submitted by CTFA; 2007.

Butyl Benzyl Phthalate

Conclusion

In a 1992 safety assessment of butyl benzyl phthalate, the Cosmetic Ingredient Review (CIR) Expert Panel[1] stated that this ingredient is safe as a cosmetic ingredient in the present practices of use and concentration. The Expert Panel reviewed newly available studies since that assessment,[2-73] along with statements/data from the cosmetics industry and the Food and Drug Administration indicating that butyl benzyl phthalate is not currently being used in cosmetic products. The Panel noted that though butyl benzyl phthalate is not being used in cosmetics, it would be considered safe in the current practices of use and concentration and did not reopen this safety assessment.

Discussion

The Panel considers that this ingredient has been used as a plasticizer in cosmetic products. Butyl benzyl phthalate was used in 2 hair sprays (aerosol fixatives) in 1989, based on voluntary reports submitted to Food and Drug Administration (FDA)[1] by industry, with concentrations of use <1%. In 2006, there were no reported uses of butyl benzyl phthalate.[74] Similarly, data from an industry survey in 2007 indicated no reported uses of this ingredient.[75]

The available use and concentration data are given in Table 1 as a function of product category.

The Expert Panel recognizes that though there are no reported uses of butyl benzyl phthalate, it could be a

Table 1. Historical and Current Cosmetic Product Uses and Concentrations for Butyl Benzyl Phthalate

Product Category (FDA 2006)[74]	1989 Uses[1]	Total Products in Category[1]	2006 Uses[74]	Total Products in Category[74]	1989 Concentrations[1] (%)	2007 Concentrations[75] (%)
Hair sprays (aerosol fixatives)	2	261	[a]	294	<1.0	[b]
Total uses/ranges for butyl benzyl phthalate	2		[a]		<1.0	[b]

Abbreviation: FDA, Food and Drug Administration.
[a] In FDA's voluntary reporting system, no uses reported for this category in 2006.
[b] In industry survey, no use concentrations reported for this category in 2007.

contaminant of other phthalates (ie, dimethyl phthalate, diethyl phthalate, and dibutyl phthalate) in cosmetic products due to the migration of butyl benzyl phthalate from the plastic container.

In consideration of the numerous studies on butyl benzyl phthalate (a reproductive toxicant) identified in the published literature since the final report on this ingredient was issued by the Expert Panel, studies relating to endocrine activity, reproductive toxicity, developmental toxicity, and carcinogenicity were of particular concern. The Panel noted that weak effects were reported in these studies, all of which were observed at high doses, compared to exposure to use concentrations of <1% butyl benzyl phthalate that have been associated with hair sprays and considered nontoxic. Regarding reproductive and developmental toxicities, the Panel considered that these studies demonstrate a no observable effect level. The Panel noted that these data, combined with recent information indicating that trace amounts (up to 100 ppm) of butyl benzyl phthalate have been detected in cosmetic products, suggest a wide margin of safety (MOS) that would preclude any risks to the health of consumers. An MOS calculation for butyl benzyl phthalate and the considerations used in determining the MOS[75] are discussed below.

The most appropriate no observable adverse effect level (NOAEL) is for developmental effects identified by the National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR).[76] The NOAEL for butyl benzyl phthalate, 182 mg/kg per d (mice) is from a study that was conducted by the NTP (1990),[77] and this NTP study is summarized in the published CIR final report on butyl benzyl phthalate.[1] It is important to note that an NOAEL of 185 mg/kg per d in Wistar rats[78] was also cited by Kavlock et al (2002).[76] However, the NOAEL of 182 mg/kg per d was used in the MOS calculation.

Expected Exposure

Hair Spray[79]

- 5.18 g/d
- 1% butyl benzyl phthalate in hair spray[1]
- 20% skin contact; from Personal Care Products Council worst case estimate (used in the 2002 dibutyl phthalate exposure estimate)
- 30% dermal absorption[80] (rat study 30% is the amount excreted in 7 days)

5.18 g/d × 1% × 20% × 30% = 3.1 mg/d per 60 kg = 0.052 mg/kg per d

Margin of Safety Calculation

182 mg/kg per d/0.052 mg/kg per d = 3500

References

1. Elder RL. Final report on the safety assessment of butyl benzyl phthalate. *JACT*. 1992;11(1):1-23.
2. Adibi JJ, Perera FP, Jedrychowski W, et al. Prenatal exposures to phthalates among women in New York City and Krakow, Poland. *Environ Health Perspect* 2003;111(14):1719-1722.
3. Anderson WAC, Castle L, Scotter MJ, Massdy RC, Springall C. A biomarker approach to measuring human dietary exposure to certain phthalate diesters. *Food Addit Contam*. 2001;18(12):1068-1074.
4. Aschengrau A, Coogan PF, Quinn MM, Cashins LJ. Occupational exposure to estrogenic chemicals and the occurrence of breast cancer: an exploratory analysis. *Am J Ind Med*. 1998;34(1):6-14.
5. Ashby J, Tinwell H, Lefevre PA, et al. Normal sexual development of rats exposed to butyl benzylphthalate from conception to weaning. *Regul Toxicol Pharmacol*. 1997;26(1):102-118.
6. Aso S, Ehara H, Miyata K, et al. A two-generation reproductive toxicity study of butyl benzyl phthalate in rats. *J Toxicol Sci*. 2005;30(spec no 2):39-58.
7. Barber ED, Cifone M, Rundell J. Results of the L5178Y mouse lymphoma assay and the Balb/3T3 cell in vitro transformation assay for eight phthalate esters. *J Appl Toxicol*. 2000;20(1):69-80.
8. British Industrial Biological Research Association (BIBRA). *Initial Submission: A 21-Day Dose Relationship Study With Butyl Benzyl Phthalate in Rats (Project Report) (With Cover Letter Dated 050592) NTIS Report No. OTS0536510*. 1984. Report No. OTS0536510.
9. Bornehag C, Sundell J, Weschler CJ, et al. The association between asthma and allergic symptoms in children and phthalates in house dust: a nested case-control study. *Environ Health Perspect*. 2004;112(14):1393-1397.
10. Butula JH, David RM, Gans G, et al. Phthalate treatment does not influence levels of IgE or Th2 cytokines in B6C3F1 mice. *Toxicology*. 2004;201(1-3):77-85.

11. Caldwell DJ. Review of mononuclear cell leukemia in F-344 rat bioassays and its significance to human cancer risk: a case study using alkyl phthalates. *Regul Toxicol Pharmacol*. 1999;30(1):45-53.
12. Ema M, Harazono A, Miyawaki E, Ogawa Y. Characterization of developmental toxicity of mono-n-benzyl phthalate in rats. *Reprod Toxicol*. 1996;10(5):365-372.
13. Ema M, Harazono A, Miyawaki E, Ogawa Y. Developmental toxicity of mono-n-benzyl phthalate, one of the major metabolites of the plasticizer n-butyl benzyl phthalate in rats. *Toxicol Lett*. 1996;86(1):19-25.
14. Ema M, Itami T, Kawasaki H. Evaluation of the embryolethality of butyl benzyl phthalate by conventional and pair-feeding studies in rats. *J Appl Toxicol*. 1991;11(1):39-42.
15. Ema M, Itami T, Kawasaki H. Teratogenic evaluation of butyl benzyl phthalate in rats by gastric intubation. *Toxicol Lett*. 1992;61(1): 1-7.
16. Ema M, Itami T, Kawasaki H. Effect of period of exposure on the developmental toxicity of butyl benzyl phthalate in rats. *J Appl Toxicol*. 1992;12(1):57-61.
17. Ema M, Itami T, Kawasaki H. Embryolethality and teratogenicity of butyl benzyl phthalate in rats. *J Appl Toxicol*. 1992;12(3): 179-183.
18. Ema M, Itami T, Kawasaki H. Teratogenic phase specificity of butyl benzyl phthalate in rats. *Toxicology*. 1993;79(1):11-19.
19. Ema M, Kurosaka R, Amamo H, Ogawa Y. Embryolethality of butyl benzyl phthalate during early pregnancy in rats. *Reprod Toxicol*. 1994;8(3):231-236.
20. Ema M, Kurosaka R, Amamo H, Ogawa Y. Comparative developmental toxicity of n-butyl phthalate and di-n-butyl phthalate in rats. *Arch Environ Contam Toxicol*. 1995;28(2):223-228.
21. Ema M, Miyawaki E. Effects on development of the reproductive system in male offspring of rats given butyl benzyl phthalate during late pregnancy. *Reprod Toxicol*. 2002;16(1):71-76.
22. Ema M, Miyawaki E, Hirose A, Kamata E. Decreased anogenital distance and increased incidence of undescended testes in fetuses of rats given monobenzyl phthalate, a major metabolite of butyl benzyl phthalate. *Reprod Toxicol*. 2003;17(4):407-412.
23. Ema M, Miyawaki E, Kawashima K. Reproductive effects of butyl benzyl phthalate in pregnant and pseudopregnant rats. *Reprod Toxicol*. 1998;12(2):127-132.
24. Ema M, Miyawaki E, Kawashima K. Developmental effects of plasticizer butyl benzyl phthalate after a single administration in rats. *J Appl Toxicol*. 1999;19(5):357-365.
25. European Union. 2007. *The Rules Governing Cosmetic Products in the European Union. Volume 1.* Cosmetics Legislation–Cosmetic Products.
26. Fujimoto Y, Usa K, Sakuma S. Effects of endocrine disruptors on the formation of prostaglandin and arachidonyl-CoA formed from arachidonic acid in rabbit kidney medulla microsomes. *Prostagland Leukot Essent Fatty Acids*. 2005;73(6):447-452.
27. Fujita T, Kobaashi Y, Wada O, et al. Full activation of estrogen receptor a activation function-1 induces proliferation of breast cancer cells. *J Bio Chem*. 2003;278(29):26704-26714.
28. Funabashi T, Kawaguchi M, Kimura F. The endocrine disrupters butyl benzyl phthalate and bisphenol A increase the expression of progesterone receptor messenger ribonucleic acid in the preoptic area of adult ovariectomized rats. *Neuroendocrinology*. 2001; 74(2):77-81.
29. Gottschalck TE, McEwen Jr, GN, eds. *International Cosmetic Ingredient Dictionary and Handbook*. 11th ed. Washington DC: CTFA; 2006.
30. Götz F, Thieme S, Dörner G. Female infertility–effect of perinatal xenoestrogen exposure on reproductive functions in animals and humans. *Folia Histochem Cytobiol*. 2001;39(suppl 2):40-43.
31. Gray Jr LE, Otsby J, Furr J, Price M, Rao Veeramachaneni DN, Parks L. Perinatal exposure to the phthalates DEHP, BBP, AND DINP, but not DEP, DMP, or DOTP, alters sexual differentiation of the male rat. *Toxicol Sci*. 2000;58(suppl 2):350-365.
32. Harris CA, Henttu P, Parker MG, Sumpter JP. The estrogenic activity of phthalate esters in vitro. *Environ Health Perspect*. 1997; 105(8):802-811.
33. Hong EJ, Ji YK, Choi KC, Manabe N, Jeung EB. Conflict of estrogenic activity by various phthalates between in vitro and in vivo models related to the expression of calbindin-D_{9k}. *J Reprod Dev*. 2005;51(2):253-263.
34. Hotchkiss AK, Parks-Saldutti LG, Ostby JS, et al. A mixture of the "antiandrogens" linuron and butyl benzyl phthalate alters sexual differentiation of the male rat in a cumulative fashion. *Biol Reprod*. 2004;71(6):1852-1861.
35. Howard PH, Banerjee S, Robillard KH. Measurement of water solubilities, octanol/water partition coefficients and vapor pressures of commercial phthalate esters. *Environ Toxicol Chem*. 1985;4(2):653-661.
36. Hubinger JC, Havery DC. Analysis of consumer cosmetic products for phthalate esters. *J Cosmet Sci*. 2006;57(2):127-137.
37. International Agency for Research on Cancer (IARC). *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*. Vol 29. Lyon, France: IARC;1982:193.
38. International Agency for Research on Cancer (IARC). *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, suppl.7 Overall Evaluation of Carcinogenicity: an Updating of IARC Monographs*. Vol 1 to 42. Lyon, France: IARC;1987:59.
39. International Agency for Research on Cancer (IARC). *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*. Vol 73. Lyon, France: IARC;1999:115-129.
40. Kang IH, Kim HS, Kim TS, et al. Antiandrogenic activity of phthalate esters (di(2-ethylhexyl)phthalate,di(n-butyl) phthalate, and butylbenzyl phthalate in the rodent 10-day Hershberger assay using immature castrated male rats. *J Toxicol Pub Health*. 2005; 21(6):187-193.
41. Kang SC, Lee BM. DNA methylation of estrogen receptor a gene by phthalates. *J Toxicol Environ Health*. 2005;68(23-24):1195-2003.
42. Kim IY, Han SY, Moon A. Phthaltes inhibit tamoxifen-induced apoptosis in MCF-7 human breast cancer cells. *J Toxicol Environ Health*. 2004;67(23-24):2025-2035.
43. Koch HM, Preuss R, Drexler H, Angerer J. Exposure of nursery school children and their parents and teachers to di-n-butylphthalate and butylbenzylphthalate. *Int Arch Occup Environ Health*. 2005;78(3):223-229.
44. Kohno H, Suzuki R, Sugie S, Tsuda H, Tanaka T. Lack of modifying effects of 4-tert-octylphenol and benzyl butyl phthalte on

3,2'-dimethyl-4-aminobiphenyl-induced prostate carcinogenesis in rats. *Cancer Sci*. 2004;95(4):300-305.
45. Larsen ST, Lund RM, Thygesen P, Poulsen OM, Nielsen GD. Investigation of the adjuvant and immuno-suppressive effects of benzyl butyl phthalate, phthalic acid and benzyl alcohol in a murine injection model. *Food Chem Toxicol*. 2003;41(3):439-446.
46. LeBoeuf RA, Kerckaert GA, Aardema MJ, Gibson DP, Brauniger R, Isfort RJ. The pH 6.7 Syrian hamster embryo cell transformation assay for assessing the carcinogenic potential of chemicals. *Mut Res*. 1996;356(1):85-127.
47. Lee BM, Koo HJ. Hershberger assay for antiandrogenic effects of phthalates. *J Toxicol Environ Health A*. 2007;70(15-16):1365-1370.
48. Li WL, Ji YB, Yang YN, Yang B. Reproductive toxicity and functional mechanism of the environmental hormone butyl benzyl phthalate. *Huan Jing Ke Xue*. 2004;25(1):1-6.
49. Liu PS, Chen YY. BBP blocks Ca^{2+} signaling coupled with purinoceptor in rat PC12 cells. *Toxicol Appl Pharmacol*. 2006;210(1-2):136-141.
50. Liu PS, Lin CM, Pan CY, Kao LS, Tseng FW. BBP blocks Ca^{2+} signaling and catecholamine secretion coupled with nicotinic acetylcholine receptors in bovine adrenal chromaffin cells. *Neurotoxicology*. 2003;24(1):97-105.
51. Mikuriya H, Ikemoto I, Tanaka A. Urinary metabolites contributing to testicular damage induced by butyl benzyl phthalate. *Jikeikai Med J*. 1988;35(3):403-409.
52. Myhr BC, Caspary J. Chemical mutagenesis at the thymidine kinase locus in L5178Y mouse lymphoma cells: results for 31 coded compounds in the National Toxicology Program. *Environ Mol Mutagen*. 1991;18(1):51-83.
53. Nagao T, Ohta R, Marumo H, Shindo T, Yoshimura S, Ono H. Effect of BBP in Sprague-Dawley rats after gavage administration: a two-generation reproductive study. *Reprod Toxicol*. 2000;14(6):513-532.
54. Nakagomi M, Suzuki E, Usumi K, et al. Effects of endocrine disrupting chemicals on the microtubule network in Chinese hamster V79 cells in culture and in Sertoli cells in rats. *Teratog Carcinog Mutagen*. 2001;21(6):453-462.
55. National Toxicology Program (NTP). *Toxicology and Carcinogenesis Studies of Butyl Benzyl Phthalate (CAS No. 85-68-7) in F344/N Rats (Feed Studies). NTIS Report No. PB98131089*. 1997. Report No. PB98131089.
56. Nativelle C, Picard K, Valentin I, Lhuguenot JC, Chagnon MC. Metabolism of n-butyl phthalate in the female Wistar rat. Identification of new metabolites. *Food Chem Toxicol*. 1999;37(8):905-917.
57. Picard K, Lhuguenot JC, Lavier-Canivenc MC, Chagnon MC. Estrogenic activity and metabolism of n-butyl benzyl phthalate in vitro: identification of the active molecule(s). *Toxicol Appl Pharmacol*. 2001;172(2):108-118.
58. Piersma AH, Verhoef A, Dortant PM. Evaluation of the OECD 421 reproductive toxicity screening test protocol using BBP. *Toxicology*. 1995;99(3):191-197.
59. Piersma AH, Verhoef A, te Biesebeek JD, Pieters MN, Slob W. Developmental toxicity of butyl benzyl phthalate in the rat using a multiple dose study design. *Reprod Toxicol*. 2000;14(5):417-425.
60. Reddy BS, Rozati R, Reddy BVR, Raman NVVSS. Association of phthalate esters with endometriosis in Indian women. *BJOG* 2006;113(5):515-520
61. Rhee GS, Kim SH, Kim SS, et al. Comparison of embryotoxicity of ESBO and phthalate esters using an in vitro battery system. *Toxicol In Vitro*. 2002;16(4):443-448.
62. Robinson EC. Lack of neuropathological changes in rats after exposure to butyl benzyl phthalate. *J Toxicol Environ Health*. 1991;32(3):345-348.
63. Saillenfait AM, Sabate MP, Gallissot F. Comparative embryotoxicities of butyl benzyl phthalate, mono-n-butyl phthalate and mono-benzyl phthalate in mice and rats: in vivo and in vitro observations. *Reprod Toxicol*. 2003;17(5):575-583.
64. Scientific Committee on Consumer Products (SCCP). Opinion on phthalates in cosmetic products. Brussels, SCCP. 2007. http://ec .europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_106.pdf. Accessed June 15, 2007.
65. Sharpe RM, Fisher JS, Millar MM, Jobling S, Sumpter JP. Gestational and lactational exposure of rats to xenoestrogens results in reduced testicular size and sperm production. *Environ Health Perspect*. 1995;103(12):1136-1143.
66. Singletary K, MacDonald C, Wallig M. Short communication. The plasticizer benzyl butyl phthalate (BBP) inhibits 7,12-dimethylbenz[a]anthracene (DMBA)-induced rat mammary DNA adduct formation and tumorigenesis. *Carcinogenesis*. 1997;18(8):1669-1673.
67. TNO Nutrition and Food Research. *Dietary One-Generation Reproduction Study With Butyl Benzyl Phthalate in Rats (With Cover Letter Dated 040793) NTIS Report Nol OTS0538169*. 1993. Report No. OTS0538169.
68. Tyl RW, Myers CB, Marr MC, et al. Reproductive toxicity evaluation of dietary butyl benzyl phthalate (BBP) in rats. *Reprod Toxicol*. 2004;18(2):241-264.
69. Uriu-Adams JY, Reece CK, Nguyen LK, et al. Effect of BBP on reproduction and zinc metabolism. *Toxicology*. 2001;159(1-2):55-68.
70. Wilson GD, d'Arcy Doherty M, Cohen GM. Selective toxicity of 1-naphthol to human colorectal tumor tissue. *Brit J Cancer*. 1985;51(6):853-863.
71. World Health Organization (WHO). *Concise International Chemical Assessment Document 17. BBP*. Geneva: WHO; 1999.
72. Yamasaki K, Takahashi M, Yasuda M. Two-generation reproductive toxicity studies in rats with extra parameters for detecting endocrine disrupting activity: introductory overview of results for nine chemicals. *J Toxicol Sci*. 2005;30:1-4.
73. Zacharewski TR, Meek MD, Clemons JH, Wu ZF, Fielden MR, Matthews JB. Examination of the in vitro and in vivo estrogenic activities of eight commercial phthalate esters. *Toxicol Sci*. 1998;46(2):282-329.
74. Food and Drug Administration (FDA). *Frequency of Use of Cosmetic Ingredients*. Washington, DC: FDA; 2006.
75. Cosmetic, Toiletry, and Fragrance Association (CTFA). 2007. *Absence of Use Concentration Data on Butyl Benzyl Phthalate in Industry Survey. Statement Provided by CTFA, now Personal Care Products Council, in 2007*.
76. Kavlock R, Boekelheide K, Chapin R, et al. NTP Center for the Evaluation of Risks to Human Reproduction: phthalates expert

panel report on the reproductive and developmental toxicity of butyl benzyl phthalate. *Reprod Toxicol*. 2002;16(5):453-487.
77. National Toxicology Program (NTP). *Developmental Toxicity of Butyl Benzyl Phthalate (CAS No. 85-68-7) in CD-1 Swiss Mice (Report No. 90-114)*. Research Triangle Park, NTP. 1990. Report No. 90-114.
78. Ema M, Murai T, Itami T, Kawasaki H. Evaluation of the teratogenic potential of the plasticizer butyl benzyl phthalate in rats. *J Appl Toxicol*. 1990;10(5):339-343.
79. Loretz L, Api AM, Barraj L, et al. Exposure for personal care products: Hairspray, spray perfume, liquid foundation, shampoo, body wash, and solid antiperspirant. *Food Chem Toxicol*. 2006; 44(12):2008-2018.
80. Elsisi AE, Carter DE, Sipes IG. Dermal absorption of phthalate diesters in rats. *Fundam Appl Toxicol*. 1989; 12(1):70-77.

t-Butyl Hydroquinone

Conclusion

In a 1991 addendum to the safety assessment of *t*-butyl hydroquinone (TBHQ),[1] the Cosmetic Ingredient Review (CIR) Expert Panel presented an amended conclusion that this ingredient may be safely used in cosmetics at concentrations $\leq$0.1%; the original safety assessment had been published earlier by Elder.[2] In 2007, the CIR Expert Panel reviewed newly available studies since that addendum,[3-41] along with updated information regarding types and concentrations of use. The CIR Expert Panel confirmed the amended conclusion and did not reopen the safety assessment of TBHQ.

Discussion

The CIR Expert Panel noted that *t*-butyl hydroquinone is now called TBHQ.[42]

t-Butyl hydroquinone was used in 266 products in 1981, with concentrations of use ranging from $\leq$0.1% to 1%, based on voluntary reports submitted to FDA by industry.[43] In 2006, TBHQ was reportedly used in 59 cosmetic products.[44] Data from an industry survey[45] in 2007 indicated that TBHQ was used at concentrations ranging from 0.008% to 0.2%.

Historical and current product usage and use concentration data as a function of product category are given in Table 1.

The Panel, aware of new co-carcinogenicity and tumor-promoting activity data, indicated an ongoing concern regarding the safety of use levels greater than the 0.1% limit established in the original safety assessment (Note: 1 current use concentration of 0.2% in hair dyes and colors was noted and is above what the Panel finds acceptable). New genotoxicity studies using both bacterial and mammalian systems reaffirmed the safety of TBHQ at concentrations up to 0.1%.

References

1. Elder RL. Final report on the safety assessment of t-butyl hydroquinone—addendum. *J Am Coll Toxicol*. 1991;10(1):1-7.
2. Elder RL. Final Report on the safety assessment of t-butyl hydroquinone. *J Am Coll Toxicol*. 1986;5(5):329-352.
3. Aalto-Korte K. Allergic contact dermatitis from TBHQ in vegetable hydraulic oil. *Contact Dermat*. 2000;43(5):303.
4. Anderson D, Phillips BJ. Comparative in vitro and in vivo effects of antioxidants. *Food Chem Toxicol*. 1999;37(9-10):1015-1025.
5. Guan Y, Chu Q, Fu L, Ye J. Determination of antioxidants in cosmetics by micellar electrokinetic capillary chromatography with electrochemical detection. *J Chromatogr A*. 2005; 1074(1-2):201-204.
6. Hirose M, Yada H, Hakoi K, Takahashi S, Ito N. Modification of carcinogenesis by a-tocopherol, t-butylhydroquinone, propyl gallate and butylated hydroxytoluene in a rat multi-organ carcinogenesis model. *Carcinogenesis*. 1993;14(11):2359-2364.
7. Ikeda GJ, Sapienza PP, Ross IA. Distribution and excretion of radiolabelled TBHQ in Fischer 344 rats. *Food Chem Toxicol*. 1998;36(11):907-914.

Table 1. Historical and Current Cosmetic Product Uses and Concentrations for TBHQ

Product Category	1981 Uses (Total Number of Products in Product Category)[43]	2005 Uses (Total Number of Products in Product Category)[44]	1981 Concentrations (%)[43]	2007 Concentrations (%)[45]
Bath preparations				
Soaps and detergents	–[a] (421)	–[a] (594)	–[a]	0.005%
Eye makeup preparations				
Eye shadow	1 (2582)	–[a] (1061)	$\leq$0.1	–
Fragrance preparations				
Colognes and toilet waters	7 (1120)	–[a] (948)	$\leq$0.1	–
Perfumes	3 (657)	–[a] (326)	$\leq$0.1	–

(continued)

Table 1. (continued)

Product Category	1981 Uses (Total Number of Products in Product Category)[43]	2005 Uses (Total Number of Products in Product Category)[44]	1981 Concentrations (%)[43]	2007 Concentrations (%)[45]
Hair-coloring preparations				
Hair dyes and colors	–[a] (1690)	25 (1600)	–[a]	0.2%[b] (after dilution)
Makeup preparations				
Blushers	3 (819)	6 (459)	≤0.1	–
Foundations	–[a] (324)	–[a] (530)	–[a]	0.05%
Lipsticks	242 (3319)	–[a] (1681)	≤0.1-1	0.04%
Makeup bases	–[a] (141)	1 (273)	–[a]	–
Rouges	2 (211)	–[a] (115)	≤0.1	–
Other makeup preparations	3 (530)	–[a] (304)	≤0.1	–
Personal hygiene products				
Underarm deodorants	–[a] (247)	–[a] (281)	–[a]	0.05%
Other personal hygiene products	–[a] (308)	8 (390)	–[a]	–
Skin care preparations				
Skin cleansing creams, lotions, liquids, and pads	–[a] (775)	–[a] (1009)	–[a]	0.008%
Depilatories	1 (32)	–[a] (49)	>0.1-1	–
Face and neck skin care preparations	–[a] (310)	10 (546)	–[a]	–
Body and hand skin care preparations	–[a] (840)	–[a] (992)	–[a]	0.02%
Moisturizers	4 (747)	1 (1200)	≤0.1	–
Paste masks (mud packs)	–[a] (271)	–[a] (312)	–[a]	0.02%
Other skin care preparations	–[a] (725)	7 (915)	–[a]	0.04%
Suntan preparations				
Suntan gels, creams, and liquids	–[a] (131)	1 (138)	–[a]	0.004%
Total uses/ranges for TBHQ	266	59	≤0.1-1	0.004%-0.2%

Abbreviations: TBHQ, t-butyl hydroquinone; FDA, Food and Drug Administration.
[a] Not reported. In some cases, ingredient uses were not reported to FDA in the voluntary industry product survey program; however, concentrations were provided. In other cases, the uses were reported, but no concentration was provided.
[b] The 0.2% concentration reported in hair dyes and colors exceeds panel recommendations.

8. Kahl R, Weinke S, Kappus H. Production of reactive oxygen species due to metabolic activation of butylated hydroxyanisole. *Toxicology*. 1989;59(2):179-194.
9. Kawabe M, Takaba K, Yoshida Y, Hirose M. Effects of combined treatment with phenolic compounds and sodium nitrite on two-stage carcinogenesis and cell proliferation in the rat stomach. *Jpn Cancer Res*. 1994;85(1):17-25.
10. Kerchaert GA, Brauninger R, LeBoeuf RA, Isfort RJ. Use of Syrian hamster embryo cell transformation assay for carcinogenicity prediction of chemicals currently being tested by the National Toxicology Program in rodent bioassays. *Environ Health Perspect*. 1996;104(suppl 5):1075-1084.
11. Le Coz CJ, Schneider GA. Contact dermatitis from TBHQ in a hair dye, with cross-sensitivity to BHA and BHT. *Contact Dermat*. 1998;39(1):39-40.
12. Li Y, Trush MA. Reactive oxygen-dependent DNA damage resulting from the oxidation of phenolic compounds by a copper-redox cycle mechanism. *Cancer Res*. 1994;54(7)(suppl):1895s-1898s.
13. Li R, Chen W, Yanes R, Lee S, Berliner JA. OKL38 is an Oxidative stress response gene stimulated by oxidized phospholipids. *J Lipid Res*. 2007;48(3):705.
14. Ma Q, Kinneer K. Chemoprotection by phenolic antioxidants. Inhibition of tumor necrosis factor alpha induction in macrophages. *J Bio Chem*. 2002;277(4):2477-2484.
15. Marchant CA and The DEREK Collaborative Group. Prediction of rodent carcinogenicity using the DEREK system for 30 chemicals currently being tested by the National Toxicology Program. *Environ Health Perspect*. 1996;104(suppl 5):1065-1073.
16. Matsuoka A, Matsui M, Miyata N, Sofuni T, Ishidate Jr M. Mutagenicity of BHA and its metabolites in short-term tests in vitro. *Mutat Res*. 1990;241(2):125-132.
17. Meding B. Occupation contact dermatitis from TBHQ in a cutting fluid. *Contact Dermat*. 1996;34(2):224.
18. Morimoto K, Tsuji K, Iio T, et al. DNA damage in forestomach from male F344 rats following oral administration of tert-butylquinone, one of the forestomach metabolites of 3-BHA. *Carcinogenesis*. 1991;12(4):703-708.
19. Morimoto K, Takahashi T, Okudaira K, Iio T, Saito Y, Takahashi A. Dose-response study on covalent binding to forestomach protein from male F344 rats following oral administration of [^{14}C]3-BHA. *Carcinogenesis*. 1992;13(9):1663-1666.
20. Murphy TH, De Long MJ, Coyle JT. Enhanced NAD(P)H:quinone reductase activity prevents glutamate toxicity produced by oxidative stress. *J Neurochem*. 1991;56(3):990-995.
21. Nakagawa Y,Moldeus P. Cytotoxic effects of phenylhydroquinone and some hydroquinones on isolated rat hepatocytes. *Biochem Pharmacol*. 1992;44(6):1059-1065.

22. Nakagawa Y. Effects of dicoumarol on cytotoxicity caused by TBHQ in isolated rat hepatocytes. *Toxicol Lett*. 1996;84(2):63-68.
23. Nishizono S, Hayami T, Ikeda I, Imaizumi K. Protection against the diabetogenic effect of feeding TBHQ to rats prior to the administration of streptozotocin. *Biosci Biotechnol Biochem*. 2000;64(6):1153-1158.
24. Ogunrinola OA, Fung DYC, Jeon IJ. Inhibition of E. coli 0157 H7 by phenolic antioxidants. 94th General Meeting of the American Society for Microbiology, Las Vegas, Nevada, USA, May 23-27. 1994.
25. Okubo T, Yokoyama Y, Kano K, Kano I. Cell death induced by the phenolic antioxidant TBHQ and its metabolite TBQ in human monocutyic leukemia U937 cells. *Food Chem Toxicol*. 2003;41(5):679-688.
26. Papas AM. Oil-soluble antioxidants in food. *Toxicol Ind Health*. 1993;9(1-2):123-149.
27. Patrick E, Juberg DR, O'Donoghue J, Maibach HI. Depigmentation with TBHQ using black guinea pigs. *Food Chem Toxicol*. 1999;37(2-3):169-175.
28. Peters M, Rivera M, Jones T, Monks T, Lau S. Glutathione conjugates of tert-butyl-hydroquinone, a metabolite of the urinary tract tumor promotor 3-tert-butyl-hydroxyanisole, are toxic to kidney and bladder. *Cancer Res*. 1996;56(5):1006-1011.
29. Rogers CG, Boyes BG, Matula TI, Stapley R. Evaluation of genotoxicity of tert-butylhydroquinone in an hepatocyte-mediated assay with V79 Chinese hamster lung cells and in strain D7 of *Saccaromyces cerevisiae*. *Mutat Res*. 1992;280(1): 17-27.
30. Schilderman PA, Van Maanen JMS, Smeets EJ, Ten Hoor F, Kleinjans JC. Oxygen radical formation during prostaglandin H synthase-mediated biotransformation of butylated hydroxyanisole. *Carcinogenesis*. 1993;14(3):347-353.
31. Schilderman PA, Van Maanen JM, Ten Vaarwerk FJ, et al. The role of prostaglandidn H synthase-mediated metabolism in the induction of oxidative DNA damage by BHA metabolites. *Carcinogenesis*. 1993;14(7):1297-1302.
32. Suzuki T, Matsuoka A, Sawada M, Hayashi M, Miyata N, Sofuni T. Cytotoxicity and micronucleus induction by 3-tert butyl-4-hydroxyanisole and its metabolites in menadione and H_2O_2-resistent cells. *Mutat Res*. 1991;253(6):278-279.
33. Tajima K, Hashizaki M, Yamamoto K, Mizutani T. Identification and structure characterization of S-containing metabolites of 3-tert-butyl-4-hydroxyanisole in rat urine and liver microsomes. *Drug Metab Dispos*. 1991;19(6):1028-1033.
34. Tajima K, Hashizaki M, Yamamoto K, Mizutani T. Metabolism of 3-tert-butyl-4-hydroxyanisole by horseradish peroxidase and hydrogen peroxide. *Drug Metab Dispos*. 1992;20(6):816-820.
35. Twerdok LE, Trush MA. Differences in quinone reductase activity in primary bone marrow stromal cells derived from C57BL/6 and DBA/2 mice. *Res Comm Chem Pathol Pharmacol*. 1990;67(3):375-386.
36. Van Ommen B, Koster A, Verhagen H, Van Bladeren PJ. The glutathione conjugates of tert-butyl hydroquinone as potent redox cycling agents and possible reactive agents underlying the toxicity of butylated hyroxyanisole. *Biochem Biophys Res Comm*. 1992; 189(1):309-314.
37. Wang H, Liu W. Optimization of a high-performance liquid chromatography system by artificial neural networks for separation and determination of antioxidants. *J Sep Sci*. 2004;27(14): 1189-1194.
38. Yamane Y, Furuichi M, Song R, et al. Expression of multidrug resistance protein/GS-X pump and gamma-glutamylcysteine synthetase genes is regulated by oxidative stress. *J Bio Chem*. 1998;273(47):31075-31085.
39. Yoshida Y, Hirose M, Takaba K, Kimura J, Ito N. Induction and promotion of forestomach tumors by sodium nitrite in combination with ascorbic acid or sodium ascorbate in rats with or without N-methyl-N'-nitro-N-nitrosoguanidine pre-treatment. *Int J Cancer*. 1994;56(1):124-128.
40. Yu R, Tan TH, Kong ANT. Butylated hydroxyanisole and its metabolite tert-butylhydroquinone differentially regulate mitogen-activated protein kinases. The role of oxidative stress in the activation of mitogen-activated protein kinases by phenolic antioxidants. *J Bio Chem*. 1997;272(46):28962-28970.
41. Gottschalck TE, McEwen Jr GN, eds. *International Cosmetic Ingredient Dictionary and Handbook*. 11th ed. Washington, DC: CTFA; 2006.
42. Elder RL, ed. Final report on the safety assessment of t-Butyl Hydroquinone. *J Am Coll Toxicol*. 1986;5(5):329-352.
43. Food and Drug Administration (FDA). *Frequency of Use of Cosmetic Ingredients*. Washington, DC: FDA; 2006.
44. Cosmetic, Toiletry, and Fragrance Association (CTFA). 2007. Concentration of Use for TBHQ. 1 page.

Chlorhexidine, Chlorhexidine Diacetate, Chlorhexidine Dihydrochloride, and Chlorhexidine Digluconate

Conclusion

In a 1993 safety assessment of chlorhexidine, chlorhexidine diacetate, chlorhexidine dihydrochloride, and chlorhexidine digluconate, the Cosmetic Ingredient Review (CIR) Expert Panel stated that "chlorhexidine and its salts are safe for use in cosmetic products at concentrations up to 0.14% calculated as chlorhexidine free base; 0.19% as chlorhexidine diacetate; 0.20% as chlorhexidine digluconate; and 0.16% as chlorhexidine dihydrochloride."[1] The Expert Panel reviewed newly available

studies since that assessment (see references),[2-24] along with updated information regarding product types and concentrations of use and did not reopen this safety assessment. The Panel confirmed that chlorhexidine, chlorhexidine diacetate, chlorhexidine dihydrochloride, and chlorhexidine digluconate are safe as cosmetic ingredients in the practices of use and concentration as given in Table 1. Chlorhexidine diacetate is not currently reported to be used, but it is expected to be safe with similar use.

Discussion

The CIR Expert Panel recognized the ongoing concern regarding potential hypersensitivity reactions to chlorhexidine-impregnated medical devices. These reactions are indicative of an immunoglobulin E (IgE)-mediated allergic reaction and are considered by the Panel as serious. The concentration limits imposed in the CIR Expert Panel safety assessment on these preservatives, however, are sufficient to ensure safety of their use in cosmetics.

References

1. Andersen FA, ed. Final report on the safety assessment of chlorhexidine, chlorhexidine diacetate, chlorhexidine digluconate, and chlorhexidine dihydrochloride. *JACT*. 1993;12(2): 201-223.
2. Andersen BL, Brandrup F. Skin reaction to chlorhexidine acetate and chlorhexidine gluconate. *Contact Dermat*. 1985;13(2): 307-309.
3. Andersen FA, ed. Note regarding the safety assessment of chlorhexidine, chlorhexidine diacetate, chlorhexidine digluconate, and chlorhexidine dihydrochloride. *Int J Toxicol*. 1999; 18 (Suppl 2):69.
4. Baillie LW, Power EG, Phillips I. Chlorhexidine hypersensitivity of ciproflaxoacin-resistant variants of Pseudomans aeruginosa POA. *J Antimicrob Chemother*. 1993;31(2):219-225.
5. Cankaya H, Ozen S, Kiroğlu F, Yurttaş V. Effects of topical chlorhexidine applied to the rabbit nasal mucosa. *Auris Nasus Larynx*. 2003;30(1):65-69.
6. Chemical Land 21. Chemical base. 2008. http://www.chemicalland21.com/lifescience/phar/CHLORHEXIDINE%20BASE.htm. Accessed March 1, 2008.
7. Cheng KK. Children's acceptance and tolerance of Chlorhexidine and bezydamine oral rinses in the treatment of chemotherapy-induced oropharyngeal mucositis. *Eur J Oncol Nurs*. 2004;8(4):341-349.
8. Eiksen NL, Sweeten KM, Blanco JD. Chlorhexidine vs. sterile vaginal wash during labor to prevent neonatal infection. *Infect Dis Obstet Gynecol*. 1997;5(4):286-290.
9. Ellenhorn MJ, Schonwald S, Ordog G, et al. *Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning*. 2nd ed. Baltimore MD: Williams and Wilkins; 1997.

Table 1. Historical and Current Cosmetic Product Uses and Concentrations for Chlorhexidine, Chlorhexidine Dihydrochloride, and Chlorhexidine Digluconate

Product Category	1986 Uses (Total Number of Products in Product Category)[a]	2005 Uses (Total Number of Products in Product Category)[25]	1986 Concentrations[a]	2008 Concentrations[26]
Chlorhexidine				
Skin care preparations				
Skin fresheners	1 (184)	–[b] (212)	> 0.1%-1%	–[b]
Oral hygiene products				
Mouthwashes and breath fresheners	1 (53)	–[b] (57)	>1%-5%	–[b]
Other oral hygiene products	–[b] (6)	1 (10)	–[b]	0.13%[1]
Chlorhexidine dihydrochloride				
Noncoloring hair preparations				
Hair conditioners	–[b] (651)	26 (715)	–[b]	0.0001%-0.001%
Eye makeup preparations				
Eye makeup remover	–[b] (100)	2 (114)	–[b]	–[b]
Skin care preparations				
Cleansing	–[b] (775)	2 (1009)	–[b]	–[b]
Noncoloring hair preparations				
Hair conditioners	–[b] (651)	26 (715)	–[b]	–[b]
Shampoos	–[b] (884)	2 (1022)	–[b]	–[b]
Hair tonics, dressings, etc	–[b] (598)	1 (623)	–[b]	–[b]
Other noncoloring hair preparations	–[b] (277)	19 (73)	–[b]	–[b]
Hair-coloring preparations				
Bleaches	–[b] (120)	1 (103)	–[b]	–[b]
Chlorhexidine digluconate				
Baby products				
Lotions, oils, powders, and creams	–[b] (60)	4 (67)	–[b]	–[b]
Other baby products	–[b] (34)	1 (64)	–[b]	–[b]

(continued)

Table 1. (continued)

Product Category	1986 Uses (Total Number of Products in Product Category)[a]	2005 Uses (Total Number of Products in Product Category)[25]	1986 Concentrations[a]	2008 Concentrations[26]
Eye makeup preparations				
Eye shadow	1 (576)	–[b] (229)	> 0.1% - 1%	–[b]
Eye lotions	–[b] (25)	–[b] (32)	–[b]	0.003%-0.04%
Mascara	–[b] (195)	–[b] (308)	–[b]	0.05%
Eye makeup remover	1 (100)	2 (114)	< 0.1%	0.0001%-0.001%
Fragrance preparations				
Other fragrance preparations	–[b] (173)	3 (187)	–[b]	–[b]
Noncoloring hair preparations				
Hair conditioners	–[b] (651)	26 (715)	–[b]	–[b]
Rinses	–[b] (42)	–[b] (46)	–[b]	0.02%
Tonics, dressings, and other hair-grooming aids	–[b] (598)	–[b] (623)	–[b]	0.02%
Hair-coloring preparations				
Bleaches	–[b] (120)	1 (103)	–[b]	–[b]
Hair lighteners	–[b] (5)	–[b] (14)	–[b]	0.04%
Makeup preparations				
Foundations	6 (324)	–[b] (530)	< 0.1%	0.0005%-0.03%
Makeup fixatives	–[b] (20)	–[b] (37)	–[b]	0.05%
Nail care products				
Cuticle softeners	1 (19)	–[b] (20)	< 0.1%	–[b]
Personal hygiene products				
Other personal hygiene products	–[b] (308)	3 (390)	–[b]	–[b]
Mouthwashes and breath fresheners	–[b] (46)	–[b] (57)	–[b]	0.2%
Underarm deodorant	–[b] (247)	–[b] (281)	–[b]	0.06%
Oral care products				
Dentifrices (aerosol, liquid, pastes, and powders)	–[b](40)	–[b] (54)	–[b]	0.002%-0.01%
Shaving preparations				
Aftershave lotions	–[b](231)	1 (260)	–[b]	–[b]
Skin care preparations				
Bath soaps and detergents	–[b] (143)	–[b] (207)	–[b]	0.02%
Skin cleansing creams, lotions, liquids, and pads	3 (775)	11 (1009)	< 0.1%	0.002%-0.05%
Face and neck skin care preparations		9 (546)		0.01%-0.03%
Body and hand skin care preparations	6 (1150)	7 (992)	< 0.1%	0.05%
Night skin care preparations	4 (200)	3 (229)	< 0.1%	–[b]
Skin fresheners	–[b] (184)	–[b] (212)	–[b]	0.05%
Moisturizers	–[b] (905)	–[b] (1200)	–[b]	0.001%-0.05%
Paste masks (mud packs)	6 (271)	4 (312)	< 0.1%	0.02%-0.05%
Other skin care preparations	–[b] (725)	6 (915)	–[b]	0.002%-0.05%
Suntan preparations				
Suntan gels, creams, and liquids	–[b](131)	–[b] (138)	–[b]	0.05%
Total uses/ranges for chlorhexidine, chlorhexidine dihydrochloride, and chlorhexidine digluconate	30	61	< 0.1%-5%	0.0001%-0.13%

[a] 0.13% in oral rinse.

[b] Not reported. In some cases, the ingredient uses were not reported to Food and Drug Administration (FDA) in the voluntary industry product survey program, however, concentrations were provided. In other cases, the uses were reported, but no concentration was provided.

10. European Chemicals Bureau. IUCLID Dataset: Chlorhexidine. 2000. http://ecb.jrc.it/documents/Existing-Chemicals/IUCLID/DATA_SHEETS/55561.pdf. Accessed March 1, 2008.
11. Food and Drug Administration (FDA). *FDA public Health Notice: Potential Hypersensitivity Reactions to Chlorhexidine-Impregnated Medical Devices*. http://www.fda.gov/cdrh/chlorhex.html. FDA: Rockville MD; 1998. Accessed March 1, 2008.
12. Garvey LH, Roed-Petersen J, Husum B. Is there a risk of sensitization and allergy to chlorhexidine in health care workers? *Acta Anaesthesiol Scand*. 2003;47(6):720-740.
13. Gottschalck TE, GN, *eds*. International Cosmetic Ingredient Dictionary and Handbook. *11th ed*, Vol. 2. Washington DC: CTFA; 2006.

14. Hirata K, Kurokawa A. Chlohexidine gluconate ingestion resulting in fatal respiratory distress syndrome. *Vet Hum Toxicol*. 2002; 44(2):89-91.
15. Ishigami S, Hase S, Nakashima H, et al. Intravenous chlorhexidine gluconate causing acute respiratory distress syndrome. *Toxicol Clin Toxicol*. 2001;39(1):77-80.
16. Kosrirukvongs P, Wanachiwanawin D, Visvesvara GS. Treatment of ancanthamoeba keratitis with chlorhexidine. *Opthamology*. 1999;106(4):798-802.
17. McEnvoy M, Mullan A. Should two senior cancer-nursing posts be integrated as one leadership function? *Int J Palliat Nurs*. 2003; 9(9):404-410.
18. Physical Chemistry. Safety data for Chlorhexidine. 2008. http://physchem.ox.ac.uk/msds/CH/chlorhexidine.html. Accessed March 1, 2008.
19. Pitten FA, Kiefer T, Buth C, Doelken G, Kramer A. Do cancer patients with chemotherapy-induced leukopenia benefit from an anti-septic chlothexidine-based oral rinse? *A double-blind, block-randomized, controlled study*. J Hosp Infect. 2003;53(4):283-291.
20. Reading AD, Rooney P, Taylor GJ. Quantitative assessment of the effect of 0.05% chlorhexidine on rat articular cartilage metabolism in vitro and in vivo. *J Orthop Res*. 2000;18(5):762-767.
21. Ronchera-Oms C, Hernández C, Jimémez NV. Antiseptic cord care reduces bacterial colonization but delays cord detachment. *Arch Dis Child*. 1994;71(1):F70.
22. Sigma-Aldrich. Chlorhexidine Diacetate Salt Monohydrate. 2008. http://www.sigmaaldrich.com/catalog/search/ProductDetail/FLUKA/24800. Accessed March 1, 2008.
23. Stingeni L, Lapomarda V, Lisi P. Occupational hand dermatitis in hospital environments. *Contact Dermat*. 1995;33(3):172-176.
24. Van Huyssteen AL, Bracey DJ. Chlorhexidine and chondrolysis in the knee. *J Bone Joint Surg Br*. 2000;81(6):995-996.
25. Food and Drug Administration (FDA). *Frequency of Use of Cosmetic Ingredients*. Washington, DC: FDA; 2006. more complete reference?
26. Personal Care Products Council. 2008. Concentration of use: Chlorhexidine, Chlorhexidine Dihydrochloride, Chlorhexidine Digluconate, and Chlorhexidine Diacetate. 1 pages.

2-Chloro-p-Phenylenediamine and 2-Chloro-p-Phenylenediamine Sulfate

Conclusion

In a 1992 safety assessment of 2-chloro-p-phenylenediamine and 2-chloro-p-phenylenediamine sulfate, the Cosmetic Ingredient Review (CIR) Expert Panel stated that these ingredients are safe as ''coal-tar'' hair dye ingredients as used in cosmetic products.[1] The Expert Panel reviewed newly available studies since that assessment (see references),[2-10] along with updated information regarding types and concentrations of use and did not reopen this safety assessment. The Expert Panel confirmed that 2-chloro-p-phenylenediamine and 2-chloro-p-phenylenediamine sulfate are safe as cosmetic ingredients in the present practices of use and concentration.

Discussion

Information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Ingredient Reporting Program (VCRP)[1] indicates that 2-chloro-p-phenylenediamine was being used in 1 hair dye at concentrations of $\leq$0.1% in 1984. Voluntary Cosmetic Ingredient Reporting Program data provided by FDA in 2006 and 2007 indicated no reported uses of 2-chloro-p-phenylenediamine,[11,12] and use concentrations of this dye were not reported in a 2007 industry survey.[13]

According to the information supplied to the FDA by industry as part of the VCRP,[1] 2-chloro-p-phenylenediamine sulfate was reported as being used in 61 hair dyes at concentrations of $\leq$0.1% to 1% in 1984. Voluntary Cosmetic Ingredient Reporting Program data provided by FDA in 2006 indicated that 2-chloro-p-phenylenediamine sulfate was being used in 24 hair dyes and in 11 hair tints.[11] Voluntary Cosmetic Ingredient Reporting Program data provided by FDA in 2007 indicated no reported uses of 2-chloro-p-phenylenediamine sulfate.[12] The results of a 2007 industry survey[13] indicated that 2-chloro-p-phenylenediamine sulfate was being used in hair dyes at a concentration of 2% (before dilution); use concentration data for this ingredient in hair tints were not included in this survey. Use frequency/use concentration data on 2-chloro-p-phenylenediamine and 2-chloro-p-phenylenediamine sulfate are included in Table 1.

The Expert Panel recognizes that there are data gaps regarding the use and concentration of these hair dyes. However, the overall information available on the types of products in which this ingredient is used and at what concentration indicate a pattern of use, which was considered by the Expert Panel in assessing safety. In order to gain more insight into ingredient use frequency patterns, the total number of products in a category could be considered along with the number of products in that category containing the ingredient.

Table 1. Historical and Current Cosmetic Product Uses and Concentrations for 2-Chloro-p-Phenylenediamine and 2-Chloro-p-Phenylenediamine Sulfate

Product Category[11]	1984 Uses (total number of products in category)[1]	2006 Uses (total number of products in category)[11]	1984 Concentrations (%)[1]	2007 Concentrations (%)[13]
2-Chloro-p-phenylenediamine				
Hair-coloring products				
Dyes and colors	1 (811)	-[a]	≤0.1	-[b]
Total uses/ranges for 2-chloro-p-phenylenediamine	1	–	≤0.1	–
2-Chloro-p-phenylenediamine sulfate				
Hair-coloring products				
Dyes and colors	61 (811)	24 (1600)	≤0.1-1	2% (before dilution)
Tints	-[a]	11 (56)	-[a]	–
Total uses/ranges for 2-chloro-p-phenylenediamine sulfate	61	35	≤ 0.1-1	2% (before dilution)

Abbreviation: FDA, Food and Drug Administration.
[a] In FDA's voluntary reporting system, no uses/use concentrations reported for this category in 1984; no uses reported for this category in 2006.
[b] In industry survey, no use concentrations reported for this category.

According to the Scientific Committee on Consumer Products (SCCP), 2-chloro-p-phenylenediamine and 2-chloro-p-phenylenediamine sulfate are reported to be used in oxidative hair dye formulations for eyebrows and eyelashes. The CIR Expert Panel strongly affirms that these practices of use are unsafe and should be discontinued.

The Expert Panel recognizes that 2-chloro-p-phenylenediamine and 2-chloro-p-phenylenediamine sulfate are used as hair dye ingredients and may be sensitizers. However, hair dyes containing these ingredients, as coal-tar hair dye products are exempt from the principal adulteration provision and from the color additive provisions in sections 601 and 706 of the Federal Food, Drug, and Cosmetic Act, when the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation. The Expert Panel expects that continuing to follow this procedure will identify prospective individuals who would have an irritation/sensitization reaction and allow them to avoid significant exposures.

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 end points. The hair dye epidemiology data are available at http://www.cir-safety.org/findings.shtml.

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References

1. Elder RL and (ed). Final report on the safety assessment of 2-chloro-p-phenylenediamine and 2-chloro-p-phenylenediamine sulfate. *JACT*. 1992;11(4):521-530.
2. Soap, Perfumery, & Cosmetics. EU Committee launches hair dye safety probes. http://www.cosmeticsbusiness.com/story.asp?sectioncode=1&storycode=1507; 2007. Accessed 2008.
3. Gottschalck TE, Bailey JE. In: *International Cosmetic Ingredient Dictionary and Handbook*.2008;12 edition. Washington DC: CTFA; 2008.
4. Hansson C, Thorneby-Andersson K. Allergic contact dermatitis from 2-chloro-p-phenylenediamine in a cream dye for eyelashes and eyebrows. *Contact Dermat*. 2001;45(4):235-236.
5. Kitchin KT, Brown JL, Kulkarni AP. Predicting rodent carcinogenicity of halogenated hydrocarbons by in vivo biochemical parameters. *Teratog Carcinog Mutagen*. 1993;13(4):167-184.
6. Sasaki YF, Fujikawa K, Ishida K, et al. The alkaline single cell gel electrophoresis assay with the mouse multiple organs: results with 30 aromatic amines evaluated by the IARC and the U.S. NTP. *Mutat Res*. 1999;440(1):1-18.
7. Scientific Committee on Consumer Products. Request for a scientfic opinion: Hair dye 2-chloro-p-phenylenediamine and its salts (CAS 615-66-70) submission II (A008). http://ec.europa.eu/health/ph_risk/committees/04_SCCP/docs/SCCP_Q_161.pdf. 2008. Accessed 2008.
8. Yasunaga K, Kiyonari A, Nakagawa M, Yoshikawa K. Different results of the Salmonella umu test between three isomers of phenylenediamine (PDA) derivatives. *Drug Chem Toxicol*. 2006;29(2):203-213.
9. Yasunaga K, Kiyonari A, Oikawa T, Abe N, Yoshikawa K. Evaluation of the Salmonella umu test with 83 NTP chemicals. *Environ Mol Mutagen*. 2004;44(4):329-345.
10. Food and Drug Administration. Information supplied to FDA by industry as part of the Voluntary Cosmetic Ingredient Report Program (VCRP). Washington DC: FDA; 2006.

11. Food and Drug Administration. Information supplied to FDA by industry as part of the VCRP. Washington DC: FDA; 2007.
12. Cosmetic, Toiletry, and Fragrance Association. Use concentration data on 2-chloro-p-phenylenediamine sulfate industry survey. Unpublished data submitted by CTFA; 2007. 2 pages.

2,4-Diaminophenol and 2,4-Diaminophenol HCl

Conclusion

In a 1994 safety assessment of 2,4-diaminophenol and 2,4-diaminophenol HCl (formerly 2,4-diaminophenol dihydrochloride), the Cosmetic Ingredient Review (CIR) Expert Panel stated that these ingredients are safe as (then) used in hair dyes at concentrations up to 0.2% (as the free base).[1] The Expert Panel reviewed newly available studies since that assessment (see references),[2-11] along with updated information regarding the type and concentration of use. The Panel determined to not reopen this safety assessment and confirmed that 2,4-diaminophenol and 2,4-diaminophenol HCl are safe as cosmetic ingredients in the current practices of use and concentration (Table 1).

Discussion

2,4-Diaminophenol HCl had been used in 3 cosmetic products in 1981. Their use concentrations were not reported at that time. The Food and Drug Administration[12] reported that 2,4-diaminophenol HCl is used in 5 hair dyes and colors. A survey of current use concentrations conducted by the Personal Care Products Council[13] reported no use concentrations of 2,4-diaminophenol and 2,4-diaminophenol HCl.

Newly available data did not raise any issues regarding the safety of 2,4-diaminophenol and 2,4-diaminophenol HCl. The Expert Panel noted that the available hair dye epidemiology studies are insufficient to conclude there is a causal relationship between hair dye use and cancer and other end points based on lack of strength in the associations and inconsistency of findings. The hair dye epidemiology data is available at http://www.cir-safety.org/findings.shtml.

The Expert Panel recognized that 2,4-diaminophenol and 2,4-diaminophenol HCl are oxidizing hair dye ingredients and may be sensitizers. However, hair dyes containing these ingredients, as coal-tar hair dye products, are exempt from the principal adulteration provision and color additive provisions in sections 601 and 706 of the Federal Food, Drug, and Cosmetic Act, when the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation. The Expert Panel expects that continuing to follow the procedure will identify prospective individuals who would have an irritation/sensitization reaction and allow them to avoid significant exposures.

References

1. Andersen FA. Final report on the safety assessment of 2,4-Diaminophenol and 2,4-Diaminophenol Dihydrochloride. *J Am Coll Toxicol*. 1994;13(5):330-343.
2. Battershill JM, Fielder RJ. Mouse-specific carcinogens: An assessment of hazard and significance for validation of short-term carcinogenicity bioassays in transgenic mice. *Human Exp Toxicol*. 1998;17(4):193-205.
3. Davies TS, Monstro A. The rodent carcinogenicity bioassay produces a similar frequency of tumor increases and decreases: implications for risk assessment. *Regul Toxicol Pharmacol*. 1994; 20(2 pt 1):281-301.
4. Diehl CA, Jafvert CT, Marley KA, Larson RA. Surfactant-assisted UV-photolysis of nitroarenes. *Chemosphere*. 2002; 46(4):553-560.
5. Elder RL ed. Final report on the safety assessment of p-phenylenediamine. *J Am Coll Toxicol*. 1985;4(2):203-266.
6. Gottschalck TE, McEwen (Jr) GN, eds. *International Cosmetic Ingredient Dictionary and Handbook*. 12th ed. Washington, DC: CTFA; 2008.

Table 1. Historical and Current Cosmetic Product Uses and Concentrations for 2,4-diaminophenol HCl

Product Category	1981 Uses[1]	2008 Uses[12]	1981 Concentrations[1]	2009 Concentrations[13]
Hair-coloring preparations				
Hair dyes and colors	3 (1056)	5 (1600)	-	-
Total uses/ranges for 2,4-diaminophenol HCL	3	5	-	-

7. Lee Y, Buchanen BG, Klopman G, Dimayuga M, Rosenkranz HS. The potential of organ specific toxicity for predicting rodent carcinogenicity. *Mutat Res*. 1996;358(1):37-62.
8. Ministry of Health, Labour and Welfare (MHLW). Japanese Standards for Cosmetic Ingredients. 2007. http://www.mhlw.go.jp/english/topics/cosmetics/index.html. Accessed May 8, 2007.
9. National Toxicology Program (NTP). NTP Technical Report on the Toxicology an Carcinogenesis Studies on 2,4-Diaminophenol Dihydrochloride (CAS No. 173-09-7) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies). 1992. http://ntp.niehs.nih.gov/?objectid=07096231-906A-5151-DABA0CA74E8EADF3. Date Accessed May 11, 2009.
10. Sigma-Aldrich. MSDS 2,4-Diaminophenol. 2009. http://www.sigmaaldrich.com/catalog/ProductDetail.do?N4=33230%7CFLUKA&N5=SEARCH_CONCAT_PNO%7CBRAND_KEY&F=SPEC. Accessed May 11, 2009.
11. Witte CP, Blasco R, Castillo F. Metabolism of 2-amino-4-nitrophenol by Rhodobacter capsulatus. *Biotechnol*. 1998;69(3):191-200.
12. Food and Drug Administration (FDA). *Frequency of Use of Cosmetic Ingredients*. FDA: Washington, DC; 2008.
13. Personal Care Products Council. 2009. Concentration of use 2,4-Diaminophenol and 2,4-Diaminophenol HCL. 1 page.

Diisopropylamine

Conclusion

In a 1995 safety assessment of diisopropylamine, the Cosmetic Ingredient Review (CIR) Expert Panel stated that this ingredient is safe as a cosmetic ingredient as used, and that diisopropylamine should not be used in products containing *N*-nitrosating agents.[1] The Expert Panel reviewed newly available studies since that assessment along with updated frequency and concentration of use information.[2-12] The Expert Panel determined to not reopen this safety assessment and confirmed that diisopropylamine is safe as a cosmetic ingredient when used in products that do not contain *N*-nitrosating agents.

Discussion

Diisopropylamine is reported to function as a pH adjuster, and reported use has increased very slightly from 1 "other skin care preparation" formulation[1,10] in 1993 to 3 bath soap and detergent formulations in 2009. Concentration of use was not reported to the Food and Drug Administration (FDA) in 1993, nor is it reported to FDA currently. A survey conducted by the Personal Care Products Council found that no uses of diisopropylamine were reported by industry[11] (Table 1).

References

1. Andersen FA. Final report on the safety assessment of diisopropylamine. *Jact*. 1995;14(3):182-192.
2. Zissu D. Histopathological changes in the respiratory tract of mice exposed to ten families of airborne chemicals. *J Appl Toxicol*. 1995;15(3):207-213.
3. Gottschalck TE, Bailey JE, eds. *International Cosmetic Ingredient Dictionary and Handbook*. 13th ed. Vol 1. Washington, DC: Personal Care Products Council; 2010.
4. Lewis RJ Sr, ed. *Sax's Dangerous Properties of Industrial Materials*. Vol 10. New York, NY: John Wiley & Sons, Inc; 2000.
5. National Institute for Occupational Safety and Health (NIOSH). International Chemical Safety Card. DIPA (Diisopropylamine). 1997. http://www.cdc.gov/niosh/ipcsneng0449.htm. Accessed September 9, 2009.
6. Andersen FA, ed. Final report on the safety assessment of disperse blue 1. *J Am Coll Toxicol*. 1995;14(6):433-451.
7. ChemIDplus Lite. Disperse Blue 1. RN: 2475-45-8. 2009. http://chem.sis.nlm.nih.gov/chemidplus/ProxyServlet?objectHandle=Search&actionHandle=getAll3DMViewFiles&nextPage=jsp%2Fcommon%2FChemFull.jsp%3FcalledFrom%3Dlite&chemid=002475458&formatType=_3D. Accessed November 13, 2009.
8. National Institute of Standards and Technology (NIST). 2-Propanamine, N-(1-methylethyl-)-. 2008. http://webbook.nist.gov/cgi/cbook.cgi?Units=SI&cTG=on&cIR=on&cTC=on&cMS=on&cTP=on&cES=on&cTR=on&cPI=on&cDI=on&ID=C108189. Accessed September 29, 2009.
9. National Toxicology Program (NTP). Testing status of 108-18-9 (diisopropylamine). 2009. http://ntp.niehs.nih.gov/index.cfm?objectid=E87C09D7-BDB5-82F8-F046E227ED8EF38D. Accessed September 9, 2009.

Table 1. Historical and Current Cosmetic Product Uses and Concentrations for Diisopropylamine

Product Category	Frequency of Use—1993[1]	Frequency of Use—2009[10]	Concentration of Use—1993[1]	Concentration of Use—2009[11]
Other skin care preparations	1		Not available	No uses reported
Bath soaps and detergents	–	3	Not available	No uses reported
Total	1	3	Not available	No uses reported

10. Food and Drug Administration (FDA). *Frequency of Use of Cosmetic Ingredients*. Washington, DC: FDA; 2009.
11. Personal Care Products Council. 2009. Use concentration survey results of diisopropylamine and isopropylamine. Unpublished data submitted by the Personal Care Products Council.
12. Gagnaire F, Azim S, Simon P, Cossec B, Bonnet P, De Ceaurriz J. Sensory and pulmonary irritation of aliphatic amines in mice: a structure-activity relationship study. *J Appl Toxicol*. 1993;13(2): 129-135.

Disperse Blue 1

Conclusion

In 1995, the Cosmetic Ingredient Review (CIR) Expert Panel[1] concluded that Disperse Blue 1 is "safe for use in hair dyes at concentrations up to 1%." In 2010, the Expert Panel reviewed new information available since the original assessment was published in 1995.[2-18] Current frequency of use data that indicate Disperse Blue 1 is no longer being used (personal communication, Don Havery, US FDA, Center for Food, Safety, and Applied Nutrition, Office of Colors and Cosmetics). The Expert Panel determined to not reopen this safety assessment and confirmed the existing conclusion.

Discussion

In 2010, Disperse Blue 1 was not used in cosmetic formulations. However, if used in cosmetics, Disperse Blue 1 would function as a hair colorant.[19] In 1994, according to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program, Disperse Blue 1 was used in 112 hair color formulations; industry reported that in 1994, Disperse Blue 1 was used at a concentration of 0.62% in semipermanent hair dyes and that it was not used in conjunction with hydrogen peroxide.[1]

Concern for the carcinogenic potential of Disperse Blue 1, as used in cosmetics, initially generated of opening a re-review of the safety assessment on Disperse Blue 1. In vitro dermal penetration data demonstrated that Disperse Blue 1 was poorly absorbed through rat skin. However, the most compelling data for not reopening the safety assessment of Disperse Blue 1 was the margin of safety (MOS) at a use concentration of 1%. Numerous risk assessments, presented below, were used to calculate the margin of safety; the results indicate that Disperse Blue 1 is safe for use in hair dyes at concentrations up to 1%.

Food and Drug Administration Risk Assessment Information

Lifetime average daily exposure via hair dye use:

0.62 (g Disperse Blue 1 applied/application; assuming 100 mL formulation/application at a maximum concentration of 0.62% in the formulation) × 0.002 (fraction Disperse Blue 1 absorbed) × 600 (applications/lifetime) = 0.744 (g Disperse Blue 1 absorbed/lifetime)

0.744 g/60 kg = 0.0124 g/kg
78 year (estimated life span) × 365 days = 28 470 days

Estimated lifetime average daily absorbed-dose rate (hair dye use): 0.0124 g/kg per 28 470 d = 0.44 μg/kg per d[17,18]

A simple linear regression analysis was used to estimate that 0.3 μg/kg per d Disperse Blue 1 would be associated with an upper-bound 1 in 1 000 000 lifetime risk of developing a bladder cancer. The total lifetime daily exposure with hair dye use calculated above, 0.44 μg/kg per d, is slightly greater than that value. This risk assessment indicates that the human cancer risks associated with the use of Disperse Blue 1 in hair-coloring formulations would be negligible, considering multiple conservative assumptions incorporated into the assessment.

Additionally, the acceptable daily intake (ADI) reported in the FDA document, using rat data from a National Toxicology Program (NTP) bioassay, was estimated to be 45 μg/kg per d, which is 100 times greater than the estimated lifetime daily dose.[18]

Conclusions about the safe use of Disperse Blue 1 depend on whether its mechanism of action is viewed as genotoxic, thereby directly producing a carcinogenic event, or as a nongenotoxic. If it is viewed as nongenotoxic, the ADI and margin of safety indicated that potential exposure to Disperse Blue 1 would not increase the risk of developing cancer. If it is viewed as genotoxic, the estimated daily dose would be associated with an upper-bound cancer risk estimate slightly exceeding 10^{-6} for humans (no uncertainty factor was applied for insufficient dermal penetration data).

Industry-Prepared Quantitative Cancer Risk Assessment

A quantitative cancer risk assessment for Disperse Blue 1 was prepared based on the No Significant Risk Level (NSRL) of 200 μg/d established under Proposition 65 by the State of California.[8] The NSRL was established using a linearized multistage model and the upper 95% confidence limit of the estimated cancer potency to extrapolate from the high oral doses used in the NTP rat bioassay to lower doses. Using the NSRL assumption of 70 kg as the adult human body weight, the equivalent average daily dose rate is 2.86 μg/kg per d. This risk assessment incorporated the dermal penetration estimate of 0.2%, as determined by Yourick

et al.[17] For this risk assessment, the estimated lifetime average daily dose of Disperse Blue 1 from hair dye use was determined as follows[18]:

Amount of Disperse Blue 1 in contact with the skin = 41 μg/cm^2

Amount systemically absorbed per use: 0.002 × 41 μg/cm^2 × 580 cm^2 (total scalp area) = 47 μg/application

Total lifetime exposure: 47 μg/application × 600 applications/lifetime × 1/60 kg body weight (bw) = 470 μg/kg bw

Estimated lifetime average daily dose: 470 μg/kg bw per 28 470 d (avg female life span) = 0.0165 μg/kg per d

Thus, the estimated human exposure is approximately 170-fold lower than the NSRL (expressed as a lifetime average daily dose rate) for Disperse Blue 1.

This risk assessment included a concentration of use value of 0.52% for Disperse Blue 1 in hair dyes. Since the existing CIR safety assessment of Disperse Blue 1 states that Disperse Blue 1 is safe at concentrations up to 1%, the risk assessment data were extrapolated to determine the margin of safety using 1% Disperse Blue 1. Assuming linear concentration dependence, the lifetime average daily dose rate from a 1% Disperse Blue 1 formulation would be 0.032 μg/kg per d, which is approximately 90-fold lower than the NSRL.

The CIR considered these inputs and offered this perspective on the risk assessment for genotoxic versus nongenotoxic mechanisms of action:

Assumptions. FDA assessment, Disperse Blue 1 is carcinogenic via a genotoxic mechanism

- 0.62 g/100 mL Disperse Blue 1 in product
- 100 mL/application
- 12 applications/year
- 50-year exposure duration
- 60-kg bw and
- 78 years = 28 470 days averaging time for nonthreshold mechanisms

Lifetime average daily-dose rate. (no correction for the fraction that actually contacts the scalp in a hair product)

[0.62 g/100 mL × 100 mL/application × 12 applications/year × 50 years]/[60 kg body weight × 28 470 days] = 2.18 × 10^{-4} g/kg per d

2.18 × 10^{-4} g/kg per d × 10^6 μg/g = 2.18 × 10^2 μg/kg per d

- 0.002 (0.2%) of Disperse Blue 1 dermal penetration[17]
  2.18 × 10^2 μg/kg per d × 0.002 = 0.44 μg/kg per d
- Uncertainty factor = 10 for lack of data on the amount remaining in the skin, which could be absorbed[18] (further investigation indicates that there is little potential for skin to serve as a reservoir,[17] so this uncertainty factor is not needed[8])
- 0.44 μg/kg per d × 10 = 4.4 μg/kg per d
- 0.02 (2%) applied material contacts the scalp[18]
- 0.44 μg/kg per d × 0.02 = 0.009 mg/kg per d ~0.01 μg/kg per d
- Industry risk assessment estimate[8]: 0.0165 μg/kg per d

Cancer Potency of Disperse Blue 1

Extrapolated from an incidence of 41 (84%) of 49 rats exhibiting smooth muscle cell tumors at 217 mg/kg per d exposure to estimate that 0.3 μg/kg per d is associated with a 10^{-6} lifetime upper-bound cancer risk.[18]

A simple linear regression equation was used to extrapolate from dose rate of 217 mg/kg per d used in the NTP rat bioassay to low doses; the linearized multistage model or the upper 95% confidence limit was not used to estimate cancer potency.

The State of California NSRL of 200 μg/d is based on[8]:

- 70 kg bw
- Linearized multistage model
- Linear multistage model to extrapolate from high to low doses in the NTP rat bioassay
- Upper 95% confidence limit of the linear term expressing upper bound potency

NSRL = 200 μg/d per 70 kg = 2.86 μg/kg per d (represents <10^{-5} lifetime cancer risk)

2.86 μg/kg per d/10 = 0.286 μg/kg per d represents <10^{-6} lifetime cancer risk.

Conclusion: Cancer Risk Assessment

Exposure estimates above[8,18] do not exceed lifetime average dose rates estimated to be associated with, at most, a 10^{-6} lifetime cancer risk.

(MOS = 17.3-30)

Assumption. Disperse Blue 1 is Carcinogenic via a Nongenotoxic Mechanism.

Exposure averaging time for a nongenotoxic (ie, threshold) effect is generally taken to be equal to the exposure duration. Assuming an averaging time (and exposure duration) of 50 years (rather than 78 years), the average daily dose rate would be (adjusting the estimates calculated above assuming a genotoxic mechanism):

0.01 μg/kg per d × 78 years/50 years = 0.016 μg/kg per d

Reference Dose Assuming a Nongenotoxic Mechanism

NOAEL = 45 mg/kg per d (NTP rat bioassay)

Reference dose[18] = 45 mg/kg per d/1000 uncertainty factor = 45 μg/kg per d

(MOS = 2812)

Assumption. Concentration[8,18] of Disperse Blue 1 is 1% (rather than 0.62% or 0.52%)

Exposure estimates[8,18]

~0.01 μg/kg per d, assuming 0.62%

0.01 μg/kg per d × 1%/0.62% = 0.016 μg/kg per d at 1%; ~0.02 μg/kg per d
0.0165 μg/kg per d, assuming 0.52%
0.0165 μg/kg per d × 1%/0.62% = 0.0317; ~0.032 μg/kg per d

Thus, exposure estimates range from 0.02 to 0.032 μg/kg per d.

MOSs for product containing 1% Disperse Blue 1. Genotoxic effect:

Range: [0.3 μg/kg per d/0.02 μg/kg per d] to [0.286 μg/kg per d/0.032 μg/kg per d] = 9 to 15

Nongenotoxic effect:
Range: [45 μg/kg per d/0.032 μg/kg per d] to [45 μg/kg per d/0.02 μg/kg per d] = 1406 to 2250

References

1. Andersen FA, ed. Final report on the safety assessment of Disperse Blue 1 *J Am Coll Toxicol.* 1995;14(6):433-451.
2. European Union CosIng Database. Substance: 1,4,5,8-tetraaminoanthraquinone (Disperse Blue 1). 2009. http://ec.europa.eu/enterprise/cosmetics/cosing/index.cfm?fuseaction=search.details&id=29167. Accessed November 29, 2009.
3. Ex-European Chemicals Bureau. Dangerous Substances Directive. 2009. http://ecb.jrc.ec.europa.eu/classification-labelling/search-classlab/. Accessed June 3, 2010.
4. Health Cananda. Results of the Health-Related Components of Categorization of the Domestic Substances List under CEPA 1999. High health priorities for action. 2006. http://www.hc-sc.gc.ca/ewh-semt/contaminants/existsub/categor/_result_substance/high-elevee-03-. Accessed November 29, 2009.
5. International Agency for Research on Cancer. Volume 48. Some flame retardants and textile chemicals, and exposures in the textile manufacturing industry. Summary of data reported and evaluation. 1990. http://monographs.iarc.fr/ENG/Monographs/vol48/volume48.pdf. Accessed November 29, 2009.
6. International Agency for Research on Cancer (IARC). IARC Monographs on the evaluation of carcinogenic risks to humans. Vol. 57. *Occupational Exposures of Hairdressers and Barbers and Personal Use of Hair Colourants; Some Hair Dyes, Cosmetic Colourants, Industrial Dyestuffs and Aromatic Amines*. Lyon, France: IARC; 1993.
7. National Toxicology Program. DHHS/National Toxicology Program; Eleventh Report on Carcinogens: Disperse Blue 1 (2475-45-8). January 2005. http://ntp.niehs.nih.gov/ntp/roc/eleventh/profiles/s081disp.pdf. Accessed November 29, 2009.
8. Personal Care Products Council Hair Colorants Technical Committee. Disperse Blue 1. Quantititative cancer risk assessment. October 29, 2010.
9. Ahuja V, Platzek T, Fink H, Sonnenburg A. Study of the sensitising potential of various textile dyes using a biphasic murine local lymph node assay. *Arch Toxicol*. 2010;84(9):709-718.
10. Baan R, Straif K, Grosse Y, et al. WHO International Agency for Research on Cancer Monograph Working Group: Carcinogenicity of some aromatic amines, organic dyes, and related exposures. *Lancet Oncol*. 2008;9(4):322-323.
11. ChemIDPlus Lite. Disperse Blue 1. RN: 2475-45-8. http://chem.sis.nlm.nih.gov/chemidplus/ProxyServlet?objectHandle=Search&actionHandle=getAll3DMViewFiles&nextPage= jsp%2Fcommon%2FChemFull.jsp%3FcalledFrom%3Dlite&chemid=002475458&formatType=_3D. Accessed November 13, 2009.
12. Coture-Haws L, Jackson BA, Turnbyll D, Dressler WE. Two approaches for assessing human safety of Disperse Blue 1. *Reg Toxicol Pharmacol*. 1994;19(1):80-96.
13. Hatch KL.Textile dye contact allergens. In: Surber C, Bircher AJ. *Current Problems in Dermatology (Basel)*. Basel, Switzerland; New York, NY: Maibach; 1995:8-16.
14. Hausen BM. Contact allergy to Disperse Blue 106 and Blue 124 in black "velvet" clothes. *Contact Dermat*. 1993;28(3):169-173.
15. Rollinson DE, Helzlsouer KJ, Pinney SM. Personal hair dye use and cancer: a systematic literature review and evaluation of exposure assessment in studies bublished since 1992. *J Toxciol Environ Health Part B*. 2006;9(5):413-439.
16. Weisberger JH. Critical review of rodent bioassays of Disperse Blue 1. Specific evaluation of data bearing on human health risk and assessment. Independent review conducted for Clairol. 1989.
17. Yourick JJ, Koeniug ML, Yourick DL, Bronaugh RL. Fate of chemicals in skin after dermal application: does the in vitro skin reservoir affect the estimate of systemic absorption? *Toxicol Appl Pharmacol*. 2004;195(3):309-320.
18. Yourick JJ, Bronaugh RL. Review of Disperse Blue 1 data. (DSAT assignment no. 006). Memo to Dr Bailey JE. March 28, 1994.
19. Gottschalck TE, Bailey JE. *International Cosmetic Ingredient Dictionary and Handbook.* 13 ed. Washington, DC: Personal Care Products Council (formerly the Cosmetic, Toiletry, and Fragrance Association); 2010.

Disperse Violet 1

Conclusion

In its 1991 safety assessment of Disperse Violet 1, the Cosmetic Ingredient Review (CIR) Expert Panel stated that this ingredient was safe as a cosmetic ingredient in the present practices of use and concentration.[1] In 2007, the CIR Expert Panel reviewed newly available studies since that assessment, along with updated information regarding types and concentrations of use.[2-50] The CIR Expert Panel confirmed that Disperse

Violet 1 is safe in the practices of use and concentrations, as given in Table 1, and did not reopen this safety assessment.

Discussion

This ingredient is a direct, non-oxidative hair dye used in 133 hair-coloring products in 1981, based on voluntary reports[1] submitted to Food and Drug Administration (FDA) by the industry, with concentrations of use $\leq 1\%$. In 2006, Disperse Violet 1 was reportedly used in 121 cosmetic products.[51] Data from an industry survey in 2007 indicated that Disperse Violet 1 was used at concentrations ranging from 0.1% to 0.7%.[15]

The available use and concentration data are given in Table 1, as a function of product category.

The Panel is aware that Disperse Red 15 is an impurity in Disperse Violet 1 but determined that the levels of this impurity have decreased since the original safety assessment. The Panel noted that Disperse Red 15 is a banned substance in Europe, except as it appears as an impurity in Disperse Violet 1.

While there is limited evidence of genotoxicity in certain assays (but not in others), the Panel noted a newly available negative oral reproductive study[9] and a negative 20-month dermal carcinogenicity in the original safety assessment that demonstrates an absence of carcinogenic or reproductive risk.

The CIR Expert Panel has concluded that the available epidemiology studies are insufficient to conclude there is a causal relationship between hair dye use and cancer and other end points, based on lack of strength of the associations and inconsistency of findings. A of hair dye epidemiology data are available at http://www.cir-safety.org/findings.shtml.

The Expert Panel recognizes that Disperse Violet 1 is used as a hair dye ingredient and may be a sensitizer. However, hair dyes containing this ingredient, as coal-tar hair products, are exempt from the principal adulteration provision and from the color additive provisions in sections 601 and 706 of the Federal Food, Drug, and Cosmetic Act, when the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation. The Expert Panel expects that following this procedure will identify prospective individuals who have had an irritation/sensitization reaction and allow them to avoid significant exposure.

References

1. Elder RL, ed. Final report on the safety assessment of disperse violet 1. *J Am Coll Toxicol.* 1991;10(1):103-111.
2. Adams RM, Maibach HI, Cledenning WW. A five-year study of cosmetic reactions. *J Am Acad Dermatol*. 1985;13(6): 1062-1069.
3. Andrew AS, Schned AR, Heaney JA, Karagas MR. Bladder cancer risk and personal hair dye use. *Int J Cancer*. 2004; 109(4):581-586.
4. Benavente Y, Garcia N, Domingo-Domenech E. Regular use of hair dyes and risk of lymphoma in Spain. *Int J Epidemiol*. 2005; 34(5):1118-1122.
5. Biological Laboratory, Wella AG. 2005. Eye and eye mucous membrane compatibility test in the albino guinea pig with 1,4-diaminoanthraquinone. Unpublished data submitted by CTFA on July 11, 2007.
6. Biological Laboratory, Wella AG. 2005. Primary skin irritation test in the albino guinea pig according to OECD guidelines, No. 404 Test substance 1,4-diaminoanthraquinone. Unpublished data submitted by CTFA on July 11, 2007.
7. Cerep. 2005. ADME: A-B Permeability-Study of Disperse Violet 1. Unpublished data submitted by CTFA on July 11, 2007.
8. Clairol. 1986. Photosensitization potential of Disperse Violet 1 in guinea pigs. Unpublished data submitted by CTFA on July 11, 2007.
9. Clairol. 1990. The toxicity of Disperse Violet 1 in the Sprague-Dawley rat: effects on growth, reproduction, and fetal growth development. Unpublished data submitted by CTFA on July 11, 2007.
10. Clairol. 1993. Acute oral toxicity: C6674/012 Rodriguez, S. Acute toxicity of Disperse Violet 1 in male and female rats. CLAIROL February 1987. Unpublished data submitted by CTFA on May 2, 2007. 6 pages.
11. Clairol. 1993. Acute eye irritation: C6676/028 Rodriguez, S. Eye irritation potential of Disperse Violet 1 in female rabbits. CLAIROL February 1987. Unpublished data submitted by CTFA on May 2, 2007. 6 pages.
12. Clairol. 1993. Primary skin irritation: C6675/016 Rodriguez, S. Primary skin irritation in rabbits with Disperse Violet 1. CLAIROL February 1987. Unpublished data submitted by CTFA on May 2, 2007. 6 pages.
13. Cosmital SA. 2002. Assessment of the potential mutagenicity of WR8023321 (1,4-diaminoanthraquinone) in the Ames reversion

Table 1. Historical and Current Cosmetic Product Uses and Concentrations of Disperse Violet 1

Product Category	1981 Uses[1]	2006 Uses[52]	1981 Concentrations[1]	2007 Concentrations[15]
Hair-coloring preparations				
Hair dyes and colors	133 (1056)	121 (1600)	≤ 1	0.1%-0.7%
Tints	(49)[a]	(56)[a]	[a]	0.5%
Rinses (coloring)	(42)[a]	(15)[a]	[a]	0.5%
Total uses/ranges of Disperse Violet 1	133	121	≤ 1	0.1%-0.7%

[a] Not reported. In some cases, uses of ingredient were not reported to Food and Drug Administration (FDA) in the voluntary industry product survey program; however, concentrations were provided. In other cases, the uses were reported but no concentration was provided.

assay with Salmonella typhimurium. Unpublished data submitted by CTFA on July 11, 2007.
14. Covance Laboratories Ltd. 2005. Disperse Violet 1 (WR 18588): induction of micronuclei in cultured human peripheral blood lymphocytes. Unpublished data submitted by CTFA on July 11, 2007.
15. Cosmetic, Toiletry, and Fragrance Association (CTFA). 2007. Use concentration survey results for Disperse Violet 1. Unpublished data submitted by CTFA on April 6, 2007. 1 pages.
16. de Sanjose S, Benevente Y, Nieters A, et al. Association between personal use of hair dyes and lymphoid neoplasms in Europe. *Am J Epidemiol*. 2006;164(1):47-55.
17. Efird JT, Holly EA, Cordier S, et al. Beauty product-related exposures and childhood brain tumors in seven countries: results from the SEARCH International Brain Tumor Study. *J Neurooncol*. 2005;72(2):133-147.
18. Forschungszentrum Seibersdorf. 1992. Teratogenicity study with "Muhlaceviolett 2R" (Disperse Violet 1) in rats. Unpublished data submitted by CTFA on July 11, 2007.
19. Gago-Dominguez M, Castelao JE, Yuan JM, Yu MC, Ross RK. Use of permanent hair dyes and bladder-cancer risk. *Int J Cancer*. 2001;91(4):575-579.
20. Gago-Dominguez M, Castelao JE. Permanent hair dyes and bladder cancer: risk modification by cytochrome P4501A2 and N-acetyltransferases 1 and 2. *Carcinogenesis*. 2003;24(3): 483-489.
21. Gottschalck TE, McEwen GN Jr, eds. *International Cosmetic Ingredient Dictionary and Handbook*. 11th ed. Washington, DC: CTFA; 2006.
22. Health Canada. Cosmetic Ingredient Hotlist. 2006. http://www.hc-sc.gc.ca/cps-spc/person/cosmet/hotlist-liste_e.html. Accessed January 18, 2007.
23. Heineman EF, Ward MH, McComb RD, Weisenburger DD, Zahm SH. Hair dyes and risk of glioma among Nebraska women. *Cancer Causes Control*. 2005;16(7):857-864.
24. Helzlsouer K, Rollison D, Pinney S. 2003. Association between hair dye use and health outcomes: Review of the literature published since 1992. Unpublished data submitted by Clairol, Inc. 107 pages.
25. Hunchareik M, Kupelnick B. Personal use of hair dyes and the risk of bladder cancer: results of a meta-analysis. *Public Health Reports*. 2005;120(1):31-38.
26. International Agency for Research on Cancer (IARC). Occupational exposures of hairdressers and barbers and personal use of hair colourants; some hair dyes, cosmetic colourants, industrial dyestuffs and aromatic amines. *IARC Monogr Eval Carcinog Risks Hum*. 1993;57:43-118.
27. Ji J, Hemminki K. Occupational and bladder cancer: a cohort study in Sweden. *Brit J Cancer*. 2005;92(7):1276-1278.
28. Kelsey KT, Hirao T, Hirao S, et al. TP53 alterations and patterns of carcinogen exposure in a US population-based study of bladder cancer. *Int J Cancer*. 2005;117(3):370-375.
29. Kogevinas M, Fernandez F, Garcia-Closas N, et al. Hair dye use is not associated with risk for bladder cancer: evidence from a case-control study in Spain. *Eur J Cancer*. 2006; 42(10):1448-1454.
30. Lin J, Dinney CP, Grossman HB, Wu X. Personal permanent hair dye use is not associated with bladder cancer risk: evidence from a case-control study. *Cancer Epidemiol Biomarkers Prev*. 2006; 15(9):1746-1749.
31. Lundy D, Eaton J. *Occupational Health Hazards Posed by Inventory U.S. Army Smoke/Obscurrant Munitions (Review Update). Wright-Patterson Air Force Base, OH, U.S. Army Medical Research Detachment*. 1994. Report No. WRAIR/RT-94-0001. AD-A276-774.
32. McCall EE, Olshan AF, Daniels JL. Maternal hair dye use and risk of neuroblastoma in offspring. *Cancer Causes Control*. 2005; 16(6):743-748.
33. MDS Pharma Services. 2003. Disperse Violet 1 Wella no. 802321-Local lymph node assay. Unpublished data submitted by CTFA on July 11, 2007.
34. Mester B, Elsner G, Nienhaus A. Hair dyes and malignant lymphoma—an overview of previous publications on epidemiology. *Zbl Arbeitsmed*. 2005;55(1):117-125.
35. Ministry of Health, Labour and Welfare (MHLW). Japanese Standards for Cosmetic Ingredients. 2007. http://www.mhlw.go.jp/english/topics/cosmetics/index.html. Accessed May 8, 2007.
36. National Academy of Sciences. Appendix I: 1,4-Diaminoanthraquinone. *Toxicity Military Smokes Obscurants*. 1999;3.
37. NOTOX BV. 2005. 90-day oral toxicity study with Disperse Violet 1/18588/by daily oral gavage in the rat. Unpublished data submitted by CTFA on July 11, 2007.
38. Park RM, Schulte PA, Bowman JD, et al. Potential occupational risks for neurodegenerative diseases. *Am J Industrial Med*. 2005; 48(1):63-77.
39. Rauscher GH, Shore D, Sandler DP. Hair dye use and risk of adult acute leukemia. *Am J Epidemiol*. 2004;160(1):9-25.
40. RCC. 2003. Cell mutation assay at the thymidine kinase locus (TK+/-) in mouse lymphoma L5178Y cells with Kayaku violet 1 WR802321. Unpublished data submitted by CTFA on July 11, 2007.
41. RCC. 2003. Micronucleus assay in bone marrow cells of the mouse with Kayaku violet 1 WR802321. Unpublished data submitted by CTFA on July 11, 2007.
42. RCC. 2005. In vitro dermal absorption through porcine ear skin with basic cream formulation with 0.5% Disperse Violet 1 WR18588. Unpublished data submitted by CTFA on August 30, 2007. 26 pages.
43. Registry of Toxic Effects and Chemical Substances (RTECS). 1997. Safety Regulatory Data—Disperse Violet 1. 2 pages.
44. Rollison DE, Helzlsouer KJ, and Pinney SM. Personal hair dye use and cancer: a systematic literature review and evaluation of exposure assessment in studies published since 1992. *J Toxicol Environ Health Part B*. 2006;9(5):413-439.
45. Scientific Committee on Consumer Products (SCCP). Disperse Violet 1 Submission II. http://europa.eu.int/comm/enterprise/cosmetics/doc/hairdyestrategyinternet.pdf. Accessed January 18, 2007.
46. Serretta V, Morgia G, Altieri V, et al. Preliminary report of a multicentric study on environmental risk factors in Ta-T1 transitional cell carcinoma of the bladder. *Urol Int*. 2006;77(2):152-158.
47. Takkouche B, Teminan M, Montes-Martinez A. Personal use of hair dyes and risk of cancer. *JAMA*. 2005;293(20):2516-2525.

48. Zhang Y, Holford TR, Leaderer B, et al. Hair-coloring product use and risk of non-Hodgkin's lymphoma: a population-based case-control study in Connecticut. *Am J Epidemiol*. 2004; 159(2):148-154.
49. Zheng T, Holford TR, Leaderer B, et al. Diet and nutrient intakes and risk of non-Hodgkin's lymphoma in Connecticut. *Am J Epidemiol*. 2004;159(5):454-466.
50. Cosmetic, Toiletry, and Fragrance Association (CTFA). 2007. Analytical information: Disperse Violet 1. Unpublished data submitted by CTFA on July 11, 2007. 1 page.
51. Food and Drug Administration (FDA). *Frequency of Use of Cosmetic Ingredients*. Washington, DC: FDA; 2006.
52. Food and Drug Administration (FDA). *Frequency of Use of Cosmetic Ingredients. Washington*, DC: FDA; 2006.

Ethyl Hexanediol

Conclusion

In 1994 earlier safety assessment of ethyl hexanediol, the Cosmetic Ingredient Review (CIR) Expert Panel stated that this ingredient is safe as (then) used as a cosmetic ingredient.[1] The Expert Panel reviewed newly available studies since that assessment along with updated frequency of use information.[2-17] The Panel determined to not reopen this safety assessment. Therefore, the Expert Panel confirmed that ethyl hexanediol is safe as a cosmetic ingredient.

Discussion

Ethyl hexanediol was used in 3 cosmetic formulations in 1993. Use concentrations were not reported at that time.[1] The Food and Drug Administration (FDA)[8] reported that ethyl hexanediol is used in 1 cosmetic formulation in 2009. A survey conducted by the Personal Care Products Council reported no uses of ethyl hexanediol (Table 1).[16]

References

1. Andersen FA. Final report on the safety assessment of ethyl hexanediol. *JACT*. 1994;13(6):418-436.
2. Gottschalck TE, Bailey JE, eds. *International Cosmetic Ingredient Dictionary and Handbook*. Vol 1. 13th ed. Washington, DC: Personal Care Products Council; 2010.
3. Ballantyne B. 2-Ethyl-1,3-hexanediol. *J Appl Toxicol*. 2005; 25(3):248-259.
4. Bushy Run Reserach Center. Initial Submission: 2-Ethyl-1,3-Hexanediol: In vitro cytogenetic studies (project report) with attachments, cover sheet and letter dated 050592. Study sponsored Union Carbide Corporation. *NTIS Order No.OTS0536321*. 1985.
5. ChemIDplus Lite. Ethohexadiol [USP]. RN: 94-96-2. http://chem.sis.nlm.nih.gov/chemidplus/ProxyServlet?objectHandle-DBMaint&actionHandle=default&nextPage=jsp/chemidlite/ResultScreen.jsp&TXTSUPERLISTID=000094962. Accessed July 21, 2009.
6. European Union. Cosmetic Ingredients and Substances Infobase. Ethyl hexanediol. http://ec.europa.eu/enterprise/cosmetics/cosing/index.cfm?fuseaction=search.details&id=33823. Accessed July 27, 2009.
7. Fang H, Tong W, Branham WS, et al. Study of 202 natural, synthetic, and environmental chemicals for binding to the androgen receptor. *Chem Res Toxicol*. 2003;16(10): 1338-1358.
8. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. FDA database. Food and Drug Administration. Washington, DC: FDA; 2009.
9. Frantz SW, Ballantyne B, Beskitt JL, Tallant MJ, Greco RJ. Pharmacokinetics of 2-ethyl-1,3-hexanediol. III. In vitro skin penetration comparisons using the excised skin of humans, rats, and rabbits. *Fundam Appl Toxicol*. 1995;28(1):1-8.
10. Frantz SW, Beskitt JL, Tallant MJ, Ballantyne B. Comparison of human skin penetration *in vitro* with *in vivo* and *in vitro* cutaneous penentration in rats with three compoounds: ethylhexanediol, glutaraldehyde, and polymer JR400. *In Vitro Toxicol*. 2004;7(2): 152-152.
11. Hu T, Kaluzhny Y, Mun GC, et al. Intralaboratory and interlaboratory evaluation of the EpiDerm 3D human reconstructed skin micronucleus (RSMN) assay. *Mutat Res*. 2009;673(2): 100-108.
12. Lewis RJ Sr. *Hawley's Condensed Chemical Dictionary*. 13th ed. New York, NY: John Wiley & Sons, Inc; 1997.

Table 1. Historical and Current Cosmetic Product Uses and Concentrations for Ethyl Hexanediol

Product Category	1993 Frequency of Use[1]	2009 Frequency of Use[8]	1993 Use Concentration[1]	2009 Use Concentration[16]
Tonics, dressings, and other hair grooming aids	1	–	[a]	No reported uses
Cleansing products	1	–	[a]	No reported uses
Other suntan preparations	1	–	[a]	No reported uses
Face and neck preparations (excluding shaving)	–	1	–	No reported uses
Total	3	1	[a]	No reported uses

Abbreviation: FDA, Food and Drug Administration.
[a] Not reported to FDA.

13. Loftsson T, Gildersleeve N, Soliman R, Bodor N. Effect of oleic acid on diffusion of drugs through hairless mouse skin. *Acta Pharm Nord*. 1989;1(1):17-22.
14. National Institute of Standards and Technology (NIST). 1,3-Hexanediol, 2-ethyl-. 2009. http://webbook.nist.gov/cgi/cbook.cgi?ID=C94962&Units=SI&Mask=80. Accessed July 21, 2009.
15. Neeper-Bradely TL, Fisher LC, Butler BL. Evaluation of the developmental toxicity potential of 2-ethyl-1,3-hexanediol in the rat by cutaneous application. *J Toxicol Cut Ocular Toxicol*. 1994; 13(3):203-214.
16. Personal Care Products Council. 2009. Memo regarding concentration of use information: ethyl hexanediol, hexandediol and 1,2-hexanediol.Unpublished data submitted by the Personal Care Products Council.
17. Van Miller JP, Losco PE, Neptun DA, Ballantyne B. Repeated exposure toxicity of 2-ethyl-1,3-hexanediol by cutaneous applications to the rat for 9 and 90 days. *Vet Hum Toxicol*. 1995;37(1):33-36.

HC Blue No. 2

Conclusion

In a 1994 safety assessment of HC Blue No. 2, the Cosmetic Ingredient Review (CIR) Expert Panel stated that HC Blue No. 2 is safe as (then) used as a coal-tar hair dye ingredient at the (then) current concentrations of use.[1] The Expert Panel reviewed newly available studies since that assessment,[2-24] along with updated information regarding types and concentrations of use. The Panel determined to not reopen this safety assessment. Therefore, the Panel confirms that HC Blue No. 2 is safe as a hair dye ingredient in the practices of use and concentration, as given in Table 1.

Discussion

The Expert Panel recognizes that HC Blue No. 2 is used as a hair dye ingredient and may be a sensitizer. However, hair dyes, hair tints, hair rinses, hair color sprays, and coloring shampoos containing these ingredients as coal-tar hair dye products are exempt from the principal adulteration provision and from the color additive provisions in sections 601 and 706 of the Federal Food, Drug, and Cosmetic Act, when the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation. The Expert Panel expects that continuing to follow this procedure will identify prospective individuals who would have an irritation/sensitization reaction and allow them to avoid significant exposures.

While the Expert Panel noted that the Scientific Committee on Consumer Products (SCCP) limited the nitrosamine content of HC Blue No. 2 to < 50 ppb, the chemical structure of this ingredient is that of a nitro aryl compound and not of an *N*-nitroso compound.

The 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 end points based on lack of strength of the associations and inconsistency of findings. The hair dye epidemiology data are available at http://www.cir-safety.org/findings.shtml.

References

1. Andersen FA. Final report on the safety assessment of HC Blue No. 2. *J Am College Toxicol*. 1994;13(5):361-373.
2. Adams RM, Maibach HI, Clendenning WW, et al. A five-year study of cosmetic reactions. *J Am Acad Dermatol*. 1985;13(4):1062-1069.
3. Chevalier G. 13-Week toxicity study by oral route (gavage) in rats followed by a 4-week treatment-free period. CIT study number 26894 TCR. Unpublished data submitted by the Personal Care Products Council. 2005:678 pages.

Table 1. Historical and current cosmetic product uses and concentrations for HC Blue No. 2

Product Category	1993 Uses (total number of products in a category)[1]	2009 Uses (total number of products in category)[25]	1993 Concentrations[1] (%)	2009 Concentrations[17] (%)
Hair-coloring products			1.7[a]	
Dyes and colors	136 (811)	163 (2481)	NA	2[b]
Hair tints	7 (15)	1 (58)	NA	-
Hair rinses	NA	- (43)	NA	0.6
Hair shampoos (coloring)	NA	3 (48)		-
Other coloring preparations	2 (207)	- (166)	NA	-
Total uses/ranges for HC Blue No. 2	145	167	1.7	0.6-2

[a] Product category for concentration not reported.
[b] 1% after dilution.

4. de Ligt RAF. In vitro percutaneous absorption of [^{14}C]-HC Blue No. 2 through human skin membranes using flow-through diffusion cells. TNO study number 6044. Unpublished data submitted by the Personal Care Products Council. 2005:54 pages.
5. Eiermann HJ, Larsen W, Maibach HI, et al. Prospective study of cosmetic reactions: 1977-1980. *J Am Acad Dermatol*. 1982;6: 909-917.
6. Elder RL, ed. Final report on the safety assessment of p-phenylenediamine. *JACT*. 1985;4(2):203-266.
7. Erexson GL. In vivo rat micronucleus assay. Covance study number 6182-110. Unpublished data submitted by the Personal Care Products Council. 2005:108 pages.
8. Food and Drug Administration (FDA). Cosmetic product warning statements: Coal tar hair dyes containing 4-methoxy-m-phenylenediamine (2,4-diaminanisole) or 4-methoxy-m-phenylenediamine sulfate (2,4-diaminoanisole sulfate). *Federal Register*. 1979;44(4):59509-59510.
9. Gaoua W. Prenatal developmental toxicity study by oral route (gavage) in rats. CIT study number 26893 RSR. Unpublished data submitted by the Personal Care Products Council. 2005:252 pages.
10. Gottschalck TE, Bailey JE. *International Cosmetic Ingredient Dictionary and Handbook*. 12th ed. Vol. 1. Washington, DC:CTFA; 2008.
11. Groult R. Validation of the analytical method and determination of homogeneity and stability of dosage forms. CIT study number 26970 AHS. Unpublished data submitted by the Personal Care Products Council. 2005;56 pages.
12. Kerckaert GA, LeBoeuf RA, Isfort RA. 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*. 1998;41(2): 189-197.
13. Kumaravel TS. HC Blue No. 2 (B037): Induction of chromosome aberrations in cultured human peripheral blood lymphocytes. Covance study number 413/79-D6172. Unpublished data submitted by the Personal Care Products Council. 2005:47 pages.
14. Lloyd M. HC Blue No. 2 (B037): Mutation at the hprt locus of L5178Y mouse lymphoma cells using the microtitre fluctuation technique. Covance study number 419/81-D6173. Unpublished data submitted by the Personal Care Products Council. 2005:48 pages.
15. Ministry of Health Labor and Welfare. MHW Ordinance No. 332, Ingredients of quasi-drugs. Products to be used directly on the body. 2000.
16. Ministry of Health Labor and Welfare. MHW Ordinance No. 331, Appendix 1. List of ingredients that cosmetics shall not contain. 2005.
17. Personal Care Products Council. 2009. Current use concentrations–HC Blue No. 2. Unpublished data submitted by the Personal Care Products Council.
18. Scientific Committee on Consumer Products (SCCP). Opinion on HC Blue No. 2 (Colipa No. B37). http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_084.pdf. 2006. Accessed April 16, 2009.
19. Sire G. Acute eye irritation in rabbits. CIT study number 29073 TAL. Unpublished data submitted by the Personal Care Products Council. 2005:18 pages.
20. Sire G. Acute oral toxicity in rats "fixed dose method". CIT study number 29770 TAR. Unpublished data submitted by the Personal Care Products Council. 2005:24 pages.
21. Sire G. Acte dermal irritation in rabbits. CIT study number 26971 TAL. Unpublished data submitted by the Personal Care Products Council. 2005:30 pages.
22. Sire G. Evaluation of skin sensitization potential in mice using the local lymph node assay (LLNA). CIT study number 26972 TSS. Unpublished data submitted by the Personal Care Products Council. 2005:39 pages.
23. Whitwell J. HC Blue No. 2 (B037): Induction of micronuclei in cultured human peripheral blood lymphocytes. Covance study number 413/80-D6172. Unpublished data submitted by the Personal Care Products Council. 2004:47 pages.
24. Williams L. HC Blue No. 2 (B037): reverse mutation in five histidine-requiring strains of Salmonella typhimurium. Covance study number 413/78-D6171. Unpublished data submitted by the Personal Care Products Council. 2005:55 pages.
25. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. *FDA Database*. 2009.

HC Red No. 3

Conclusion

In a 1992 safety assessment of HC Red No. 3, the Cosmetic Ingredient Review (CIR) Expert Panel stated that HC Red No. 3 is safe as (then) used as a coal-tar hair dye ingredient at the (then) current concentrations, with the condition that it should not be used in products containing *N*-nitrosating agents.[1] The Expert Panel reviewed newly available studies since that assessment (see references),[1-22] along with updated information regarding types and concentrations of use and did not reopen the safety assessment. The Expert Panel confirmed that HC Red No. 3 is safe as a hair dye ingredient in the practices of use and concentration, as given in Table 1.

Discussion

Although there is an increase in the number, type, and use concentration of HC Red No. 3, the CIR Expert Panel found

Table 1. Historical and Current Cosmetic Product Uses and Concentrations[a] of HC Red No. 3

Product Category	1984 Uses (Total Number of Products in a Category[1])	2008 Uses (Total Number of Products in a Category[23])	1992 Concentrations (%)[1]	2008 Concentrations (%)[9]
Hair-coloring products				
Dyes and colors	68 (811)	218 (1600)	≤0.1-1	0.1-2, 14[a]
Hair tints	NA	2 (56)	NA	–
Hair rinses	NA	5 (15)	NA	2
Hair color sprays (aerosol)	NA	– (4)	NA	0.03
Shampoos (coloring)	NA	5 (27)	NA	–
Total uses/ranges for HC Red No. 3	68	230	≤0.1-1	NA

Abbreviation: NA, not available.
[a] Two percent after dilution.

that both the newly available studies and the studies in the original report support the safety of the new use and concentration of this ingredient in hair dye products. The Expert Panel determined the studies show that there is little to no dermal absorption of HC Red No. 3.

The Expert Panel recognizes that HC Red No. 3 is used as a hair dye ingredient and may be a sensitizer. However, hair dyes, hair tints, hair rinses, hair color sprays, and coloring shampoos containing these ingredients as coal-tar hair dye products are exempt from the principal adulteration provision and from the color additive provisions in sections 601 and 706 of the Federal Food, Drug, and Cosmetic Act, when the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation. The Expert Panel expects that continuing to follow this procedure will identify prospective individuals who would have an irritation/sensitization reaction and allow them to avoid significant exposures.

The 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 end points based on lack of strength in the associations and inconsistency of findings. The hair dye epidemiology data are available at http://www.cir-safety.org/findings.shtml.

References

1. Elder RL. Final report on the safety assessment of HC Red No. 3. *J Am Coll Toxicol*. 1992;11(suppl 1):509-519.
2. Chapdelaine J. 2000. Local lymph node assay #0787XB05.008, study #990115 (summary). Report to Clairol, Chrysalis Preclinical Services. Unpublished data submitted by the Personal Care Products Council. 1 page.
3. Elder RL. ed. Final report on the safety assessment of p-phenylenediamine. *J Am Coll Toxicol*. 1985;4(1):203-266.
4. Food and Drug Administration (FDA). Cosmetic product warning statements: coal tar hair dyes containing 4-methoxy-m-phenyle nediamine (2,4-diaminanisole) or 4-methoxy-m-phenylenediamine sulfate (2,4-diaminoanisole sulfate). *Federal Register*. 1979;44(2): 59509-59510.
5. Gottschalck TE, Bailey JE, eds. *International Cosmetic Ingredient Dictionary and Handbook*. 12th ed. Vol. 1. Washington DC: CTFA; 2008.
6. International Agency for Research on Cancer (IARC). Occupational exposures of hairdressers and barbers and personal use of hair colourants; some hair dyes, cosmetic colourants, industrial dyestuffs and aromatic amines. *IARC Monograph Eval carcino Risks Hum*. 1993;57:43-118.
7. Ministry of Health Labour and Welfare (MHLW). *MHW Ordinance No. 332, Ingredients of quasi-drugs. Products to be used directly on the body*. 2000. 2-2, 1-chrome, Kasumigaseki, Chiyoda-ku, Tokyo 100-8045, Japan: Ministry of Health, Labor and Welfare, Pharmaceutical and Medical Safety Bureau, Inspection and Guidance Division.
8. Ministry of Health Labour and Welfare (MHLW). *MHW Ordinance No. 331, Appendix 1. List of ingredients that cosmetics shall not contain*. 2005. 2-2, 1-chrome, Kasumigaseki, Chiyoda-ku, Tokyo 100-8045, Japan: Ministry of Health, Labor and Welfare, Pharmaceutical and Medical Safety Bureau, Inspection and Guidance Division.
9. Personal Care Products Council. 2008. *Current use concentrations–HC Red No. 3*. Unpublished data provided by the Council. 1 page.
10. Proctor and Gamble. 2005. HC Red No. 3: In vitro penetration from a formulation through human skin (summary). P&G Study #2719-53854. Unpublished data provided by the Council. 1 page.
11. Proctor and Gamble. 2005. Oral (gavage) doseage-range developmental toxicity study of GT@03959 in rats (summary). P&G Study #2719-53981. Unpublished data provided by the Council. 1 page.
12. Proctor and Gamble. 2005. Oral (gavage) developmental toxicity study of GTS03959 in rats (summary). P&G Study #2719-53861. Unpublished data provided by the Council. 1 page.
13. Proctor and Gamble. 2005. Bacterial mutation test (Ames)(summary). P&G Study #2719-54751. Unpublished data provided by the Council. 1 page.
14. Proctor and Gamble. 2005. In vitro chromosome aberratin assay, P&G study #2747-53908. Unpublished data submitted by the Council. 1 page.
15. Proctor and Gamble. 2005. In vitro mouse lymphoma (L5167Y TK+/-) mutation assay (summary). P&G Study #2719-53856. Unpublished data provided by the Council. 1 page.
16. Rosenkranz HS, Ennever FK. An association between mutagenicity and carcinogenic potency. *Mutat Res*. 1990;244:(1):61-66.

17. Rosenkranz HS and Klopman G. Structural relationships between mutagenicity, maximum tolerated dose, and carcinogenicity in rodents. *Environ Mol Mutagen*. 1993;21:(2):193-206.
18. Safepharm Laboratories. 1992. HC Red 3/B050: Micronucleus test in the mouse (summary). Study #436/11. Report to Sonala Parfumerien GmbH. Unpublished data provided by the Council. 1 page.
19. Scientific Committee on Consumer Products (SCCP). Request for a scientific opinion: HC Red No. 3 (CAS 2871-01-4) submission II (B050). 2005. http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_q_081.pdf. Accessed June 15, 2007.
20. Unilever. 2001. Local lymph node assay (LLNA) in mice (identification of contact allergens) (summary). Unilever Study #KS010165, including analytical study #AC010141. Unpublished data provided by the Council. 1 page.
21. Wella. 2003. Analysis of DNA damage induced by in vivo exposure of mice to HC Red No. 3 [2-((4-amino-2-nitrophenyl)amino)ethanol] using the comet and micronucleus (summary) Wella Study #20824C. Unpublished data provided by the Council. 2 pages.
22. Wella. 2005. Analysis of the mutagenicity of Big Blue mice exposed orally to HC Red No. 3 for 8 weeks using the cII assay (summary). Wella Study #C123-002. Unpublished data provided by the Council. 1 page.
23. Food and Drug Administration (FDA). *Frequency of Use of Cosmetic Ingredients*. Washington, DC: FDA; 2008.

HC Yellow No. 2

Conclusion

In a 1994 safety assessment of HC Yellow No. 2, the Cosmetic Ingredient Review (CIR) Expert Panel stated that this ingredient is safe as (then) used in cosmetic products.[1] The Expert Panel reviewed newly available studies since that assessment (see references),[2-16] along with updated information regarding types and concentrations of use. The Panel determined to not reopen this safety assessment. Therefore, the Panel confirmed that HC Yellow No. 2 is safe as a cosmetic ingredient in the practices of use and concentration, as given in Table 1.

Discussion

HC Yellow No. 2 had been used in 91 cosmetic products in 1981. Use concentrations were not reported at that time. The Food and Drug Administration (FDA)[17] reported that HC Yellow No. 2 is used in 134 hair dyes and colors and 4 hair shampoos. A survey of current use concentrations conducted by the Personal Care Products Council[18] reported a range of 0.2% to 2% in hair dyes and colors.

Newly available data did not raise any new issues about the safety of HC Yellow No. 2. The Expert Panel noted that the available hair dye epidemiology studies are insufficient to conclude there is a causal relationship between hair dye use and cancer and other end points based on the lack of strength of the associations and inconsistency of findings. A discussion of the available hair dye epidemiology data is available at http://www.cir-safety.org/findings.shtml.

The Expert Panel recognizes that HC Yellow No. 2 is used as a hair dye ingredient and may be a sensitizer. However, hair dyes containing these ingredients, as coal-tar hair dye products, are exempt from the principal adulteration provision and from the color additive provisions in sections 601 and 706 of the Federal Food, Drug, and Cosmetic Act, when the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation. The Expert Panel expects that continuing to follow this procedure will identify prospective individuals who would have an irritation/sensitization reaction and allow them to avoid significant exposures.

The Expert Panel considered the addition of HC Yellow No. 5, 9, 11, and 12 to this safety assessment. It was decided that these dyes were chemically different from the original ingredient and that the available data on HC Yellow No. 2 could not be extended to these other hair dyes.

References

1. Andersen FA. Final report on the safety assessment of HC yellow no. 2. *J Am Coll Toxicol*. 1994;13(3):157-166.
2. Chapdelaine J. Local lymph node assay #0787XB05.007, Study #99012, report to Clairol, Chrysalis Preclinical Services. In:

Table 1. Historic and Current Cosmetic Product Uses and Concentrations for HC Yellow No. 2.

Product Category	1981 Uses[1]	2007 Uses[17]	1981 Concentrations[1] (%)	2008 Concentrations[18] (%)
Hair-coloring products				
Dyes and colors	91	134	-	0.2-2
Shampoos	-	4	-	-
Total uses/ranges for HC Yellow No. 2	91	138	-	0.2-2

Summary of Studies on HC Yellow No. 2. Unpublished data submitted by the Personal Care Products Council; 2000. 2 pages.
3. Gottschalck TE, Bailey J. In: *International Cosmetic Ingredient Dictionary and Handbook*.2008;13th edition. Washington DC: CTFA; 2008.
4. Personal Care Products Council. In vitro human skin penetration ^{14}C labelled HC yellow #2, study #GLP-94032. Unpublished data submitted by the Council; 1995. 1 page.
5. Proctor and Gamble. A 14-day range-finding oral toxicity study in rats with GTS03975, P&G Study #2747-53906. Unpublished data submitted by the Council; 2005. 2 pages.
6. Proctor and Gamble. A 91-day oral gavage toxicity study with GTS03975 in rats with a 28-day recovery phase, P&G study #2747-53907. Unpublished data submitted by the Council; 2005. 2 pages.
7. Proctor and Gamble. Bacterial mutation test (Ames), P&G study #2747-53905. Unpublished data submitted by the Council; 2005. 1 page.
8. Proctor and Gamble. In vitro penetration from a formulation through human skin, P&G Study #2747-53910. In: *Summary of Studies on HC Yellow No. 2*. Unpublished data submitted by the Council; 2005. 1 page.
9. Proctor and Gamble. In vitro chromosome aberratin assay, P&G study #2747-53908. Unpublished data submitted by the Council; 2005. 1 page.
10. Proctor and Gamble. In vitro mouse lymphoma (L5167Y/TK$^{+/-}$) mutation assay, P&G study #2747-53909. Unpublished data submitted by the Council; 2005. 1 page.
11. Proctor and Gamble. In vivo micronucleus assay, P&G study #2747-53905. Unpublished data submitted by the Council; 2005. 1 page.
12. Proctor and Gamble. In vivo unscheduled DAN synthesis (UDS) test in rats, P&G study #2747-54629. Unpublished data submitted by the Council; 2005. 1 page.
13. Proctor and Gamble. Oral (gavage) developmental toxicity study of GTS03975 in rats, P&G study #2747-53904. Unpublished data submitted by the Council; 2005. 1 page.
14. Proctor and Gamble. Oral (gavage) dosage-range developmental toxicity study of GTS03975. Unpublished data submitted by the Council; 2005. 1 page.
15. Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP). Opinion of the scientific committee on cosmetic products and non-food products intended for consumers concerning HC yellow no. 9 COLIPA no. B69; 2003. 20 page.
16. Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP). Opinion of the Scientific Committee on Cosmetic Products and Non-Food Products intended for consumers concerning HC yellow no. 11 COLIPA no. B63; 2003.18 pages.
17. Food and Drug Administration (FDA). *Cosmetic product formulation and frequency of use data*. Washington DC: FDA; 2007.
18. Personal Care Products Council. Concentration of use HC Yellow No. 2, HC Yellow No. 5*, HC Yellow No. 9*. HC Yellow No. 11* and HC Yellow No. 12*. Unpublished data submitted by the Council; 2008. 1 page.

Hydroxybenzomorpholine

Conclusion

In its 1991 safety assessment of hydroxybenzomorpholine, the Cosmetic Ingredient Review (CIR) Expert Panel stated that this ingredient is safe as used in cosmetic products.[1] In 2007, the expert panel reviewed newly available studies since that assessment, along with updated information regarding types and concentrations of use.[2-4] The panel confirmed the safety of hydroxybenzomorpholine in hair dyes and colors in the practices of use and concentrations as given in Table 1 and did not reopen the safety assessment.

Discussion

The Food and Drug Administration[2] voluntary reporting program included no uses for hydroxybenzomorpholine, compared to 43 uses in hair dyes and colors in 1989, mostly in the $\leq$0.1% range.[1] Cosmetic, Toiletry, and Fragrance Association (CTFA)[3] reported that this hair dye ingredient currently is used up to 0.03%, based on an industry survey.

The expert panel considered the opinion of the European Commission's Scientific Committee on Consumer Products (SCCP), which included unpublished data submitted by

Table 1. Historical and Current Cosmetic Product Uses and Concentrations for Hydroxybenzomorpholine

Product Category	1989 Ingredient Uses[1]	2006 Ingredient Uses[2]	1989 Use Concentrations[1]	2007 Use Concentrations[3]
Hair dyes and colors	43	–	$\leq$0.1%-1%	0.03%
Total uses/ranges for hydroxybenzomorpholine	43	–	$\leq$0.1%-1%	0.03%

industry.[4] It was noted that the SCCP limited nitrosamine content to 1% in any finished product. The CIR Expert Panel acknowledged that *N*-nitrosohydroxybenzomorpholine may be an impurity of hydroxybenzomorpholine. In addition, hydroxybenzomorpholine is subjected to nitrosation in the presence of *N*-nitrosating agents that may be included in a cosmetic formulation. Therefore, the expert panel reiterated that this ingredient should not contain *N*-nitroso impurities, nor should it be used in products where *N*-nitroso compounds may be formed.

References

1. Elder RL., ed Final report on the safety assessment of hydroxybenzomorpholine. *J Am Coll Toxicol*. 1991;10:205-213.
2. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. *Washington*, DC: FDA; 2006.
3. Cosmetic, Toiletry, and Fragrance Association (CTFA). 2007. Use concentration data for hydroxybenzomorpholine. Unpublished data submitted by CTFA. 1 page.
4. Scientific Committee on Consumer Products (SCCP). 2006. Opinion on hydroxybenzomorpholine. COLIPA no A25. 30 pages.

Isopropyl Isostearate

Conclusion

In its 1992 safety assessment of isopropyl isostearate, the Cosmetic Ingredient Review (CIR) Expert Panel stated that this ingredient was safe as used in cosmetic products.[1] In 2007, the Expert Panel found no newly available studies since that assessment, but did review updated information regarding the types and concentrations of use. This re-review confirms that isopropyl isostearate is safe in the practices of use and concentration, as given in Table 1 and did not reopen this safety assessment.

Discussion

Isopropyl isostearate was used in 78 cosmetic products in 1989, based on voluntary reports submitted to Food and Drug Administration (FDA by industry), with concentrations of use ranging from ≤0.1% to 50%.[1] In 2005, isopropyl isostearate was reportedly used in 69 cosmetic products.[2] Data from an industry survey in 2007 indicated that isopropyl isostearate was used at concentrations ranging from 0.5% to 65%.[3] The Panel noted that there was an increase in concentration to

Table 1. Historical and Current Cosmetic Product Uses and Concentrations of Isopropyl Isostearate in Cosmetics

Product Category	1989 Uses (total number of products in product category)[4]	2005 uses[2]	1989 Concentrations (total number of products in product category)[4]	2007 Concentrations[3]
Baby products				
Lotions, oils, powders, and creams	-[a] (60)	2 (67)	-[a] (67)	-
Eye makeup preparations				
Eyebrow pencils	11 (1135)[b]	-[a] (124)	0.1%-10%	-
Eyeliners		-[a] (639)		-
Eye shadow		8 (1061)		2%-5%
Eye lotions		-[a] (32)		-
Eye makeup remover		1 (114)		3%
Mascara		-[a] (114)		0.6%
Other eye makeup preparations		-[a] (229)		2%
Fragrance preparations				
Powders	-[a] (273)	2 (324)	-[a] (324)	1%
Noncoloring Hair Preparations				
Shampoos	-[a] (884)	1 (1022)	-[a] (1022)	65%
Makeup preparations				
Blushers	40 (3194)[b]	-[a] (459)	≤0.1%-50%	0.5%-30%
Face powders		-[a] (447)		0.6%-30%
Foundations		-[a] (530)		12%-13%
Leg and body paints		-[a] (10)		-
Lipsticks		-[a] (1681)		12%-24%
Makeup bases		-[a] (273)		7%-30%
Rouges		-[a] (115)		6%
Makeup fixatives		-[a] (37)		-[a]
Other makeup preparations		19 (304)		1%-10%

(continued)

Table 1. (continued)

Product Category	1989 Uses (total number of products in product category)[4]	2005 uses[2]	1989 Concentrations (total number of products in product category)[4]	2007 Concentrations[3]
Personal hygiene products				
Underarm deodorants	-[a] (247)	-[a] (281)	-[a]	5%
Shaving Preparations				
Other shaving preparations	-[a] (63)	1 (64)	-[a] (64)	-[a]
Skin care preparations				
Skin cleansing creams, lotions, liquids, and pads	20 (3110)[b]	2 (1009)	≤0.1%-10%	2%-3%
Depilatories		-[a] (49)		-[a]
Face and neck skin care preparations		1 (546)		2%-4%
Body and hand skin care preparations		5 (992)		0.5%-4%
Foot powders and sprays		-[a] (43)		-[a]
Moisturizers		18 (1200)		0.7%-3%
Night skin care preparations		4 (229)		2%
Paste masks (mud packs)		1 (312)		-[a]
Skin fresheners		-[a] (212)		-[a]
Other skin care preparations	7	4 (915)	1%-25%	-[a]
Total uses/ranges for isopropyl isostearate	71	69	≤0.1%-50%	0.5%-65%

[a] Not reported. In some cases, ingredient uses were not reported to Food and Drug Administration (FDA) in the voluntary industry product survey program, however, concentrations were provided. In other cases, the uses were reported, but no concentration was provided.
[b] In 1989, these uses were combined.

65% in rinse-offs, but the original data supported the safety of this concentration.

The available usage and use concentration data are given in Table 1 as a function of product category.

References

1. Elder RL. Final report on the safety assessment of isopropyl isostearate. *J Am Coll Toxicol*. 1992;11(1):43-49.
2. Food and Drug Administration. *Frequency of Use of Cosmetic Ingredients*. Washington, DC: FDA; 2006.
3. Cosmetic, Toiletry, and Fragrance Association. Use concentration survey results for isopropyl isostearate. Unpublished data submitted by CTFA; 2007.
4. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. Washington DC: FDA; 1989.

Lauramine Oxide and Stearamine Oxide

Conclusion

In 1994, the Cosmetic Ingredient Review (CIR) Expert Panel stated[1] that lauramine oxide and stearamine oxide are safe as cosmetic ingredients for rinse-off products, but that in leave-on products, the concentration of lauramine oxide should be limited to 3.7% and that of stearamine oxide should be limited to 5%. The Expert Panel reviewed newly available studies since that assessment (see references),[2-4] along with updated information regarding types and concentrations of use. The Panel decided to not reopen this safety assessment. Therefore, the panel confirmed that lauramine oxide and stearamine oxide are safe as cosmetic ingredients in rinse-off products, but that in leave-on products, the concentration of lauramine oxide and stearamine oxide should be limited to 3.7% and 5%, respectively.

Discussion

The product formulation data submitted to the Food and Drug Administration (FDA) in 1992 reported that lauramine oxide and stearamine oxide were used in a total of 9 and 37 cosmetic product formulations, respectively (Table 1). According to information supplied to FDA by industry as part of the Voluntary Cosmetic Registration Program (VCRP), lauramine oxide and stearamine oxide were used in a total of 83 and 77 formulations, respectively, in 2009 (Table 1). A survey of current use concentrations conducted by the Personal Care Products Council[5] reported that lauramine oxide and stearamine oxide were used in ranges of 0.01% to 15% and 0.07% to 1%, respectively (Table 1).

Table 1. Historical and Current Cosmetic Product Uses and Concentrations of Lauramine Oxide and Stearamine Oxide

Product Category[6]	1992 Uses[1]	2007 Uses[7]	2009 Uses[8]	2008 Concentrations (%)[5]
Lauramine oxide				
Baby products				
Other		4 (138)	4 (138)	–
Bath products				
Soaps and detergents		24 (1329)	24 (1329)	0.2-15
Bubble baths		8 (262)	13 (262)	2
Noncoloring hair care products				
Conditioners		2 (1249)	2 (1249)	0.2 – 0.7
Permanent waves		2 (141)	–	–
Rinses	3 (83)	–	–	–
Shampoos	3 (953)	11 (1403)	10 (1403)	0.4
Tonics, dressings, etc	3 (548)	8 (1097)	8 (1097)	0.2-1
Other		2 (716)	1 (716)	–
Makeup				
Foundations		3 (635)	3 (635)	0.01
Personal hygiene products				
Other		1 (514)	6 (514)	0.5-2
Shaving products				
Shaving cream		1 (162)	1 (162)	0.08
Skin care products				
Cleansing creams, lotions, liquids, and pads		7 (1368)	7 (1368)	0.6-3
Body and hand creams, lotions, etc		1 (1513)	1 (1513)	0.2-0.9
Moisturizers		3 (2039)	3 (2039)	0.9
Total uses/ranges for lauramine oxide and total uses/ranges for ingredient	9	77	83	0.01-15
Stearamine oxide				
Noncoloring hair care products				
Conditioners	18 (666)	12 (1249)	8 (1249)	0.07-1
Rinses	5 (83)	–	–	–
Shampoos	9 (953)	3 (1403)	3 (1043)	–
Other		2 (716)	1 (716)	0.3
Hair-coloring products				
Dyes and colors		63 (2481)	63 (2481)	–
Tints		1 (58)	1 (58)	–
Skin care products				
Face and neck creams, lotions, etc		1 (1195)	1 (1195)	–
Paste masks/mud packs		1 (418)	–	–
Other	5 (848)			
Total uses/ranges for stearamine oxide and total uses/ranges for Ingredient	37	83	77	0.07-1

References

1. Andersen FA. Final report on the safety assessment of lauramine oxide and stearamine oxide. *J Am Coll Toxicol*. 1994;13(3): 231-245.
2. Kosswig K, Huls AG. Surfactants. In: Elvers B, Gerhartz W, eds. *Ullmann's Encyclopedia of Industrial Chemistry*, vol. A25. 5 ed. New York, NY: VCH Publishers; 1994:747-817.
3. Amine Oxides Consortium. Screening Information Data Set (SIDS) Initial Assessment Report for SIDS Initial Assessment Meeting (SIAM) 22: Amine Oxides. Paris France, Organisation for Economic Co-operation and Development (OECD); 2006: 1-426.
4. Gottschalck TE, Bailey JE. *International Cosmetic Ingredient Dictionary and Handbook*. 12th ed. Washington DC: CTFA; 2008.
5. Personal Care Products Council. Concentration of Use—Lauramine Oxide, Stearamine Oxide and Potential Additions; 2008.
6. Food and Drug Administration. *Frequency of use of cosmetic ingredients*. Washington DC: FDA; 2008.
7. Food and Drug Administration. *Cosmetic product formulation and frequency of use data*. Washington DC: FDA; 2007.
8. Food and Drug Administration. *Frequency of use of cosmetic ingredients*. Washington DC: FDA; 2009.

Methenamine

Conclusion

In a 1992 safety assessment of methenamine, the Cosmetic Ingredient Review (CIR) Expert Panel stated[1] that this ingredient is safe in cosmetic products at concentrations not to exceed 0.16%. The Expert Panel reviewed newly available studies since that assessment (see references),[2-36] along with updated information regarding product types and concentrations of use, and did not reopen this safety assessment. The Panel confirmed that methenamine is safe as cosmetic ingredients at concentrations not to exceed 0.16%.

Discussion

Methenamine was used in 7 products in 1981, based on voluntary reports provided to Food and Drug Administration (FDA)[1] by industry with concentrations of use of <1%. In 2008, methenamine was reportedly used in 31 products.[37] For example, of the 288 "other" eye makeup products reported, only 1 contained methenamine. Most uses are in the shampoo product category, where 27 of 1403 products on the market were reported to contain methenamine. Data[38] from an industry survey in 2008 indicated that methenamine was used at 0.002%. Table 1 presents the available use and concentration information.

The Expert Panel noted that methenamine functions as a formaldehyde releaser. A fundamental equilibrium exists between these releasers and free formaldehyde itself, resulting in a steady state of availability of formaldehyde in aqueous solutions. Data in the original safety assessment, along with all of the new data available since then, confirmed that, if the level of preservative is kept low, then the level of formaldehyde will not present any safety concerns.

The Expert Panel considered the addition of methenammonium chloride to the safety assessment. It was decided that the methyl group added to the organic amine ring structure of methenammonium chloride made the 2 ingredients too dissimilar to extrapolate the safety data of methenamine to methenammonium chloride.

References

1. Elder RL (ed). Final report on the safety assessment of methenamine. *J Am College Toxicol*. 2011;11(4):531-558.
2. Aalto-Korte K. Simultaneous allergic reactions to quaternium-15 and methenamine. *Contact Dermat*. 2000;42(6):365.
3. Dastychova E, Necas M, Pencikova K, and Cerny P. KontaktnÍ senzibilizace na pomocné látky v dermatologických externech a kosmetických prípavcích. [Contact sensitization to auxiliary substances in dermatological external and cosmetic preparations]. *Ceska Slov Farm*. 2004;53(3):151-156.
4. de Groot AC, de Cook PAJJM, Coenraads PJ, et al. Methyldibromoglutaronitrile is an important contact allergen in The Netherlands. *Contact Dermat*. 1996;34(2):118-120.
5. Dickie H, Taylor JS, Evey P, Merk HF. Delayed readings of a standard screening patch test tray: Frequency of "lost," "found," and "persistent" reactions. *Am J Contact Dermat*. 2000;11(4):213-217.

Table 1. Historical and Current Cosmetic Product Uses and Concentrations for Methenamine

Product Category (total number of products in the category as given by FDA (2007)	1981 Uses[1]	2007 Uses[37]	1981 Concentrations[1] (%)	2007 Concentrations[38] (%)
Methenamine				
Eye makeup[a]	6	–	<1.0	–
Other (288)	–	1	–	–
Fragrance products				
Powders (278)	–	–	–	0.002
Noncoloring hair care products				
Conditioners (1249)	–	1	–	–
Shampoos (1403)	–	27	–	–
Makeup				
Other (406)	–	1	–	–
Skin care products[b]	1		<1.0	–
Skin cleansing creams, lotions, liquids, and pads (1368)	–	1	–	–
Total uses/ranges for methenamine	7	31	<1.0	0.002

Abbreviation: FDA, Food and Drug Administration.
[a] Listed as mascara and other eye makeup preparations in the original safety assessment.
[b] Listed as face, body, and hand skin care preparations (excluding shaving preparations) in the original safety assessment.

6. Gelfand HH. Respiratory allergy due to chemical compounds encountered in the rubber, lacquer, shellac, and beauty culture industries. *J Allergy*. 1963;34:374-381.
7. Restani P, Restelli AR, and Galli CL. Formaldehyde and hexamethylenetetramine as food additives: chemical interactions and toxicology in Goodman, LS and Gilman, A The Pharmacological Basis of Therapeutics. 2nd ed (New York: Macmillan) p. 1087. *Food Addit Contam*. 1992;9(5):597-605.
8. Gottschalck TE, Bailey JE. *International Cosmetic Ingredient Dictionary and Handbook*.12th ed. Washington, DC: CTFA; 2008.
9. Hausen BM. Contact allergy to pentylene glycol. *Dermatitis*. 2007;18(2):99-100.
10. Hectorne KJ, Fransway AF. Diazolindinyl urea: incidence of sensitivity, patterns of cross-reactivity and clinical relevance. *Contact Dermat*. 1994;30(1):16-19.
11. Kiec-Swierczynska M, Krecisz B, Swierczynska-Machura D. Uczulenie kontaktowe na srodki konserwujae azwarte w kosmetykach [Contact allergy to preservatives contained in cosmetics]. *Med Pr*. 2006;57(3):245-249.
12. Knoff T. Methenamine hippurate. Short-term catheterization in gynecological surgery. A double-blind comparison of hiprex and placebo. *Tidsskrift for Den Norske Laegeforening*. 1985;105(7): 498-499.
13. Kranke B, Szolar-Platzer C, Aberer W. Reactions to formadehyde and formaldehyde releasers in a standard series. *Contact Dermat*. 1996;35(3):192-193.
14. Ismail-Zade RS. Whole body hyperthermia supplemented with urotropin in the treatment of malignant tumors. *Exp Oncol*. 2005;27(1):61-64.
15. Lee BB, Haran MJ, Hunt LM, et al. Spinal-injured neuropathic bladder antisepsis (SINBA) trial. *Spinal Cord*. 2007;45(8):542-550.
16. Lenczewski ME, McGavin ST, VanDyke K. Comparison of automated and traditional minimum inhibitory concentration procedures for microbiological cosmetic preservatives. *J AOAC Intern*. 1996;79(6):1294-1299.
17. Lindsay CD, Hambrook JL. Protection of A549 cells against the toxic effects of sulphur mustard by hexamethylenetetramine. *Human Exp Toxicol*. 1997;16(2):106-114.
18. Magen E, Mishal J, Schlesinger M. Sensitizations to allergens of TRUE test in 864 consecutive eczema patients in Israel. *Contact Dermat*. 2006;55(6):370-371.
19. Merget R, Topcu M, Friese K, Vormberg R, Fuchs T, Raulf-Heimsoth M, Breitstadt R. A cross-sectional study of workers in the chemical industry with occupational exposure to hexamethylenetetramine. *Arch Occup Environ Health*. 1999;72(8):533-538.
20. Mohebbi-Fani M, Shekarforoosh S, Maleki M, Vahedi N. Primary evaluation of methenamine as a NPN compound with probably effects on increasing ruminal escaped protein. *J Vet Med A*. 2002; 49(5):239-243.
21. Pavitrapok C, Williams DA. Determination of methenamine, methenamine mandelate and methenamine hippurate in phamaceutical preparations using ion-exchange HPLC. *J Pharmaceutical Biomed Anal*. 2006;40(5):1243-1248.
22. Perez RG. Case report. *Contact Dermat*. 2003;49:77-79.
23. Prue C, Martinson ME, McAnally PM, Stagner WC. Postmarketing survey results of T.R.U.E. Test, A new allergen patch test. *Am J Contact Dermat*. 1998;9(1):6-10.
24. Rappeneau S, Baeza-Squiban A, Marano F, Calver JH. Efficent protection of human brochial epithelial cells against sulfur and nitrogen mustard cytotoxicity using drug combinations. *Toxicol Sci*. 2000;58(1):153-160.
25. Saary MJ, House RA, Holness DL. Dermatitis in a particleboard manufacturing facility. *Contact Dermat*. 2001;44(6): 325-330.
26. Schotz HJ, Guttu K. Value of urinary pophylaxis with methenamine in gynecologic surgery. *Acta Obstet Gynecol Scand*. 2002; 81(8):743-746.
27. Science Lab.com. Material safety data sheet methenamine MSDS. 2005.
28. Selvaag E, Thune P. Photosensitivity reaction to methenamine hippurate: a case report. *Photodermatol Phtoimmunol Photomed*. 1994;10(6):259-260.
29. Skinner SL, Marks JG. Allergic contact dermatitis to preservatives in topical medicaments. *Contact Dermat*. 1998;9(4): 199-201.
30. Smith CN, Lindsay DD, Upshall DG. Presence of methenamine/glutathione mixtures reduces the cytotoxic effect of sulphur mustard on cultured SVK-14 human keratinocytes in vitro. *Human Exp Toxicol*. 1997;16(5):247-253.
31. Strom JG, Jun HW. Effect of urine pH and ascorbic acid on the rate of conversion of methenamine to formaldehyde. *Biopharmeceutics Drug Disposition*. 1993;14(1):61-69.
32. Susak Z, Mindov R, Isakov E. The use of methenamine as an antiperspirant for amputees. *Posthertics Orthotics Internat*. 1996;20(3):172-175.
33. Tan EL, Shah HS, Leister KJ, et al. Transforming growth factor-a (TGF-a) in a semisolid dosage form: preservative and vehicle selection. *Parmac Res*. 1993;10(8):1238-1242.
34. Templet JT, Hall S, Belsito DV. Etiology of hand dermatitis among patients referred for patch testing. *Dermatitis*. 2004; 15(1):25-32.
35. White JML, McFadden JP, White IR. A review of 241 subjects who were patch tested twice: could fragrance mix I cause active sensitization? *Contact Dermatol Allergy*. 2008;158(3): 518-521.
36. Zoller L, Bergman R, Weltfriend S. Preservatives sensitivity in Israel: a 10-year overview (1995-2004). *Contact Dermat*. 2006; 55(4):227-229.
37. Food and Drug Administration (FDA). *Frequency of Use of Cosmetic Ingredients*. Washington DC: FDA; 2007.
38. Personal Care Products Council. 2008. Concentration of use–Methenamine. Unpublished data submitted by the Personal Care Products Council. 1 page.

1-Naphthol

Conclusion

In its 1989 safety assessment of 1-naphthol, the Cosmetic Ingredient Review (CIR) Expert Panel[1] stated that this ingredient was safe for use as a cosmetic ingredient in the present practices of use and concentration. In 2007, the CIR Expert Panel reviewed newly available studies since that assessment,[2-34] along with updated information regarding types and concentrations of use. The CIR Expert Panel confirmed that 1-naphthol is safe in the practices of use and concentration, as given in Table 1 and did not reopen this safety assessment.

Discussion

1-Naphthol, an oxidizing hair dye,[1] was reported to have use in a total of 236 hair dyes and colors at concentrations from less than 0.1% up to 5%. The Food and Drug Administration (FDA) in 2006 reported that there were 627 total cosmetic uses.[20] An industry survey[15] of current use concentrations found use concentrations between 0.01% and 3%. Table 1 presents the available use and use concentration data.

The CIR Expert Panel determined that the available epidemiology studies are insufficient to conclude there is a causal relationship between hair dye use and cancer and other end points, based on lack of strength of the associations and inconsistency of findings. A list of hair dye epidemiology data is available at http://www.cir-safety.org/findings.shtml.

The Expert Panel recognizes that 1-naphthol is used as a hair dye ingredient and may be a sensitizer. However, hair dyes containing these ingredients, such as coal-tar hair dye products, are exempt from the principal adulteration provision and from the color additive provisions in sections 601 and 706 of the Federal Food, Drug, and Cosmetic Act when the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation. The Expert Panel expects that continuing to follow this procedure will identify prospective individuals who would have an irritation/sensitization reaction and allow them to avoid significant exposures.

References

1. Elder RL. Final report on the safety assessment of 1-naphthol. *JACT*. 1989;8:749-768.
2. Chao YE, Kupper LL, Serdar B, Egeghy PP, Rappaport SM, Nylander-French LA. Dermal exposure to Jet Fuel JP-8 significantly contributes to the production of urinary naphthols in fuel-cell maintenance workers. *Environ Health Perspect*. 2006;114(2): 182-185.
3. Cho TM, Rose RL, Hodgson E. In vitro metabolism of naphthalene by human liver microsomal cytochrome P450 enzymes. *Drug Metab Dispos*. 2006;34(1):176-183.
4. Cosmetic, Toiletry, and Fragrance Association (CTFA). 1998. Oral (gavage) dose-range developmental toxicity study of RE-1141.02 in rats, P&G Study No. BTSO704/02 (Protocol 916-020). Unpublished data provided by CTFA. 1 page.
5. Cosmetic, Toiletry, and Fragrance Association (CTFA). 2001. Local lymph node assay, Unilever Study No. KS010165. Unpublished data provided by CTFA. 1 page.
6. Cosmetic, Toiletry, and Fragrance Association (CTFA). 2001. 13-Week oral gavage toxicity study with RE-1141.03 in rats, P&G Study No. BTS0704/03. Unpublished data provided by CTFA. 2 pages.
7. Cosmetic, Toiletry, and Fragrance Association (CTFA). 2003. 2-Week oral gavage range finding toxicity study with RE1141. 01, P&G Study No. BTS0704/01. Unpublished data provided by CTFA. 1 page.
8. Cosmetic, Toiletry, and Fragrance Association (CTFA). 2003. Oral (gavage) developmental toxicity study of RE-141.02 in rats, P&G Study No. BTS004/02 (Protocol 916-020). Unpublished data provided by CTFA. 1 page.
9. Cosmetic, Toiletry, and Fragrance Association (CTFA). 2005. 1-Naphthol: in vitro penetration from a formulation through human skin, P&G Study No. 2751-53936. Unpublished data provided by CTFA. 1 page.
10. Cosmetic, Toiletry, and Fragrance Association (CTFA). 2005. Bacterial mutation test (Ames), P&G Study No. 2751-53938. Unpublished data provided by CTFA. 1 page.

Table 1. Historical and Current Cosmetic Product Uses and Concentrations for 1-Naphthol

Product Category	1987 Uses (Total Number of Products in a Category)[1]	2006 Uses (Total Number of Products in a Category)[20]	1987 Concentrations (%)[1]	2006 Concentrations (%)[15]
Hair coloring products				
Dyes and colors	236	618 (1600)	≤0.1-5	0.01-3
Tints	–	8 (56)	–	–
Lighteners with color	–	1 (14)	–	–
Other hair coloring preparations[a]	–	(73)	–	0.1
Total uses/ranges for 1-naphthol	236	627	≤0.1-5	0.01-3

[a] Coloring shampoo.

11. Cosmetic, Toiletry, and Fragrance Association (CTFA). 2005. In vitro chromosome aberration assay, P&G Study No. 2751-53934. Unpublished data provided by CTFA. 1 page.
12. Cosmetic, Toiletry, and Fragrance Association (CTFA). 2005. In vitro mouse lymphoma (L5167Y/TK+/−) mutation assay, P&G Study No. 2751-53935. Unpublished data provided by CTFA. 1 page.
13. Cosmetic, Toiletry, and Fragrance Association (CTFA). 2005. In vivo micronucleus assay, P&G Study No. 2751-53943. Unpublished data provided by CTFA. 2 pages.
14. Cosmetic, Toiletry, and Fragrance Association (CTFA). 2005. In vivo unscheduled DNA synthesis assay, P&G Study No. 2751-54595. Unpublished data provided by CTFA. 1 page.
15. Cosmetic, Toiletry, and Fragrance Association (CTFA). 2006. Current use concentration—1-Naphthol. Unpublished data provided by CTFA. 1 page.
16. Dechelotte P, Varrentrapp M, Meyer HJ, Schwenk M. Conjugation of 1-naphthol in human gastric epithelial cells. *Gut*. 1993; 34(2):177-180.
17. Elder RL, ed. Final report on the safety assessment of p-phenylenediamine. *JACT*. 1985;4:203-266.
18. European Union. È1976, Council Directive 1976/768/EEC of 27 July 1976 on the Approximation of the Laws of the Member States Relating to Cosmetic Products, as amended through Commission Directive 2003/83/ECÈÈ. 2005. Accessed October 12, 2006.
19. Food and Drug Administration (FDA). Cosmetic product warning statements: coal tar hair dyes containing 4-methoxy-m-phenylenediamine (2,4-diaminanisole) or 4-methoxy-m-phenylenediamine sulfate (2,4-diaminoanisole sulfate). *Federal Register*. 1979;44:59509-59510.
20. Food and Drug Administration (FDA). *Frequency of Use of Cosmetic Ingredients*. Washington, DC: FDA; 2006.
21. Gottschalck TE, McEwen GN Jr, *eds.* International Cosmetic Ingredient Dictionary and Handbook. Vol 2. 11th ed. Washington DC: CTFA; 2006.
22. Meeker JD, Ryan L, Barr DB, et al. The relationship of urinary metabolites of carbaryl/napthalene and chlorpyrifos with human semen quality. *Environ Health Perspect*. 2004; 112(17):1665-1670.
23. Meeker JD, Singh NP, Ryan L, et al. Urinary levels of insecticide metabolites and DNA damage in human sperm. *Hum Reprod*. 2004;19(11):2573-2580.
24. Meeker JD, Ryan L, Barr DB, Hauser R. Exposure to nonpersistent insecticides and male reproductive hormones. *Epidemiology*. 2006;17(1):61-68.
25. Ministry of Health Labour and Welfare (MHLW). MHW Ordinance No. 332, Ingredients of quasi-drugs. Products to be used directly on the body. 2000. *2-2, 1-chrome, Kasumigaseki, Chiyoda-ku, Tokyo 100-8045*, Japan: Ministry of Health, Labor and Welfare, Pharmaceutical and Medical Safety Bureau, Inspection and Guidance Division.
26. Ministry of Health Labour and Welfare (MHLW). MHW Ordinance No. 331, Appendix 1. List of ingredients that cosmetics shall not contain. 2005. *2-2, 1-chrome, Kasumigaseki, Chiyoda-ku, Tokyo 100-8045*, Japan: Ministry of Health, Labor and Welfare, Pharmaceutical and Medical Safety Bureau, Inspection and Guidance Division.
27. Narbonne JF, Cassand P, Alzieu P, Grolier P, Mrlina G, Calmon JP. Structure-activity relationships of the N-methylcarbamate series in Salmonella typhimurium. *Mutat Res*. 1987;191(1):21-27.
28. Poole A, Buckley P. 1-Naphthol—single and repeated dose (30-day) oral toxicity studies in the mouse. *Food Chem Toxicol*. 1989;27(4):233-238.
29. Preuss R, Angerer J, Drexler H. Naphthalene—an environmental and occupational toxicant. *Int Arch Occup Environ Health*. 2003; 76(8):556-576.
30. Serdar B, Egeghy PP, Waidyanatha S, Gibson R, Rappaport SM. Urinary biomarkers of exposure to jet fuel (JP-8). *Environ Health Perspect*. 2003;111(14):1760-1764.
31. Serdar B, Waidyanatha S, Zheng Y, Rappaport SM. Simultaneous determination of urinary 1- and 2-naphthols, 3- and 9-phenanthrols, and 1-pyrenol in coke oven workers. *Biomarkers*. 2003;8(2):93-109.
32. Hart BA, Simons JM, Rijkers GT, Hoogvliet JC, Van Dijk H, Labadie RP. Reaction products of 1-naphthol with reactive oxygen species prevent NADPH oxidase activation in activated human neutrophils, but leave phagocytosis intact. *Free Radic Biol Med*. 1990;8(3):214-249.
33. Vaananen V, Hameila M, Kontsas H, Peltonen K, Heikkila P. Air concentrations and urinary metabolites of polycyclic aromatic hydrocarbons among paving and remixing workers. *J Environ Monit*. 2003;5(5):739-746.
34. Wilson GD, d'Arcy Doherty M, Cohen GM. Selective toxicity of 1-naphthol to human colorectal tumor tissue. *Brit J Cancer*. 1985; 51(6):853-863.

Phenoxyethanol

Conclusion

In its 1990 safety assessment of phenoxyethanol, the Cosmetic Ingredient Review (CIR) Expert Panel[1] stated that this ingredient is safe as a cosmetic ingredient in the present practices of use and concentration. In 2007, the Expert Panel reviewed newly available studies since that assessment,[2-61] along with updated information regarding types and concentration of use. The Panel confirmed that phenoxyethanol is safe in the present practices of use and concentration given in Table 1 and did not reopen the safety assessment.

Discussion

Phenoxyethanol was used in 253 products in 1987, based on voluntary reports provided to Food and Drug Administration

Table 1. Historical and Current Cosmetic Product Uses and Concentrations of Phenoxyethanol

Product Category[62]	1987 Uses[1]	Total Products in Category[1]	2006 Uses[62]	Total Products in Category[62]	1987 Concentrations (%)[1]	2006 Concentrations (%)[63]
Baby products						
Shampoos	–[a]		4	38	–[a]	0.3-0.7
Lotions, oils, powders, and creams	–		16	67	–	0.02-0.8
Other	–		5	64	–	0.6 (in baby wipes)
Bath products						
Oils, tablets, and salts	–		5	207	–	0.09-0.5
Bubble baths	–		24	256	–	0.5
Capsules	–		1	5	–	0.5
Soaps and detergents			21	594		0.4-1
Other	8[b]	665[b]	45	276	≤0.1 to 1[b]	0.5
Eye makeup						
Eyebrow pencils			1	124		0.5-1
Eyeliners	23[b]	1550[b]	17	639	≤0.1 to 5[b]	0.02-1
Eye shadow			51	1061		0.3-1
Eye lotions			10	32		0.3-0.5
Eye makeup remover			36	114		0.1-1
Mascara			121	308		0.1-1
Other			27	229		0.5-1 (in a brow powder and an eye gloss)
Fragrance products						
Colognes and toilet waters			5	948		–[c]
Perfumes			3	326		1
Powders	4[b]	853[b]	4	324		1
Sachets			–[a]		≤0.1 to 1[b]	–
Other			23	187		0.7 (in an alcohol-free cologne)
Noncoloring hair products						
Conditioners			121	715		0.1-1
Sprays/aerosol fixatives			5	294		0.5
Straighteners			–			0.7 (0.4 after dilution)
Permanent waves			–			1 (0.5 after dilution)
Rinses			4	46		–
Shampoos			155	1022		0.2-1
Tonics, dressings, etc			71	623		0.2-1
Wave sets	54[b]	3008[b]	1	59	≤0.1 to 1[b]	–
Other			93	464		0.8-1 (0.8 in a hair mask; 1 in a wax)
Hair-coloring products						
Dyes and colors			69	1600		0.05
Tints			–			–
Rinses			–			0.7
Shampoos			–			–
Color sprays			–			–
Lighteners with color			–			–
Bleaches			1	103		–
Other			1	73		–
Makeup						
Blushers	7	451	13	459	≤0.1 to 1	0.3-1
Face powders	–		35	447	–	0.1-1
Leg and body paints	–		1	10	–	–
Lipsticks	–		16	1681	–	0.4-0.9
Makeup						
Foundations			77	530		0.3-1
Makeup bases	20[b]	645[b]	17	273	≤0.1 to 1[b]	0.001-1
Rouges			5	115		0.5
Makeup fixatives			8	37		0.5-0.7
Other			47	304		0.5-0.7 (0.5 in a concealor)

(continued)

Table 1. (continued)

Product Category[62]	1987 Uses[1]	Total Products in Category[1]	2006 Uses[62]	Total Products in Category[62]	1987 Concentrations (%)[1]	2006 Concentrations (%)[63]
Nail care products						
Basecoats and undercoats	–[a]		–[a]	43	–[a]	–[c]
Cuticle softeners	1	23	3	20	≤1	–
Nail creams and lotions	–			1	13	–
Nail polishes and enamels	–		3	398	–	–
Other	–		4	58	–	–
Personal hygiene products						
Underarm deodorants	–		14	281	–	0.3-1
Douches	–		2	8	–	0.2-1
Feminine deodorants	–		–		–	–
Other	–		31	390	–	0.3-1 (0.3, 0.5, 0.7, and 1 in body washes)
Shaving products						
Aftershave lotions	–		17	260	–	0.2-0.6
Preshave lotions	–		–		–	–
Shaving cream	–		7	135	–	0.3-0.7
Other	–		7	64	–	0.6-1 (1 in a skin balm)
Skin care products						
Skin cleansing creams, lotions, liquids, and pads			243	1009		0.2-1
Depilatories			–	49		0.5-1
Face and neck creams, lotions, powder and sprays			170	546		0.004-1 (1 in face and neck sprays)
Body and hand creams, lotions, powder and sprays			176	992		0.5-1
Foot powders and sprays	3684[b]	109[c]	15	43	≤0.1 to 5[b]	0.5
Moisturizers			297	1200		0.2-1 (0.5 in moisturizing sprays)
Night creams, lotions, powder and sprays			69	229		0.3-1 (0.5 in night sprays)
Paste masks/mud packs			75	312		0.004-0.9
Skin fresheners			18	212		0.5-0.7
Other			178	915		0.0002 to 1 (0.8 in a bust firmer)
Suntan products						
Suntan gels, creams, and liquids	10[b]	240[b]	16	138	≤0.1 to 1[b]	0.2-1
Indoor tanning preparations			32	74		0.5-1
Other			13	41		0.2-0.5
Total uses/ranges for phenoxyethanol	253		2550		≤0.1 to 5	≤0.0002-1

[a] In FDA's voluntary reporting system, no uses/use concentrations reported for this category in 1987; no uses reported for this category in 2006.
[b] This category was combined when the original safety assessment was performed and is now 2 or more separate categories.
[c] In industry survey, no use concentrations reported for this category.

(FDA)[1] by industry, at concentrations of ≤0.15% to 5%. Data provided to FDA in 2006 indicated that phenoxyethanol was being used in 2550 products.[62] Current use concentration data from a cosmetics industry survey[63] indicated that phenoxyethanol was being used in cosmetics at concentrations ranging from ≤0.0002% to 1%.

The available usage and use concentration data are given in Table 1, as a function of product category.

The CIR Expert Panel recognized data gaps regarding in use and concentration data for this ingredient. However, the overall information available on types of products in which this ingredient is used and at what concentration indicates a pattern of use that was considered by the CIR Expert Panel in assessing safety. In order to gain more insight into ingredient use frequency patterns, the total number of products in a category could be considered along with the number of products in that category containing the ingredient.

The CIR Expert Panel acknowledged the significant increase in ingredient use frequency that has occurred and noted that this is probably driven primarily by the use of a preservative system that incorporates phenoxyethanol and methyldibromo glutaronitrile (phenoxyethanol [4 parts]: methyldibromo glutaronitrile [1 part]).[13] It has been suggested that methyldibromo glutaronitrile is the allergen in this system.[13]

In considering that skin care products (sprays) are among the new product uses of phenoxyethanol, the CIR Expert Panel noted the absence of inhalation toxicity data from the safety assessment. However, in the absence of these data, the Panel determined that phenoxyethanol can be used safely in hair sprays because the ingredient particle size is not respirable. The Panel reasoned that the particle size of anhydrous hair sprays (60-80 μm) and pump hair sprays (>80 μm) is large compared to the median aerodynamic diameter of 4.25 ± 1.5 μm for a respirable particulate mass.

References

1. Elder RL. Final report on the safety assessment of phenoxyethanol. *JACT*. 1990;9:259-277.
2. Aalto-Korte K, Jolanki R, Estlander T, Alanko K, Kanerva L. Occupational allergic contact dermatitis caused by Euxyl K 400. *Contact Dermat*. 1996;35(3):193-194.
3. Anselmi C, Ettorre A, Andreasi M, Centini M, Nderi P, Di Stefano A. In vitro induction of apoptosis vs. necrosis by widely used preservatives: 2-phenoxyethanol, a mixture of isothiazolinones, imidazolidinyl urea, and 1,2-pentanediol. *Biochem Pharmacol*. 2002;63(3):437-453.
4. Berne B, Bostrom A, Grahnen AF, Tammela M. Adverse effects of cosmetics and toiletries reported to the Swedish Medical Products Agency 1989-1994. *Contact Dermat*. 1996; 34(5):359-362.
5. Birnie AJ, English JS. 2-phenoxyethanol-induced contact urticaria. *Contact Dermat*. 2006;54(6):349.
6. Bohn S, Bircher J. Phenoxyethanol-induced urticaria. *Allergy*. 2001;56(9):922-923.
7. Boyvat A, Akyol A, Gurgey E. Contact sensitivity to preservatives in Turkey. *Contact Dermat*. 2005;52(6):329-332.
8. Breslin WJ, Phillips JE, Lomax LG, et al. Hemolytic activity of ethylene glycol phenyl ether (EGPE) in rabbits. *Fundam Appl Toxicol*. 1991;17(3):466-481.
9. Bruze M, Gruvberger B, Agrup G. Sensitization studies in the guinea pig with the active ingredients of Euxyl® K 400. *Contact Dermat*. 1988;18(1):37-39.
10. Buhrer C, Bahr S, Siebert J, Wettstein R, Geffers C, Obladen M. Use of 2% 2-phenoxyethanol and 0.1% octenidine as antiseptic in premature newborn infants of 23-26 weeks gestation. *J Hosp Infect*. 2002;51(4):305-307.
11. Correale CE, Marks JG Jr. Contact dermatitis in a woodworker. *Am J Contact Dermat*. 2002;13(1):42-44.
12. Dastychova E, Necas M, Pencikova K, Cerny P. Contact sensitization to pharmaceutic aids in dermatologic cosmetic and external use preparations. *Ceska Slov Farm*. 2004;53(3):151-156.
13. de Groot AC, van Ginkel JWCJW, Weijland JW. Methyldibromo glutaronitrile (Euxyl K 400): an important "new" allergen in cosmetics. *J Am Acad Dermatol*. 1996;35(5)(Pt 1):743-747.
14. de Leeuw J, Den Hollander P. A patient with contact dermatitis to jogging cream. *Contact Dermat*. 1987;17(4):260-261.
15. Dieter MP, Jameson CW, Maronpot RR, Langenbach R, Braun AG. The chemotherapeutic potential of glycol alkyl ethers: structure-activity studies of nine compounds in a Fischer-rat leukemia transplant model. *Cancer Chemother Pharmacol*. 1990;26(3):173-180.
16. Dow Chemical Company. *Initial Submission: Hemolytic Investigations of 2-Phenoxyethanol in Rabbits and Rats (With Cover Letter Dated 09/24/92) NTIS Report No. OTS0555916*. 1985. Report No. OTS0555916.
17. Dow Chemical Company. *Evaluation of 2-Phenoxethanol in the Chinese Hamster Ovary Cell/Hypoxanthine-Guanine-Phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay (With Cover Letter Dated 091687) NTIS Report No. OTS0516430*. 1987. Report No. OTS0516430.
18. Dow Chemical Company. *Evaluation of 2-Phenoxyethanol in the Rat Bone Marrow Chromosomal Aberration Assay (Final Report) (With Cover Letter Dated 020888) NTIS Report No. OTS0514028*. 1988. Report No. OTS0514028.
19. European Union. 2006. *The Rules Governing Cosmetic Products in the European Union*. Vol 1. Cosmetics legislation–Cosmetic products.
20. Food and Drug Administration (FDA). Preservatives in vaccines. *2007. http://www.fda.gov/cber/vaccine/thimerosal.htm#pres. Accessed* 2007.
21. Gallo R, Marro I, Sorbara S. Contact allergy from phenoxyethanol in Fitostimoline® gauzes. *Contact Dermat*. 2005; 53(4):241.
22. Geier J, Schnuch A, Fuchs T. Increasing incidence of contact allergens due to methyldibromo/glutaronitrile in Germany. *Allergologie*. 1996;19(5):399-402.
23. Geier J, Lessmann H, Deickel H, et al. Patch test results with the metalworking fluid series of the German Contact Dermatitis Research Group (DKG). *Contact Dermat*. 2004;51(3): 118-130.
24. Geier J, Schnuch A, Brasch J, Gefeller O. Patch testing with methyldibromoglutaronitrile. *Am J Contact Dermat*. 2000;11(1): 207-212.
25. Goossens A, Beck MH, Haneke E, et al. Adverse cutaneous reactions to cosmetic allergens. *Contact Dermat*. 1999;40(2):112-113.
26. Goossens L, Claes J, Drieghe J, Put E. Antimicrobials: preservatives, antiseptics and disinfectants. *Contact Dermat*. 1998; 39:(133):134.

27. Gottschalck TE, McEwen GN Jr, *eds. International Cosmetic Ingredient Dictionary and Handbook*. Vol 11. Washington, DC: CTFA; 2006.
28. Gruvberger B, Bruze M. Preservatives. *Clin Dermatol*. 1997; 15(4):493-497.
29. Hausen BM. The sensitizing potency of Euxyl K® 400 and its components 1,2-dibromo-2,4-dicyanobutane and 2-Phenoxyethanol. *Contact Dermat*. 1993;28(3):149-153.
30. Hoechst Celanese Corporation. *14-day dermal study with 2-phenoxyethanol in rabbits (with cover letter dated 073093) NTIS Report No. OTS0537779*. 1993. Report No. OTS0537779.
31. Hernandez B, Ortiz-Frutos FJ, Garcia M, Palencia S, Garcia MC, Iglesias L. Contact urticaria from 2-phenoxyethanol. *Contact Dermat*. 2002;47(1):54.
32. Hupuczi P, Papp Z. Postoperative ascites associated with intraperitoneal antiseptic lavage. *Obstet Gynecol*. 2005;105(5)(Pt 2): 1267-1268.
33. Isaksson M, Bruze M, Hornblad Y, Svenionius E, Wihl JA. Contact allergy to corticosteroids in asthma/rhinitis patients. *Contact Dermat*. 1999;40(6):327-328.
34. Jackson JM, Fowler JF. Methyldibromoglutaronitrile (Euxyl K 400): a new and important sensitizer in the United States? *J Am Acad Dermatol*. 1998;38(6)(Pt 1):934-937.
35. Kramer A, Roth B, Muller G, Rudolph P, Klocker N. Influence of the antiseptic agents polyhexanide and octenidiene on FL cells and on healing of experimental superficial aseptic wounds in piglets. *Skin Pharmacol Physiol*. 2004;17(3):141-146.
36. Langer S, Sedigh Salakdeh M, Goertz O, Steinau HU, Steinstraesser L, Homann HH. The impact of topical antisdeptics on skin microcirculation. *Eur J Med Res*. 2004;9(9):449-454.
37. Lee E, An S, Choi D, Moon S, Chang I. Comparative of objective and sensory skin irritations of several cosmetic preservatives. *Contact Dermat*. 2007;56(3):131-136.
38. Lockley DJ, Howes D, Williams FM. Cutaneous metabolism of glycol ethers. *Arch Toxicol*. 2005;79(3):160-168.
39. Ministry of Health Labour and Welfare (MHLW). Unofficial translation of MHW Ordinance No. 331, Attached Appendix 3 [The ingredients restricted in all types of cosmetics]. 2001. 2-2, 1-chrome, Kasumigaseki, Chiyoda-ku, Tokyo 100-8045, Japan: Ministry of Health, Labor and Welfare, Pharmaceutical and Medical Safety bureau, Inspection and Guidance Division.
40. Morohoshi K, Yamamoto H, Kamata R, Shiraishi F, Koda T, Morita M. Estrogenic activity of 37 components of commercial sunscreen lotions evaluated by in vitro assays. *Toxicology in Vitro*. 2005;19(4):457-469.
41. Morton WE. Occupational phenoxyethanol neurotoxicity: a report of three cases. *J Occup Med*. 1990;32(1):42-45.
42. Pratt MD, Belsito DV, DeLeo VA. North American Contact Dermatitis Group patch-test results, 2001-2002 study period. *Dermatitis*. 2004;15(4):176-183.
43. Primka EJ III, Taylor JS. Three cases of contact allergy after chemical burns from methylchloroisothiazolinone/methylisothiazolinone: One with concomitant allergy to methyldibromo glutaronitrile/phenoxyethanol. *Am J Contact Dermat*. 1997;8(1):43-46.
44. Rodriguez E, Valbuena MC, Ey M, de Quitana LP. Casual agents of photoallergic contact dermatitis diagnosed in the national institute of dermatology of Columbia. *Photodermatol Photoimmunol Photomed*. 2006;22(4):189-192.
45. Roper S, Howes D, Blain PG, Williams FM. Percutaneous penetration of 2-phenoxyethanol through rat and human skin. *Food Chem Toxicol*. 1997;35(10-11):1009-1016.
46. Roper CS, Howes D, Blain PG, Williams FM. A comparison of the absorption of a series of ethoxylates through rat skin in vitro. *Toxicol in Vitro*. 1998;12(1):57-65.
47. Ross JS, Cronin E, White I, Rycroft RJG. Contact dermaitis from Euxyl K 400 in a cucumber eye gel. *Contact Dermat*. 1992;26(1): 60.
48. Sasseville D. Hypersensitivity to preservatives. *Dermatol Ther*. 2004;15(3):251-263.
49. Schmuck G, Steffens W, Bomhard E. 2-Phenoxyethanol: a neurotoxicant? *Arch Toxicol*. 2000;74(4-5):281-287.
50. Schnuch A, Geier J, Uter W, Frosch PJ. Patch testing with preservatives, antimicrobials and industrial biocides. Results from a multicentre study. *Br J Dermatol*. 1998;138(3):467-476.
51. Senff H, Exner M, Gotz J, Goos M. Allergic contact dermatitis from Euxyl K 400. *Contact Dermat*. 1989;20(5):381-382.
52. Starek A, Jarosz J, Szymczak W. Comparison of the hemolytic activity of isopropoxyethanol and phenoxyethanol. *Int J Occup Med Environ Health*. 2004;17(3):339-346.
53. Stern M, Klausner M, Alvarado R, Renskers K, Dickens M. Evaluation of the EpiOcular tissue model as an alternative to the Draize eye irritation test. *Toxicol in Vitro*. 1998;12(4):455-461.
54. Tanii H, Saito S, Hashimoto K. Structure-toxicity relationship of ethylene glycol ethers. *Arch Toxicol*. 1992;66(5):368-371.
55. Thompson TR, Belsito DV. Regional variation in prevalence and etiology of allergic contact dermatitis. *Am J Contact Dermat*. 2002;13(4):177-182.
56. Tokunaga H, Takeuchi O, Ko R, Uchino T, Ando M. Studies for analyzing phenoxyethanol and parabens in commercial lotions. *Bull Natl Inst Health Sci*. 2003;(121):25-29.
57. Tosti A, Guerra L, Bardazzi F, Gasparri F. Euxyl K 400: a new sensitizer in cosmetics. *Contact Dermat*. 1991;25(2):89-93.
58. Tosti A, Vincenzi C, Trevisi P, Guerra L. Euxyl K 400L incidence of sensitization, patch test concentration and vehicle. *Contact Dermat*. 1995;33(3):193-195.
59. Vigan M, Brechat N, Girardin P. Sensitization to Euxyl K400, a prospective study in 1217 patients. *Eur J Dermatol*. 1996;6(5): 175-177.
60. Vogt T, Landthaler M, Stolz W. Generalized eczema in an 18-month-old boy due to phenoxyethanol in DPT vaccine. *Contact Dermat*. 1998;38(1):50-51.
61. Wong CSM, Beck MH. Occupational contact allergy to methyldibromoglutaronitrile in abrasive cleaners and work creams. *Contact Dermat*. 2001;44(5):311-312.
62. Food and Drug Administration (FDA). *Frequency of Use of Cosmetic Ingredients*. Washington, DC: FDA; 2006.
63. Cosmetic, Toiletry, and Fragrance Association (CTFA). 2007. Use concentration data on phenoxyethanol from industry survey. Unpublished data provided by CTFA. 3 pages.

Phenyl Methyl Pyrazolone

Conclusion

In a 1992 safety assessment of phenyl methyl pyrazolone (PMP), the Cosmetic Ingredient Review (CIR) Expert Panel concluded that "phenyl methyl pyrazolone is safe as a cosmetic ingredient in the present practices of use and concentration."[1] The Expert Panel reviewed the studies performed since that assessment[2-16] as well as updated use and concentration data. The Expert Panel confirmed that PMP is safe in the practices of use and concentration given in Table 1 and did not reopen the safety assessment.

Table 1. Historical and Current Cosmetic Product Uses and Concentrations for Phenyl Methyl Pyrazolone

Product Category	1984 Uses[1]	2007 Uses[17]	1984 Concentrations[1] (%)	2007 Concentrations[18] (%)
Hair coloring products				
Dyes and colors	125	375	0.1-1	0.3-0.4
Tints	–	1	–	–
Lighteners with color	–	2	–	–
Total uses/ ranges for phenyl methyl pyrazolone	125	378	0.1-1	0.3-0.4

Discussion

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 end points based on lack of strength of the associations and inconsistency of findings. Information on the available hair dye epidemiology data is available at http://www.cir-safety.org/findings.shtml.

The Expert Panel recognizes that PMP is used as a hair dye ingredient and may be used as a sensitizer. However, hair dyes containing these ingredients, such as coal-tar hair dye products are exempt from the principal adulteration provision and from the color-additive provisions in sections 601 and 706 of the Federal Food, Drug, and Cosmetic Act, when the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation. The Expert Panel expects that continuing to follow this procedure will identify prospective individuals who would have an irritation/sensitization reaction and allow them to avoid significant exposures.

References

1. Elder RL, ed.Final report on the safety assessment of phenyl methyl pyrazolone. *JACT.* 1992;11(4):475-488.
2. Cinelli S. 1998. 1-Phenyl-3-Methyl-5-Pyrazolone: Unscheduled DNA Synthsis (UDS) after in vivo Treatment. Research Toxicology Centre Report No. 5908-M-05697. Unpublished data submitted by CTFA, November 8, 2007. 44 pages.
3. Clouzeau J. 1992. 9-Phenyl-3-Methyl-5-Pyrazolone: Acute Oral Toxicity in Rats. Centre International de Toxicologie (CIT) Study No. 9008. Unpublished data submitted by CTFA, November 8, 2007. 30 pages.
4. Clouzeau J. 1992. 1-Phenyl-3-Methyl-5-Pyrazolone: Acute Eye Irritation in Rabbits on the Test Substance diluted at 1% CIT Study No. 9010 TAL. Unpublished data submitted by CTFA, November 8, 2007. 24 pages.
5. Clouzeau J. 1992. 1-Phenyl-3-Methyl-5-Pyrazolone: Acute Dermal irritation in Rabbits on the Test Substance diluted at 1%. CIT Study No. 9009 TAL. Unpublished data submitted by CTFA, November 8, 2007. 23 pages.
6. de Jouffrey S. 1998. Phenyl Methyl Pyrazolong: Acute oral Toxicity in Rats. CIT Study No. 16194 TAR. Unpublished data submitted by CTFA, November 8, 2007. 33 pages.
7. Erexcon G. 2005. In vivo rat micronucleus assay in phenylmethyl pyrazolone (A039). Covance Study No. 6182-123. Unpublished data submitted by CTFA, November 8, 2007. 54 pages.
8. Gottschalck TE, McEwen GN Jr, eds. *International Cosmetic Ingredient Dictionary and Handbook*. 11th ed. Washington DC: CTFA; 2006.
9. Haag V. 2005. Phenylmethyl pyrazolong (A039): 13-week toxicity study by oral route (gavage) in rats followed by a 4-week treatment free period. CIT Study No. 26900 TCR. Unpublished data submitted by CTFA, November 8, 2007. 696 pages.
10. Haddouk H. 2005. Phenylmethyl pyrazolone: Bacterial Reverse Mutation Test. CIT Study No. 26979 MMO. Unpublished data submitted by CTFA, November 8, 2007. 38 pages.
11. Lloyd M. 2005. Phenylmethyl pyrazolone: Mutation at the hprt locus of L5178Y Mouse Lymphoma Cells using the Microtitre® Fluctuation Technique. Covance Study No. 413/110. Unpublished data submitted by CTFA, November 8, 2007.
12. National Cancer Institute (NCI). 1978. Technical Report Series No. 141: Bioassay of 1-phenyl-3-methyl-5-pyrazolone for possible carcinogenicity. U.S. Department of Health, Education, and Welfare. Public Health Service, National Institutes for Health. Unpublished data submitted by CTFA, November 8, 2007.
13. Savary MH. 1991. 9-Phenyl-3-Methyl-Pyrazol-5-one: Assessment of possible embryotoxic or teratogenic effects by oral route in rats. CIT Study No. 6696 RSR. Unpublished data submitted by CTFA, November 8, 2007. 190 pages.

14. Sire G. 2004. Phenylmethyl pyrazolong (A039): Evaluation of skin sensitization potential in mice using the local lymph node assay (LLNA). CIT Study No. 26978 TSS. Unpublished data submitted by CTFA, November 8, 2007. 53 pages.
15. Sire G. 2005. Phenylmethyl pyrazolona: In vitro mammalian Cell Gene Mutation Test in L5178Y TK$^{+/-}$ Mouse Lymphoma Cells. CIT Study No. 27704 MLY. Unpublished data submitted by CTFA, November 8, 2007. 44 pages.
16. Toner F. 2005. The In Vitro percutaneous Absorption of Radiolabelled Phenylmethyl Pyrazolone through human skin. Inveresk Study No. 774960. Unpublished data submitted by CTFA, November 8, 2007. 86 pages.
17. Food and Drug Administration (FDA). *Frequency of Use of Cosmetic Ingredients*. Washington DC: FDA; 2007.
18. Cosmetic, Toiletry, and Fragrance Association (CTFA). 2007. Current use concentrations—Phenyl Methyl Pyrazolone. Unpublished data provided by the CTFA. 1 page.

N-Phenyl-*p*-Phenylenediamine, *N*-Phenyl-*p*-Phenylenediamine HCl, and *N*-Phenyl-*p*-Phenylenediamine Sulfate

Conclusion

In a 1994 safety assessment of *N*-phenyl-*p*-phenylenediamine, *N*-phenyl-*p*-phenylenediamine HCl, and *N*-phenyl-*p*-phenylenediamine sulfate, the Cosmetic Ingredient Review (CIR) Expert Panel stated that these ingredients are safe as (then) used in hair dyes at concentrations up to 1.7% (as the free base).[1] The expert panel reviewed newly available studies since that assessment along with updated information regarding type and frequency of use.[1-39] The expert panel determined not to reopen this safety assessment. Therefore, the panel confirmed that *N*-phenyl-*p*-phenylenediamine, *N*-phenyl-*p*-phenylenediamine HCl, and *N*-phenyl-*p*-phenylenediamine sulfate are safe for use in hair dyes at concentrations up to 1.7% (as the free base).

Discussion

In 1993, *N*-phenyl-*p*-phenylenediamine and *N*-phenyl-*p*-phenylenediamine HCl were used in 9 and 11 hair dyes and colors requiring caution statements, respectively; *N*-phenyl-*p*-phenylenediamine sulfate was not reported to be used in 1993. Use concentrations were not reported at that time.[1] In 2009, *N*-phenyl-*p*-phenylenediamine HCl was no longer reported to the Food and Drug Administration (FDA) as being used, while *N*-phenyl-*p*-phenylenediamine and *N*-phenyl-*p*-phenylenediamine sulfate increased in use to 25 and 105 hair dyes and colors requiring caution statements, respectively.[40] A survey by the Personal Care Products Council of current use concentrations found that *N*-phenyl-*p*-phenylenediamine is being used at 0.04%; no uses were reported for *N*-phenyl-*p*-phenylenediamine HCl or sulfate[41] (Table 1).

Newly available data did not raise any issues regarding the safety of *N*-phenyl-*p*-phenylenediamine, *N*-phenyl-*p*-phenylenediamine HCl, and *N*-phenyl-*p*-phenylenediamine sulfate. In considering hair dye epidemiology 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 end

Table 1. Historical and Current Cosmetic Product Uses and Concentrations for *N*-Phenyl-*p*-Phenylenediamine, *N*-Phenyl-*p*-Phenylenediamine HCl, and *N*-Phenyl-*p*-Phenylenediamine Sulfate[a]

Product Category	1993 Frequency of Use[1]	2009 Frequency of Use[45]	1993 Concentration of Use[1]	2009 Concentration of Use[46]
N-Phenyl-*p*-Phenylenediamine				
Hair dyes/colors (requiring caution stmt)	9	25	Not reported	0.04%
Total	9	25	–	0.04%
N-Phenyl-*p*-phenylenediamine HCl				
Hair dyes/colors (requiring a caution stmt)	11	None reported	Not reported	Not reported
Total	11	–	–	–
N-Phenyl-*p*-phenylenediamine sulfate				
Hair dyes/colors (requiring a caution stmt)	None reported	105	Not reported	Not reported
Total		105	–	–

[a]Refs. 1-6,8-13,15-27,30-32,34-38,42-44,47-52.

points, based on lack of strength of the associations and inconsistency of findings. The most recent comprehensive review of available epidemiology studies concluded that there is insufficient evidence to support a causal association between personal hair dye use and a variety of tumors and cancers. A summary of the available hair dye epidemiology data is available at http://www.cir-safety.org/ findings.shtml.[42-44]

The expert panel recognizes that *N*-phenyl-*p*-phenylenediamine, *N*-phenyl-*p*-phenylenediamine HCl, and *N*-phenyl-*p*-phenylenediamine sulfate are oxidative hair dye ingredients and may be sensitizers. However, hair dyes containing these ingredients, as coal-tar hair dye products, are exempt from the principal adulteration provision and color-additive provisions in sections 601 and 706 of the Federal Food, Drug, and Cosmetic Act when the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation. The expert panel expects that continuing to follow the procedure will identify prospective individuals who would have an irritation/sensitization reaction and allow them to avoid significant exposures.

References

1. Andersen FA. Final report on the safety assessment of *N*-phenyl-*p*-phenylenediamine, *N*-phenyl-*p*-phenylenediamine hydrochloride, and *N*-phenyl-*p*-phenylenediamine sulfate. *JACT*. 1994; 13(5):374-394.
2. Gottschalck TE, Bailey JE, eds. *International Cosmetic Ingredient Dictionary and Handbook*. Vol 2. 13th ed. Washington, DC: Personal Care Products Council; 2010: 2240-2241.
3. Ashby J, Tennant RW. Chemical structure, Salmonella mutagenicity and extent of carcinogenicity as indicators of genotoxic carcinogenesis among 222 chemicals tested in rodents by the U.S. NCI/NTP. *Mutat Res*. 1988;204(1):17-115.
4. BioReliance. 2004. Unscheduled DNA synthesis (UDS) test with mammalian liver cells *in vivo*. Rodol Gray Base B Lot No. 217. KU040163. Study AA93BT.381.BTL (Secondary reference in SCCP 2006).
5. BioReliance. 2005. Mammalian erythrocyte micronucleus test. Rodol Gray B Base Lot 217. KMN040162. Study AA93BT (Secondary reference in SCCP 2006).
6. Burnett C, Goldenthal EI, Harris SB, et al. Teratology and percutaneous toxicity studies on hair dyes. *J Toxicol Environ Health*. 1976;1(6):1027-1040.
7. Chem IDPlus Lite. p-Aminodiphenylamine. http://chem.sis.nlm.nih.gov/chemidplus/ProxyServlet?objectHandle=DBMaint&actionHandle=default&nextPage=jsp/chemidlite/ResultScreen.jsp&TXTSUPERLISTID=000101542. Accessed July 21, 2009.
8. ChemIDplus Lite. p-Aminodiphenylamine HCl. http://chem.sis.nlm.nih.gov/chemidplus/ProxyServlet?objectHandle=DBMaint&actionHandle=default&nextPage=jsp/chemidlite/ResultScreen.jsp&TXTSUPERLISTID=002198596. 2009. Accessed July 21, 2009.
9. ChemIDplus Lite. p-Aminodiphenylamine Sulfate. http://chem.sis.nlm.nih.gov/chemidplus/ProxyServlet?objectHandle=DBMaint&actionHandle=default&nextPage=jsp/chemidlite/ResultScreen.jsp&TXTSUPERLISTID=004698297. 2009. Accessed July 21, 2009.
10. Covance. 2004. Rodol Gray Base B Lot No. 217. Induction of micronuclei in cultured human peripheral blood lymphocytes. KIM040180. Study No. 375/312 (Secondary reference in SCCP 2006).
11. European Union. Cosmetic Ingredients and Substances Infobase. *N*-Phenyl-*p*-Phenylenediamine HCl. http://ec.europa.eu/enterprise/cosmetics/cosing/index.cfm?fuseaction=search.details&id=35562. Accessed July 27, 2009.
12. European Union. Cosmetic Ingredients and Substances Database. *N*-Phenyl-*p*-Phenylenediamine Sulfate. http://ec.europa.eu/enterprise/cosmetics/cosing/index.cfm?fuseaction=search.details&id=35563. Accessed July 27, 2009.
13. European Union. Cosmetic Ingredients and Substances Infobase. *N*-Phenyl-*p*-Phenylenediamine. http://ec.europa.eu/enterprise/cosmetics/cosing/index.cfm?fuseaction=search.details&id=35561. Accessed July 27, 2009.
14. Food and Drug Administration (FDA). *Frequency of Use of Cosmetic Ingredients.* FDA Database. Washington, DC: FDA; 2009.
15. Groom, CA, Luong JH, Thatipalmala R. Dual functionalities of 4-aminodiphenylamine in enzymatic assay and mediated biosensor construction. *Anal Biochem*. 1995;231(2):393-399.
16. Heddle JA, Khan MA, Urlando C, Pellegrino S. Measuring gene mutations in vivo. *Prog Clin Bio Res*. 1991;372:281-289.
17. Inveresk. 2004. The *in vitro* percutaneous absorption of [14C]-NPPPD in Complete Dye Base C and Complete Dye Base U test preparations through pig skin. KSA040138 (Secondary reference is SCCP 2006).
18. Kaniwa MA, Isama K, Nakamura A, et al. Identification of causative chemicals of allergic contact dermatitis using a combination of patch testing in patients and chemical analysis. Application to cases from industrial rubber products. *Contact Dermat*. 1994;30(1):20-25.
19. Kitchin KT, Brown JL, Kulkarni AP. Predictive assay for rodent carcinogenicity using in vivo biochemical parameters: operational characteristics and complementarity. *Mutat Res*. 1992;266(2):253-272.
20. *Hawley's Condensed Chemical Dictionary*. 13 ed. New York, NY: John Wiley; 1997.
21. Monsanto. 1989. *In vitro* chromosome aberration assay in CHO cells with 4-aminodiphenylamine (4-ADPA) (PK-85-318). Cited in: Document #OTS 0516609, NTIS, Springfield, VA (Secondary reference in SCCP 2006).
22. Monsanto. 1989. GPRT mammalian cell gene mutation assay wtih 4-aminodiphenylamine (4-ADPA) (PK-85-318). Cited in: Document #OTS 0516609, NTIS, Springfield (Secondary reference in SCCP 2006).
23. Monsanto. 1989. Study on the developmental toxicity of rats administered 4-ADPA. Document #OTS 05166092, NTIS, Springfield, VA. (Secondary reference in SCCP 2006.)
24. Monsanto. 1989. A developmental toxicity study in rats with (4-ADPA) 4-Aminodiphenyl Amine. Document #OTS 05166091, NTIS, Springfield, VA. (Secondary reference in SCCP 2006.)
25. Monsanto. 1989. *In vitro* hepatocyte DNA repair (UDS)assay with 4-aminodiphenylamine (4-ADPA) (PK-85-317) Cited in:

Document #OTS 0516609, NTIS, Springfield, VA. (Secondary reference in SCCP 2006.)
26. Monsanto. 1989. In vivo-in vitro hepatocyte DNA repair (UDS) and DNA replication assay with 4-NDPA, 4-ADPA, DADPE, and DNDPE. (SR-86-317.) Cited in: Document #OTS 0516609, NTIS, Springfield, VA. (Secondary reference in SCCP 2006.)
27. Monsanto. 1989. Ames/Salmonella mutagenicity assay with 4-Aminodiphenylamine (4-ADPA (PK-85-317). Available in: Document #OTS 0516609, NTIS, Springfield, VA. (Secondary reference in SCCP.)
28. National Institute for Occupational Safety and Health (NIOSH). N-Phenyl-1,4-Benzenediamine. http://www.cdc.gov/niosh/ipcsneng/neng1446.html. Accessed July 21, 2009.
29. 1,4-Benzenediamine, N-Phenyl-. http://webbook.nist.gov/cgi/cbook.cgi?ID=C101542&Units=SI&Mask=400. Accessed July 28, 2009.
30. National Toxicology Program (NTP). Sister chromatid exchange assay using N-Phenyl-p-Phenylenediamine. Study ID 887002. 1984. http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=invitrosce.scedata&study_no=887002&cas_no=101%2D54%2D2&endpointlist=SCE. Accessed July 29, 2009.
31. NTP. Chromosome aberration assay using *N*-Phenyl-*p*-Phenylenediamine. Study ID 887002. 1985. http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=invitroca.cadata&study_no=887002&cas_no=101%2D54%2D2&endpointlist=CAB. Accessed July 28, 2009.
32. NTP. Mouse lymphoma study of N-Phenyl-p-Phenylenediamine. Study ID 867606. Date not given. 2009. http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=mouselymphoma.studyDetails&study_no=867606&cas_no=101-54-2&endpointlist=ML,ML-N. Accessed July 28, 2009.
33. Personal Care Products Council (the Council). Concentration of use—*N*-Phenyl-*p*-Phenylenediamine, *N*-Phenyl-*p*-Phenylenediamine HCl, and *N*-Phenyl-*p*-Phenylenediamine Sulfate. *Unpublished data provided by the Council*. May 29, 2009.
34. RCC. 2004. Rodol Gray B Lot No. 217: Local lymph node assay (LLNA) in mice. (Identification of contact allergens.) KSL040161. Study NO. 854598.
35. RCC. 2004. Rodol Gray B Lot No. 217: Local lymph node assay (LLNA) in mice. (Identification of contact allergens.) KSL040317. Study No. 856276.
36. Rosenkranz HS, Klopman G. Structural basis of the mutagenicity of phenylazoaniline dyes. *Mutat Res*. 1989;221(3):217-234.
37. Sasaki YF, Fujikawa K, Ishida K, et al. The alkaline single cell gel electrophoresis assay with mouse multiple organs: results with 30 aromatic amines evaulated by the IARC and U.S. NTP. *Mutat Res.* 1999;440(1):1-18.
38. Sasaki YF, Fujikawa K, Ishida K, et al. Erratum to: The alkaline single cell gel electrophoresis assay with mouse multiple organs: results with 30 aromatic amines evaluated by the IARC and U.S. NTP'. [Mutation Res. 440 (1999) 1-18]. *Mutat Res*. 1999;444(1):249-255.
39. Scientific Committee on Consumer Products (SCCP). Opinion of *N*-Phenyl-*p*-phenylenediamine COLIPA N A9. December 19, 2006. http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_089.pdf. Accessed July 21, 2009.
40. Food and Drug Administration (FDA). *Frequency of Use of Cosmetic Ingredients. FDA Database*. Washington, DC: FDA; 2009.
41. Personal Care Products Council (the Council). Concentration of use—*N*-Phenyl-*p*-Phenylenediamine, *N*-Phenyl-*p*-Phenylenediamine HCl, and *N*-Phenyl-*p*-Phenylenediamine Sulfate. *Unpublished data provided by the Council*. May 29, 2009.
42. Baan R, Straif K, Grosse Y, et al. Who international agency for research on cancer monograph working group: carcinogenicity of some amines, organic dyes, and related exposures. *Lancet Oncol*. 2009;9(4):322-323.
43. International Agency for Research on Cancer (IARC). IARC working group on the evaluation of carcinogenic risks to humans: occupational exposures of hairdressers and barbers and personal use of hair colourants; some hair dyes, cosmetic colourants, industrial dyestuffs and aromatic amines. *IARC Monogr Eval Carcinog Risks Hum*. 1993;57:73-118.
44. Rollinson, DE, Helzlsouer KJ, Pinney SM. Personal hair dye use and cancer: a systematic literature review and evaluation of exposure assessment in studies published since 1992. *J Toxicol Environ Health Part B*. 2009;9(5):413-439.
45. Food and Drug Administration (FDA). *Frequency of Use of Cosmetic Ingredients. FDA Database*. Washington, DC: FDA; 2009.
46. Personal Care Products Council (the Council). Concentration of use—*N*-Phenyl-*p*-Phenylenediamine, *N*-Phenyl-*p*-Phenylenediamine HCl, and *N*-Phenyl-*p*-Phenylenediamine Sulfate. *Unpublished data provided by the Council*. May 29, 2009.

Polyoxymethylene Urea

Conclusion

In a 1995 safety assessment of polyoxymethylene urea, the Cosmetic Ingredient Review (CIR) Expert Panel stated that this ingredient is safe as a cosmetic ingredient. Cosmetics containing polyoxymethylene urea should be formulated to ensure that concentrations of free formaldehyde do not exceed 0.2%. It cannot be concluded that polyoxymethylene urea is safe for use in cosmetic products intended to be aerosolized.[1] The Expert Panel reviewed newly available studies (see references)[2-14] since that assessment, along with updated frequency

Table 1. Historical and Current Cosmetic Product Uses and Concentrations for Polyoxymethylene Urea

Product Category	Frequency[1] of Use 1993	Frequency of Use 2009	Concentration[1] of use 1993	Concentration[14] of use 2009
Eye shadow	6	20	Not reported	0.02%
Perfumes	1	1	Not reported	–
Powders (dusting/talcum)	–	2	–	0.05%
Blushers (all types)	4	8	Not reported	0.1-5%
Face powders	8	1	Not reported	0.02%
Lipstick	2	–	Not reported	0.1%
Rouges	4	–	Not reported	–
Other makeup preps	–	2	–	–
Basecoats and undercoats	2	2	Not reported	–
Other manicuring preparations	1	1	Not reported	–
Other personal cleanliness products	–	1	–	–
Skin cleansing	–	–	–	0.005%
Total	28	38	Not reported	0.005-5%

and concentration of use information. The Expert Panel determined to not reopen this safety assessment and confirmed that polyoxymethylene urea is safe as a cosmetic ingredient, except those that are intended to be aerosolized, when formulated to ensure that concentrations of free formaldehyde do not exceed 0.2%.

Discussion

Polyoxymethylene urea is reported to function as a bulking agent and reported use has increased from 28 cosmetic formulations[1] in 1993 to 38 formulations[15] in 2009, but product use did not change. Concentration of use was not reported to the Food and Drug Administration (FDA) in 1993, nor is it reported to the Food and Drug Administration (FDA) currently. In a survey conducted by the Personal Care Products Council, industry reported use concentrations in 2009 of 0.005% to 5% (Table 1).[14]

References

1. Andersen FA (ed). Final report on the safety assessment of polyoxymethylene urea. *J Am Coll Toxicol.* 1995;14:(3):204-220.
2. ChemIDPlusLite. Polynoxylin. http://chem.sis.nlm.nih.gov/chemidplus/jsp/common/ChemInfo.jsp?calledFrom=lite&type=names. Accessed November 1, 2009.
3. European Commission. Polyoxymethylene Urea. http://ec.europa.eu/enterprise/cosmetics/cosing/index.cfm?fuseaction=search.details&id=79100. Accessed November 1, 2009.
4. Food and Drug Administration. List of indirect additives used in food contact substances: Poly(Formaldehyde-Co-Urea). http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?filter=&sortColumn=36%28%25%3AH%2152ED0%21AP%2C%2C1%3D%2F5Q9Q%2CF@++%0A&rpt=iaListing&displayAll=true. Accessed November 1, 2009.
5. Food and Drug Administration. *Frequency of Use of Cosmetic Ingredients*. Washington DC: FDA Database; 2009.
6. Gottschalck TE, Bailey JE, eds. *International Cosmetic Ingredient Dictionary and Handbook*. 13th ed, vol. 2. Washington DC: Personal Care Products Council (formerly the Cosmetic, Toiletry, and Fragrance Association.); 2010.
7. Hazardous Substances Database. Polynoxylin. http://toxnet.nlm.nih.gov/cgi-bin/sis/search. Accessed November 1, 2009.
8. The Merck Index. Monograph number: 09868; Title Ureaform. http://themerckindex.cambridgesoft.com/TheMerckIndex/default.asp?formgroup=basenp_form_group&dataaction=db&dbname=The Merck Index; 2009. Accessed November 1, 2009.
9. Bell HK, King CM. Allergic contact dermatitis from urea-formaldehyde resin in medium-density fibreboard (MDF). *Contact Dermat.* 2002;46(4):247:247.
10. Kanerva L, Jolanki R, Estlander T. Allergic and irritant patch test reactions to plastic and glue allergens. *Contact Dermat*. 1997; 37(6):301-302.
11. Lewis RJ Sr. Sax's Dangerous Properties of Industrial Materials. 10 ed. New York, NY: John Wiley & Sons, Inc; 2000.
12. Sommer S, Wilklinson SM, Dodman B. Contact dermatitis due to urea-formaldehyde resin in shin-pads. *Contact Dermat*. 1999; 40(3):159-160.
13. Tarvainen K. Analysis of patients with allergic patch test reactions to a plastics and glues series. *Contact Dermat*. 1995;32(6): 346-351.
14. Personal Care Products Council. Concentration of use—polyoxymethylene urea. Unpublished data received from the Council; 2009. 1 page.
15. Food and Drug Administration. Frequency of use of cosmetic ingredients. Washington DC: FDA Database; 2009.

Polyquaternium-7

Conclusion

In 1995, the Cosmetic Ingredient Review (CIR) Expert Panel concluded that polyquaternium-7 was safe as used in cosmetic formulations.[1] The expert panel reviewed the information available since that assessment,[2,3] along with updated frequency and concentration of use information. The Expert Panel confirmed the existing conclusion.

Discussion

The use of polyquaternium-7 in cosmetic formulations has increased greatly, from 138 reported[1,4] uses in 1994 to 975 uses in 2010. Concentration of use was not reported to the Food and Drug Administration (FDA) in 1994, nor is it reported to FDA currently. In response to a survey conducted by the Personal Care Products Council, industry reported current use concentrations of 0.009%-5% for polyquaternium-7 (Table 1).[5]

The Panel noted that polyquaternium-7 is now used in aerosolized products and noted the absence of inhalation toxicity data. However, in the absence of these data, the Panel determined that polyquaternium-7 can be used safely in hair sprays, because the product particle size is not respirable. The Panel reasoned that the particle size of aerosol hair sprays (around 38 μm) and pump hair sprays (>80 μm) is large compared to respirable particle sizes (≤10 μm). Polyquaternium-7 is now also used in leave-on type

Table 1. Historical and Current Cosmetic Product Uses and Concentrations of Polyquaternium-7

Product	Frequency of Use 1994 (# in Category)[1]	Frequency of Use 2010[4] (# in Category 2009)[6]	Concentration of Use 1994[1]	Concentration of Use (%) 2010[5]
Baby shampoos	2 (19)	7 (56)	NA	NR
Other baby products	1 (23)	8 (143)	NA	0.04
Bath oils, tablets, and salts	NR	NR (313)	NR	0.009
Bubble baths	2 (214)	15 (169)	NA	0.05-0.4
Other bath preparations	4 (132)	14 (234)	NA	NR
Eye shadow	NR	2 (1215)	NR	NR
Mascara	NR	6 (499)	NR	NR
Other fragrance preparation	2 (136)	1 (566)	NA	NR
Hair conditioner	16 (614)	31 (1226)	NA	0.01-0.3
Hair spray (aerosol fixatives)	NR	10 (312)	NR	NR
Permanent waves	4 (387)	1 (69)	NA	0.07-5
Rinses (non-coloring)	1 (58)	2 (33)	NA	0.2
Shampoos (non-coloring)	37 (852)	234 (1361)	NA	0.04-1
Tonics, dressings, and other hair grooming aids	19 (563)	34 (1205)	NA	0.2-3
Other hair preparations	3 (376)	21 (807)	NA	0.2-3
Hair dyes and colors (required caution statements)	NR	16 (2393)	NR	0.04
Hair shampoos (coloring)	3 (15)	1 (40)	NA	NR
Hair color sprays (aerosol)	NR	NR (7)	NR	0.02
Bath soaps and detergents	26 (343)	292 (1665)	NA	0.09-0.3
Other personal cleanliness products	3 (321)	198 (792)	NA	0.08-0.2
Aftershave lotion	1 (229)	3 (367)	NA	0.2
Shaving cream	4 (147)	2 (122)	NA	0.09
Shaving soap	NR	1 (10)	NR	NR
Cleansing	8 (746)	51 (1446)	NA	0.02-1
Face and neck (excluding shave)	NR	3 (1583)	NR	0.06-0.08
Body and hand (excluding shave)	NR	9 (1744)	NR	0.3
Moisturizing	NR	3 (2508)	NR	NR
Skin fresheners	NR	1 (259)	NR	NR
Other skin care preparations	1 (790)	8 (1308)	NA	0.4
Other suntan preparations	1 (61)	1 (62)	NA	NR
Total	138	975	NA	0.009-5

Abbreviations: NR, not reported as used in that category; NA, concentration of use data not reported at that time.

products and products that are applied to the eye. The panel was satisfied that data in the report supported the safety of these uses.

In the 1995 safety assessment, the Expert Panel[1] acknowledged the presence of acrylamide as an impurity in polyquarternium-7. An extrapolation using the current use concentration and the greatest amount of acrylamide impurity given in the 1995 report confirmed that the amount of residual acrylamide was not of concern. The Expert Panel confirmed that polyquaternium-7 is safe as used in cosmetic formulations.

References

1. Andersen FA, ed. Final report on the safety assessment of Polyquaternium-7. *JACT*. 1995;14(6):476-484.
2. Food and Drug Administration. 21 CFR 176.170. Diallyldimethylammonium chloride with acrylamide (CAS Reg. No. 26590-05-6). http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?FR=176.170&CFRPart=&FRSearch=. Accessed November 22, 2009.
3. Gallo R, Basso M, Voltolini S, Guarrera M. Allergic contact dermatitis from laureth-9 and polyquaternium-7 in a skin-care product. *Contact Dermat*. 2001;45(6):356-357.
4. Food and Drug Administration (FDA). Frequency of use data for polyquaternium-7. FDA Database. Updated February 18. Received March 2010 in response to an FOIA request. 2010.
5. Personal Care Products Council (Council). Concentration of use of polyquaternium-7. Industry survey. 2010. Unpublished data received from Council (February 25). 1 page.
6. Food and Drug Administration (FDA). *Frequency of use of cosmetic ingredients.* FDA Database. Washington, DC: FDA; 2009.

Potassium Bromate and Sodium Bromate

Conclusion

In a 1994 assessment of potassium bromate and sodium bromate, the Cosmetic Ingredient Review (CIR) Expert Panel stated that these ingredients may be used in cosmetic permanent wave formulations at concentrations not to exceed 10.17%, measured as sodium bromate.[1] The Expert Panel reviewed newly available studies since that assessment, along with updated information regarding types and concentrations of use[2-96] (Table 1). The Expert Panel determined not to reopen this safety assessment. Therefore, the Expert Panel confirms that potassium bromate and sodium bromate are safe as cosmetic permanent wave formulations at concentrations not to exceed 10.17%, measured as sodium bromate.

Table 1. Historical and Current Cosmetic Product Uses and Concentrations for Sodium Bromate

Product Category (no. of total products)[97]	1991 Uses[1]	2009 Uses[98]	1984 Concentrations[1] (%)	2009 Concentrations[99] (%)
Sodium bromate				
Noncoloring hair care products				
Straighteners (144)	61[a]	–	–	8
Permanent waves (141)		–	10-25	8
Other (716)		1	–	–
Total uses/ranges for sodium bromate	61	1	10-25	8

[a]The uses were not broken down into categories but are assumed to have been within these categories.

Discussion

The Expert Panel examined the large amount of new carcinogenicity data produced since the original safety assessment. The new biomarker and short- and long-term carcinogenicity studies did not reveal any new or different findings on potassium bromate and sodium bromate. As used in cosmetics, these chemicals do not present a carcinogenicity risk.

The Expert Panel did confirm that the conclusion restricts safe use in "cosmetic permanent wave formulations." Information was provided to the Expert Panel that the single use of sodium bromate in the "other" category is a nonaerosol hair spray product. This use is not covered by the conclusion in this safety assessment.

References

1. Andersen FA. Final report on the safety assessment of sodium bromate and potassium bromate. *J Am College Toxicol*. 1994; 13(5):400-414.
2. Allen J, Collins BW, Lori A, et al. Erythrocyte and spermatid micronucleus analyses in mice chronoically exposed to potassium bromate in drinking water. *Environ Mol Mutagen*. 2000; 36(250):253.
3. Arai T, Kelly VP, Minowa W, Noda T, Nishimura S. The study using wild-type and *Ogg1* knockout mice exposed to potassium bromate shows no tumor induction despite an extensive accumulation of 8-hydroxyguanine in kidney DNA. *Toxicology*. 2006; 221:179-186.
4. Awogi T, Murata K, Uejima M, et al. Induction of micronucleated reticulocytes by potassium bromate and potassium chromate in CD-1 male mice. *Mut Res*. 1992;278(181):185.

5. Ballmaier D, Epe B. Oxidative DNA damage induced by postassium bromate under cell-free conditions and in mammalian cells. *Carcinogenesis*. 1995;16(2):335-342.
6. Ballmaier D, Epe B. DNA damage b bromate: mechanism and consequences. *Toxicology*. 2006;221:166-171.
7. Bao L, Yao X-S, Tsi D, et al. Protective effects of bilberry (*Vaccinium myrtillus* L.) extract on $KBRO_3$-induced kidney damage in mice. *J Agric Food Chem*. 2008;56(2):420-425.
8. Cadenas S, Barja G. Resveratrol, melatonin, vitamin E, and PBN protect against renal oxidative DNA damage induced by the kidney carcinogen $KBrO_3$. *Free Rad Biol Med*. 1999;26(11/12):1531-1537.
9. Chipman JK, Davies JE, Parsons JL, Nair J, O'Neill GO, Fawell JK. DNA oxidation by potassium bromate; A direct mechanism or linked to lipid peroxidation? *Toxicology*. 1998;126(2):93-102.
10. Chipman JK, Parsons JL, Beddows EJ. The muliple influences of glutathione on bromate genotoxicity: implications for the dose-response relationship. *Toxicology*. 2006;221(187):189.
11. Cho DH, Hong JT, Chin K, Cho TS, Lee BM. Organotropic formation and disappearance of 8-hydroxydeoxyguanosine in the kidney of Sprague-Dawley rats exposed to adriamycin and $KBrO_3$. *Cancer Lett*. 1993;74(141):145.
12. Crosby LM, Morgan KT, Gaskill B, Wolf DC, DeAngelo A. Origin and distribution of potassium bromate-induced testicular and peritoneal mesotheliomas in rats. *Toxicol Pathol*. 2000;28(2): 253-266.
13. Crosby LM, Hyder KS, DeAngelo A, et al. Morpholigic anlaysis correlates with gene expression changes in curltured F344 rat mesothelial cells. *Toxicol Appl Phamacol*. 2000;169(3):205-221.
14. De Vriese A, Vanholder R, Lameire N. Severe acute renal failure due to bromate intoxication: Report of a case and discussion of management guidelines based on a review of the literature. *Nephrol Dialy Transplant*. 1997;12(1):204-209.
15. DeAngelo AB, George MH, Kilburn SR, Moore TM, Wolf DC. Carcinogenicity of potassium bromate administered in the drinking water to male $B6C3F_1$ mice and F344/N Rats. *Toxicol Pathol*. 1998;26(5):587-594.
16. Delker D, Hatch G, Allen J, et al. Molecular biomarkers of oxidative stress associated with bromate carcinogenicity. *Toxicology*. 2006;221(2-3):158-165.
17. El-Sokkary GH. Melatonin protects against oxidative stress induced by the kidney carcinogen $KBrO_3$. *Neuroendocrinol Lett*. 2000;21(6):461-468.
18. Environmental Protection Agency. *Toxicological Review of Bromate (CAS No. 15541-45-4)*. Washington, DC, 2001. www.epa.gov/iris. Report No. EPA/635/R-01/002. 57 pages.
19. Farombi EO, Alabi MC, Akuru TO. Kolaviron modulates cellular redox status and impairment of membrane protein activities induced by potassium bromate ($KBrO_3$) in rats. *Pharmocol Res*. 2002;45(1):63-68.
20. Food and Drug Administration (FDA). Food for human consumption. 4-1-2008. 21, Chapter I, Subchapter B: pp.172.730. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=172.730. Accessed April 28, 2009.
21. Fujie K, Shimazu H, Matsuda M, Sugiyama T. Acute cytogenetic efects of potassium bromate on rat bone marrow cells in vivo. *Mutat Res*. 1988;206(4):455-458.
22. George SE, Wolf DC, Brooks LR, Bailey KC, Hooth MJ, Nelson GM. Changes in cecal microbial metabolism of rats induced by individual and a mixture of drinking water disinfection by-products. *Cancer Lett*. 2004;204(1):15-21.
23. Giri U, Iqbal M, Athar M. Potassium bromate ($KBrO_3$) induces renal proliferative response and damage by elaborating oxidative stress. *Cancer Lett*. 1999;135(2):181-188.
24. Gottschalck TE, Bailey JE. *International Cosmetic Ingredient Dictionary and Handbook*. Washington DC: CTFA; 2008.
25. Guo TL, McCay JA, Karrow NA, et al. Immunotoxicity of sodium bromate in female B6C3F1 mice: a 28-day drinking water study. *Drug Chem Toxicol*. 2001;24(2):129-149.
26. Harrington-Brock K, Collard DD, Chen T. Bromate induces loss of heterozygosity in the *Thymidine kinase* gene of L5178Y/$Tk^{+/-}$-3.7.2C mouse lymphoma cells. *Mut Res*. 2003;537(1):21-28.
27. Hayashi M, Kishi M, Sufuni T, Ishidate M. Micronucleus tests in mice on 39 food addtitives and eight miscellaneous chemicals. *Food Chem Toxicol*. 1988;26(6):487-500.
28. Hayashi M, Sutou S, Shimada H, Sato S, Sasaki YF, Wakata A. Difference between intraperitoneal and oral gavage application in the micronucleus test: The 3rd collaborative study by CSGMT/JEMS.MMS. *Mut Res*. 1989;223(4):329-344.
29. Hollenbach S, Dhénaut A, Eckert I, Radicella JP, Epe B. Overexpression of Ogg1 in mammalian cells: effects on induced and spontaneous oxidative DNA damage and mutagenesis. *Carcinogenesis*. 1999;20(9):1863-1868.
30. Hooth MJ, McDorman KS, Hester SD, et al. The carcinogenic response of Tsc2 mutant Long-Evans (Eker) rats to a mixture of drinking water disinfection by-products was less than additive. *Toxicol Sci*. 2002;69(2):322-331.
31. International Occupational Safety and Health Information Centre. Potassium bromate ICSC: 1115. http://www.ilo.org/public/english/protection/safework/cis/products/icsc/dtasht/_icsc11/icsc1115.htm. 2003. Accessed April 28, 2009.
32. Joint FAO/WHO Expert Committee on Food Additives. Evaluation of certain food additives and naturally occurring toxicants. Geneva, World Health Organization. 1992. pp. 1-60. The report is 60 pages; Food and Agricultural Organization of the United Nations.
33. Joint FAO/WHO Expert Committee on Food Additives. *Evaluation of Certain Food Additives and Contaminants*. Switzerland, WHO. 1995. Report No. 859. pp. 1-54.
34. Jondeau A, Dahbi L, Bani-Estivals MH, Chagnon MC. Evaluation of the sensitivity of three sublethal cytotoxicity assays in human HepG2 cell line using water contaminants. *Toxicology*. 2006; 226(2-2):218-228.
35. Karbownik M, Stasiak M, Zygmunt A, Zasada K, Lewiñski A. Protective effects of melatonin and indole-3-propionic acid against lipid peroxidation, caused by potassium bromate in the rat kidney. *Cell Biochem Funtions*. 2006;24(6):483-489.
36. Karbownik M, Stasiak M, Zasada K, Zygmunt A, Lewinski A. Comparison of potential portective effects of melatonin, indole-3-propionic acid, and propylthiouracil against lipid peroxidation caused by potassium bromate in the thyroid gland. *J Cell Biochem*. 2005;95(1):131-138.
37. Kasai H, Nishimura S, Kurokawa Y, Hayashi Y. Oral administration of the renal carcinogen, potassium bromate, specifically

porduces 8-hydroxydeoxyguanosine in rat target organ DNA. *Carcinogenesis*. 1987;8(12):1959-1961.

38. Kawana K, Nakaoka T, Horiguchi Y, Watanabe S, Watanabe S, Kawauchi S. Toxicological study of potassium bromate. II. Hepatotoxic effects of the potassium bromate and benzo[*a*]pyrene simultaneous administration in mice. *Jpn J Toxicol Environ Health*. 1991;4(37):266-275.
39. Kaya FF, Topaktas M. Genotoxic effects of potassium bormate on human peripheral lymphocytes in vitro. *Mutat Res*. 2007; 626(1-2):48-52.
40. Khan N, Sharma S, Sultana S. Attenuation of potassium bromate-induced nephrotoxicity by courmarin (1,2-benzopyrone) in Wistar rats: chemoprevention against free radical-mediated renal oxidative stress and tumor promotion response. *Redox Rep*. 2004; 9(1):19-28.
41. Khan N, Sarwat S. Modulatory effect of *Ficus racemosa*: diminution of potassium bromate-induced renal oxidative injury and cell proliferation response. *Basic Clin Parmacol Toxicol*. 2005;97(5): 282-288.
42. Khan N, Sultana S. Inhibition of potassium bromate-induced renal oxidative stress and hyperproliferative response by *Nymphaea alba* in Wistar rats. *J Enzyme Inhib Med Chem*. 2005;20(3):275-283.
43. Kutom A, Bazilinski NG, Magana L, Dunea G. Bromate intoxication: Hairdressers' anuria. *Am J Kidney Dis*. 1990;15(1):84-85
44. Lee Y-S, Choi J-Y, Park M-K, Choi E-M, Kasai H, Chung M-H. Induction of oh^{8}Gua glycosylase in rat kidneys by potassium bromate ($KBrO_3$), a renal oxidative carcinogen. *Mut Res*. 1996; 364(3):227-233.
45. Lichtenberg R, Zeller WP, Gatson R. Bromate poisoning. *J Pediatr*. 1989;114(5):891-894.
46. Luan Y, Suzuki T, Palanisamy R, et al. Potassium bromate treatment predominantly causes large deletions, but not GC>TA transversion in human cells. *Mut Res*. 2007;619(1-2):113-123.
47. McDorman KS, Hooth MJ, Starr TB, Wolf DC. Analysis of preneoplastic and neoplastic renal lesions in *Tsc2* mutant Long-Evans (Eker) rats following exposure to a mixture of drinking water disifection by-products. *Toxicology*. 2003; 187(1):1-12.
48. McDorman KS, Chandra S, Hooth MJ, Hester SD, Schoonhoven R, Wolf DC. Induction of transitional cell hyperplasia in the urinary bladder and aberrant crypt foci in the colon of rats treated with individual and a mixture of drinking water disinfection by-products. *Toxicol Pathol*. 2003;31(2):235-242.
49. McDorman KS, Pachkowski BF, Nakamura J, Wolf DC, Swenberg JA. Oxidative DNA damage from potassium bromate exposure in Long-Evans rats is not enhanced by a mixture of drinking water disinfection by-products. *ChemBiol Interact*. 2005;152(2-3):107-117.
50. McLaren J, Boulikas T, Vamvakas S. Induction of poly(ADP-ribosyl)ation in the kidney after in vivo application of renal carcinogens. *Toxicology*. 1994;88(1-3):101-112.
51. Mikalsen S-O, Sanner T. Increased gap junctional intercelluar communication in Syrian hamster embryo cells treated with oxidative agents. *Carcinogenesis*. 1994;15:(2):381-387.
52. Morgan KT, Ni H, Brown HR, Yoon L, Qualls CW Jr, Crosby LM. Application of cDNA microarray technology to in vitro toxicology and the selection of genes for a real-time RT-PCR-based screen for oxidative stress in Hep-G2 cells. *Toxicol Pathol*. 2002;30(4):435-451.
53. Murata M, Bansho Y, Inoue S, et al. Requirement of glutathione and cysteine in guanine-specific oxidation of DNA by carcinogenic potassium bromate. *Chem Res Toxicol*. 2001;14(6): 678-685.
54. Nakajima M, Kitazawa M, Oba K, Kitagawa Y, Toyoda Y. Effect of route of administration in the micronucleus test with potassium bromate. *Mut Res*. 1989;223(4):399-402.
55. Nakano K, Okada S, Toyokuni S, Midorikawa W. Renal changes induced by chronic oral administration of potassium bromate or ferric nitrilotriacetate in Wistar rats. *Jpn Arch Intern Med*. 1989; 36(2):41-47.
56. Nesslany F, Zennouche N, Simar-Meintières Talahari I, Nkili-Mboui E-N, Marzin D. In vivo comet assay onisolated kidney cells to distinguish genotoxic carcinogens from epigenetic carcinogens or cytotoxic compounds. *Mut Res*. 2007;630(1-2):28-41.
57. Nishioka H, Fujii H, Sun B, Aruoma OI. Comparative efficacy of oligonol, catechin and (-)-epigallocatchin 3-*O*-gallate in madulating the potassium bromate-induced renal toxicity in rats. *Toxicology.* 2006;226(2-3):181-187.
58. Parsons JL, Chipman JK. The role of glutathione in DNA damage by potassium broate *in vitro*. *Mutagenesis*. 2000; 15(4):311-316.
59. Plewa MJ, Kargalioglu Y, Vankerk D, Minear RA, Wagner ED. Mammalian cell cytotoxicity and genotoxicity analysis of drinking water disinfection by-products. *Environ Mol Mut*. 2002;40(2): 134-142.
60. Poul JM, Huet S, Godard T, Sanders P. Lack of genotoxicity of potassium iodate in the alkaline comet assay and in the cyokinesis-block micronucleus test. Comparison to potassium bromate. *Food Chem Toxicol*. 2004;42(2):203-209.
61. Richter H, Vamvakas S. S-(1,2-dichlorovinyl-L-cystein-induced dedifferentiation and p53 gene mutations in LLC-PK_1 cells: a comparative investigation with 2-(2-chloroethyl)cysteine, potassium bromate, cis-platinum and styrene oxide. *Toxicol Lett*. 1998; 94(2):145-157.
62. Robbiano L, Carrozzino R, Porta Puglia C, Corbu C, Brambilla G. Correlation between inductionof DNA fragmentation and micronuclei formation in kidney cells from rats andhumans and tissue-specific carcinogenic activity. *Toxicol Appl Phamacol*. 1999; 161(2):153-159.
63. Sai K, Takagi A, Umemura T, Hasegawa R, Kurokawa Y. Regulation of 8-hydroxydeoxyguanosine formation in rat kidney to lipid peroxidation, glutathione level and relative organ weight after a singel administration of potassium bromate. *Jpn J Cancer Res*. 1991;82(2):165-169.
64. Sai K, Umemura T, Takagi A, Hasegawa R, Kurokawa Y. The protective role of glutathione, cysteine and vitamine C against oxidative DNA damage induced in rat kidney by potassium bormate. *Jpn J Cancer Res*. 1992;83(1):45-51.
65. Sai K, Hayashi M, Takagi A, Hasegawa R, Sufuni T. Effects of antioxidants on induction of micronuclei in rat peripherol blood reticulocytes by potassium bromate. *Mutat Res*. 1992;269(1): 113-118.

66. Sai K, Uchiyama S, Ohno Y, Hasegawa R, Kurokawa Y. Generation of active oxygen species in vitro by the interaction of potassium bomate with the rat kidney cell. *Carcinogenesis*. 1992;13(3): 333-339.
67. Sai K, Hayashi M, Takagi A, Hasegawa R, Sofuni T, Kurokawa Y. Effects of antioxidants on induction of micronuclei in rat peripheral blood reticulocytes by potassium bromate. *Mut Res*. 1992; 269(1):113-118.
68. Sai K, Tyson CA, Thomas DW, Dabbs JE, Hasegawa R, Kurokawa Y. Oxidative DNA damage induced by potassium bromate in isolated rat renal proximal tubules and renal nuclei. *Cancer Lett*. 1994;87(1):1-7.
69. Sashiyama H, Ifie Y, Ohtake Y, cute renal failure and hearing loss due to sodium bromate poisoning: A case report and review of the literature. *Clin Nephrol*. 2002;58(6):455-457.
70. Shiao Y-H, Kamata SI, Li LM, et al. Mutations in the VHL gene from potassium bormate-induced rat clear cell renal tumors. *Caner Lett*. 2002;187(1-2):207-214.
71. Speit G, Haupter S, Schütz P, Kreis P. Comparative evaluation of the genotoxic properties of potassium bormate and postassium superoxide in V79 Chinese hamster cells. *Mutat* Res. 1999; 439(2):213-221.
72. Tamaguchi T, Wei M, Hagihara N, Omori M, Wanibuchi H, Fukushima S. Lack of mutagenic and toxic effects of low dose potassium bromate on kidneys in the Big Blue rat. *Mut Res*. 2008;652(1):1-11.
73. Tanaka K, Oikawa K, Fukuhara C Metabolism of potassium bromate in rats II. In vitro studies. *Chemosphere*. 1984;13(11):1213-1219.
74. Tono Y, Ushisako Y, Morimitsu T, Takenaka M. Cochlear implants in deafened patients due to potassium bormate poisoning. *Advanc Otorhinolaryngol*. 1997;52:315-317.
75. Uchida HA, Sugiyama H, Kanehisa S, et al. An elderly patient with severe acute renal failure due to sodium bormate intoxication. *Int Med*. 2006;45:(3):151-154.
76. Ueno S, Kashimoto T, Susa N, et al. Estimation of hydroxyl radical generation by salicylate hydroxylation method in kedney of mice exposed to ferric nitrolotriacetate and potassium bromate. *Free Radical Res*. 2007;41:(11):1246-1252.
77. Umemura T, Sai K, Takagi A, Hasegawa R, Kurokawa Y. A possible role for cell proliferation in potassium bromate ($KBrO_3$) carcinogenesis. *J Cancer Res Clin Oncol*. 1993;119(8):463-369.
78. Umemura T, Sai K, Takagi A, Hasegawa R, Kurokawa Y. A possible role for oxidative stress in potassium bromate ($KBrO_3$) carcinogenesis. *Carcinogenesis*. 1995;16(3):593-597.
79. Umemura T, Atsuya T, Sai K, Hasegawa R, Kurokawa Y. Oxidative DNA damage and cell proliferation in kedneys of male and female rats during 13-weeks exposure to potassium bromate ($KBrO_3$). *Arch Toxicol*. 1998;72(264):269.
80. Umemura T, Kodama Y, Kurodawa Y, Williams GM. Lack of oxidative DNA damage or initiation of carcinogenesis in the kidneys of male F344 rats given subchronic exposure to *p*-dichlorobenzene (pDCB) at a carcinogenic dose. *Arch Toxicol*. 2000;73(1):54-59.
81. Umemura T, Kodama Y, Karbownik M, et al. Dose-related changes of oxidative stress and cell proliferation in kidneys of male and female F344 rats exposed to potassium bromate. *Cancer Sci*. 2004;95(5):393-398.
82. Umemura T, Kanki K, Kuroiwa Y In vivo mutagenicity and initiation frollowing oxidative DNA lesion in the kidneys of rats given potassium bromate. *Cancer Lett*. 2006;97(9):829-835.
83. Umemura T, Tasaki M, Kijima A, et al. Possible participatio of oxidative stress in causatio of cell proliferation and in vivo mutagenicity in kedneys of *gpt* delta rats treated with postassium bromate. *Toxicology*. 2008;257(1-2):46-52.
84. Watanabe S, Togashi S-I, Fukue T. Contribution of nitric oxide to potassium bromate-induced elevation of methaemoglobin concentration in mouse blood. *Biol Pharm Bull*. 2002;25(10):1315-1319.
85. Wolf DC, Crosby LM, George MH, et al. Time- and dose-dependent development of potassium bromate-induced tumors in male Fischer 344 rats. *Toxicol Pathol*. 1998;26(724):729.
86. Young Y-H, Chuu J-J, Liu S-H, Lin-Shiau S-Y. Toxic effects of potassium bromate and thioglycolate on vestibuloocular reflex systems of guinea pigs and humans. *Toxicol Appl Pharmacol*. 2001;177:(103):111.
87. Zasada K, Chuu J-J, Liu SH, Lin-Shiau S-Y. Toxic effects of potassium bromate and thioglycolate on vestibuloocular reflex systems of guinea pigs and humans. *Toxicol Appl Phamacol*. 2001;177(2):103-111.
88. Smith CC, O'Donovan MR, Martin EA. hOOG1 recognizes oxidative damage using the comet assay with greater specificity than FPG or ENDOIII. *Mutagenesis*. 2006;21(3):185-190.
89. Are 4-hydroxy-2(E)-noneal derived mercapturic acid and ^{1}H NMR metabonomics potential biomarkers of chemically induced oxidative stress in the kidney? *Toxicology*. 2007;230(2-3): 244-255.
90. Rahaman A, Ahmed S, Khan N, Sultana S, Athar M. Glyceryl trinitrate, a nitric oxide donor, suppresses renal oxidant damage coused by potassium bromate. *Redox.Rep.* 2002;4(6): 263-269.
91. Bantle JA, Finch RA, Fort DJ, et al. Phase III interlaboratory study of FETAX part 3. FETAX validation using 12 compounds with and without an exogenous metabolic activation system. *J Appl Toxicol*. 1999;19(6):447-472.
92. National Toxicology Program. NTP Report of the Toxicology Studies of Sodium Bromate (CAS NO. 7789-38-0) in Genetically modified (FVB Tg.AC Hemizygous) Mice (Dermal and Drinking Water Studies) and Carcinogenicity Studies of Sodium Bromate in genetically Modified (B6.129-*Trp53*^{tm1Brd} [N5} Haploinsufficient) Mice (Drinking Water STudies). 2007. Report No. 07-4423. pp. 1-170.
93. Gayer PT. Toxic mechanism of bormate poisoning in a dog: a case study. *Vetinary Hum Toxicol*. 1994;36(3):208-211.
94. Mattioli F, Martelli A, Gosmar M, et al. DNA fragmentation and DNA repair synthesis induced in rat and human thyroid cells by chemicals cardingenic to the rat thyroid. *Mut Res*. 2006;609(2): 146-153.
95. Chuu J-J, Hsu C-J, Lin-Shiau S-Y. The determental effects of potassium bromate and thioglycolate on auditory brainstem response of guinea pigs. *Chinese J Physiol*. 2000;43(2):91-96.

96. Food and Drug Administration (FDA). Requirements for specific standardized and related products: requirements for specific standardized ceral flours and related products. 2008. 21 CFR 137.105, 155.
97. Food and Drug Administration (FDA). VCRP total number of products in each product catagory, March, 2008; 2009.
98. Food and Drug Administration (FDA). *Cosmetic Product Formulation and Frequency of Use Data*. Washington, DC, 2009.
99. Personal Care Products Council. 2009. Concentration of use–Potassium bromate and sodium bromate. Unpublished data submitted by the Personal Care Products Council. 1 page.

Quaternium-22

Conclusion

In 1995, the Cosmetic Ingredient Review (CIR) Expert Panel concluded that quaternium-22 is safe in the present practices of use.[1] The Expert Panel reviewed information available since that assessment[2,3] along with updated frequency and concentration of use information. The Expert Panel confirmed the existing conclusion.

Quaternium-22 is reported to function as an antistatic agent, film former, and hair-conditioning agent.[4] Reported use[1,5] has decreased from 80 reported uses in 1994 to 58 uses in 2010, but the types of use have generally remained the same. Concentration of use was not reported to the Food and Drug Administration (FDA) in 1994, nor is it reported to FDA currently. In response to a survey conducted by the Personal Care Products Council,[6] industry reported current use concentrations of 0.06% to 2% for quaternium-22 (Table 1).

Discussion

The Panel noted that quaternium-22 is now used in aerosolized products and noted the absence of inhalation toxicity data. However, in the absence of these data, the Panel determined that quaternium-22 can be used safely in hair sprays, because the product particle size is not respirable. The Panel reasoned

Table 1. Historical and Current Cosmetic Product Uses and Concentrations of Quaternium-22

Product	Frequency of Use—1994 (# in Category)[1]	Frequency of Use—2010[5] (# in Category)[7]	Concentration of Use (1994)[1]	Concentration of Use (%; 2010)[6]
Bubble baths	2 (208)	NR (169)	NA	0.5
Other bath preparations	3 (111)	NR (234)	NA	NR
Eye liner	NR	1 (754)	NR	NR
Mascara	34 (178)	17 (499)	NA	0.06-1
Hair conditioner	4 (597)	5 (1226)	NA	1
Hair spray (aerosol fixatives)	1 (294)	1 (312)	NA	NR
Hair straighteners	NR	NR (178)	NR	0.3
Permanent waves	NR	NR (69)	NR	0.2
Shampoos (non-coloring)	17 (845)	7 (1361)	NA	0.6
Tonics, dressings, and other hair grooming aids	2 (494)	3 (1205)	NA	0.06-0.7
Other hair preparations	2 (356)	3 (807)	NA	0.5
Hair dyes and colors (required caution statements)	NR	NR (1458)	NR	2 (1% after dilution)
Hair bleaches	NR	NR (149)	NR	2
Bath soaps and detergents	5 (335)	7 (1665)	NA	0.09-2
Other personal cleanliness products	1 (296)	NR (792)	NA	NR
Cleansing skin care preparations	1 (702)	5 (1446)	NA	0.2
Face and neck creams, lotions, and powders	NR	NR (1583)	NR	0.6
Moisturizing	1 (806)	7 (2508)	NA	NR
Paste masks (mud packs)	NR	1 (441)	NR	NR
Other skin care preparations	1 (745)	1 (1308)	NA	0.06
No. of uses listed under trade name	6	NR	NA	NR
Total	80	58	NA	0.06-2

Abbreviations: NR, not reported as used in that category; NA, concentration of use data not reported at that time.

that the particle size of aerosol hair sprays (around 38 μm) and pump hair sprays (>80 μm) is large compared to respirable particle sizes (≤10 μm).[8-10]

References

1. Andersen FA, ed. Final report on the safety assessment of quaternium-22*JACT*1995;14(6):485-497.
2. Le Coz CJ, Leclere JM, Arnoult E, et al., and Members of Revidal-Gerda. Allergic contact dermatitis from shellac in mascara. *Contact Dermat*. 2002;46(3):149-152.
3. Scheman AJ. Contact allergy to quaternium-22 and shellac in mascara. *Contact Dermat*. 1998;38(6):342-343.
4. Gottschalck TE, Bailey JE. *International Cosmetic Ingredient Dictionary and Handbook.* 13 ed. Washington, DC: Personal Care Products Council; 2010.
5. Food and Drug Administration (FDA). Frequency of use data for quaternium-22. *FDA Database.* 2010. February 18.
6. Personal Care Products Council (Council). Concentration of use of Quaternium-22. Industry survey. 2010. Unpublished data received from Council (February 25). 1 p.
7. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. *FDA Database*. Washington, DC: FDA; 2009.
8. World Health Organization. *Hazard Prevention and Control in the Work Environment: Airborne Dust*. Geneva: WHO; 1999. WHO/SDE/OEH/99.14 i.
9. International Commission on Radiological Protection. Human respiratory model for radiological protection. *Ann ICRP*. 1994; 24:1-458.
10. Oberdorster G, Oberdorster E, Oberdorster J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. *Environ Health Perspect*. 2005;113(7):823-839.

Shellac

Conclusion

In a 1986 safety assessment of shellac, the Cosmetic Ingredient Review (CIR) Expert Panel stated that cosmetic-grade shellac is safe for use in cosmetic formulations at concentrations up to 6%. The Expert Panel reviewed studies performed since that assessment (see references)[1-6] as well as updated the use and concentration data. The Panel confirmed that shellac is safe in the present practices of use and concentration given in Table 1 and did not reopen the safety assessment.

Discussion

In 1986, shellac was used in 69 reported product formulations at concentrations up to 1%. As of 2006, shellac is used in 11 reported product formulations at concentrations up to 6%. The reported use and concentration data are shown in Table 1. The Panel concluded that shellac continues to be safe in its present uses and concentrations.

The Panel considered adding Shellac Wax and Ammonium Shellacate to this safety assessment, but found the data inadequate to do so.

References

1. Gallow R, Marro I, Pavesi A. Allergic contact dermatitis from shellac in mascara. *Contact Dermat*. 2005;53(4):238-239.
2. Le Coz CJ, Leclere JM, Arnoult E, Raison-Peyron N, Pons-Guiraud A, Vigan M. Members of Revidal-Gerda. Allergic contact dermatitis from shellac in mascara. *Contact Dermat*. 2002;46(3): 149-152.
3. Magerl A, Pirker C, Frosch PJ. Allergic contact eczema from shellac and 1,3-butylene glycol in an eyeliner. *J German Soc Dermatol*. 2003;1(4):300-302.
4. Orton DI, Salim A, Shaw S. Allergic contact cheilitis due to shellac. *Contact Dermat*. 2001;44(4):250.
5. Rademaker M, Kirby JD, White IR. Contact cheilitis to shellac, Lanpol 5 and colophony. *Contact Dermat*. 1986;15(5):307-308.

Table 1. Historical and Current Cosmetic Product Uses and Concentrations for Shellac

Product Category	1986 Uses[7]	2006 Uses[8]	1986 Concentrations[7] (%)	2006 Concentrations[9] (%)
Eye makeup				
Eyeliners	21 (382)	4 (639)	1-10	
Mascara	42 (429)	6 (308)	0.01-0.25	2-6
Noncoloring hair care products				
Sprays/aerosol fixatives	6 (38)	1 (294)	0.01-1	
Total use/range	69 (859)	11 (1241)	0.01-10	2-6

6. Strauss RM, Orton KI. Allergic contact cheilitis in the United Kingdom: a retrospective study. *Am J Contact Dermat*. 2003; 14(3):75-77.
7. Final report on the safety assessment of shellac. *JACT*. 1986;5(5): 309-327.
8. Food and Drug Administration. Frequency of use of cosmetic ingredients. Washington DC: FDA; 2006.
9. Cosmetic Toiletry and Fragrance Association. Concentration of use for shellac. Unpublished data submitted by CTFA; 2006.

Steapyrium Chloride and Lapyrium Chloride

Conclusion

In its 1991 safety assessment of steapyrium and lapyrium chloride, the Cosmetic Ingredient Review (CIR) Expert Panel[1] concluded that these ingredients are safe as cosmetic ingredients in the present practice of use and concentration. In 2007, the Expert Panel found no newly available studies since that assessment but did review updated information regarding types and concentrations of use. The Panel confirmed the safety of steapyrium and lapyrium chloride in the practices of use given in Table 1 and did not reopen this safety assessment.

Discussion

Steapyrium and lapyrium chloride were used in 36 and 38 products, respectively, in 1981, based on voluntary reports provided to Food and Drug Administration (FDA) by industry, at concentrations of >0.1% to 5% for steapyrium chloride and ≤0.1% to 5% for lapyrium chloride.[1] Data provided to FDA in 2007 indicated that steapyrium chloride and lapyrium chloride are being used in 18 and 12 products, respectively.[2] Current use concentration data from a cosmetics industry survey[3] indicated that steapyrium chloride is being used in cosmetics at

Table 1. Historical and Current Cosmetic Product Uses and Concentrations for Steapyrium and Lapyrium Chloride

Product Category	1986 Uses (Total Formulations)[1]	2007 Uses (Total Formulations)[2]	1986 Concentrations[1] (%)	2007 Concentrations[3] (%)
Steapyrium chloride				
Baby products				
Shampoos	1 (35)	–	>0.1-1	–
Noncoloring hair care products				
Conditioners	8 (478)	6 (715)	>0.1-5	1-3
Rinses	5 (158)	1 (46)	>0.1-5	–
Shampoos	1 (909)	–	>1-5	–
Other	–	1 (464)	–	–
Hair-coloring products				
Dyes and colors	1 (811)	–	>1-5	–
Tonics, dressings, and so on	–	1 (623)	–	0.1-3
Shaving products				
Aftershave lotions	2 (282)	–	>0.1-1	–
Skin care products				
Skin-cleansing creams, lotions, liquids, and pads	2 (680)	1 (1009)	>0.1-1	–
Depilatories				
Face and neck creams, lotions, powder, and sprays	7 (832)		>0.1-1	–
Body and hand creams, lotions, powder, and sprays		1 (992)		
Foot powders and sprays				
Moisturizers	3 (747)	5 (1200)	>0.1-5	–
Night creams, lotions, powder, and sprays	2 (219)	–	>1-5	–
Suntan products				
Suntan gels, creams, liquids, and sprays	3 (164)	2 (138)	>0.1-1	–
Other	1 (28)	–	>0.1-1	–

(continued)

Table 1. (continued)

Product Category	1986 Uses (Total Formulations)[1]	2007 Uses (Total Formulations)[2]	1986 Concentrations[1] (%)	2007 Concentrations[3] (%)
Total uses/ranges for steapyrium chloride	36 (5343)	18 (5187)	>0.1-5	0.1-3
Lapyrium chloride				
Baby products	2 (56)		>0.1-1	
Lotions, oils, powders, and creams	–	2 (67)	–	–
Fragrance products				
Colognes and toilet waters	5 (1120)	1 (948)	>0.1-1	–
Noncoloring hair care products				
Conditioners	3 (478)	–	>0.1-1	–
Tonics, dressings, and so on	1 (290)	–	>0.1-1	–
Wave sets	1 (180)	1 (59)	≤0.1	–
Makeup				
Other	1 (530)	–	>0.1-1	–
Personal hygiene products				
Underarm deodorants	5 (239)	3 (281)	>0.1-1	–
Other	7 (227)	3 (390)	>0.1-5	0.03 (0.03 % in a body wash)
Shaving products				
Aftershave lotions	2 (282)	2 (260)	>0.1-1	–
Skin care products				
Skin cleansing creams, lotions, liquids, and pads	4 (680)	–	≤0.1-1	–
Depilatories				
Face and neck creams, lotions, powder, and sprays	4 (832)	–	≤0.1-5	–
Body and hand creams, lotions, powder, and sprays				
Foot powders and sprays				
Moisturizers	2 (747)	(1200)	>0.1-1	1
Night creams, lotions, powder, and sprays				
Paste masks/mud packs				
Skin fresheners	1 (260)		0.1-1	–
Skin lighteners				
Hormone preparations				
Other				
Total uses/ranges for lapyrium chloride	38 (5921)	12 (3205)	≤0.1- 5	0.03

concentrations ranging from 0.1% to 3% and that lapyrium chloride is being used at a concentration of 0.03%.

Historical and current product usage and use concentration data as a function of product category are given in Table 1. The CIR Expert Panel recognized that there are data gaps regarding the use and concentration of these ingredients. However, the overall information available on the types of products in which these ingredients are used and at what concentrations indicates a pattern of use, which was considered by the CIR Expert Panel in assessing safety. In order to gain more insight into the ingredient use frequency patterns, the total number of products in a category could be considered along with the number of products in that category containing the ingredient.

References

1. Elder RL. Final report on the safety assessment of steapyrium chloride and lapyrium chloride. *J Am Coll Toxicol*. 1991;10(1): 87-97.
2. Food and Drug Administration. *Frequency of use of cosmetic ingredients*. Washington DC: FDA; 2007.
3. Cosmetic, Toiletry, and Fragrance Association. *Concentration of use for steapyrium and lapyrium chloride*. Washington D.C., 1 page.