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40th Anniversary Overview and Rereview Summaries From 2011 to 2015

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Welcome to this special edition celebrating the 40th year of the Cosmetic Ingredient Review (CIR). The CIR was established in 1976 and was the result of a collaborative effort between government, industry, and consumer groups. The CIR was created solely for the purpose of assessing the safety of cosmetic ingredients, and it does so in an independent, open, unbiased, and expert manner. The CIR identifies, gathers, and analyzes scientific data for the development of safety assessment monographs, which are used by its Expert Panel to determine safety.

All determinations of safety are made by the CIR Expert Panel—an independent, nonprofit scientific body of world-renowned scientists and physicians who have been publicly nominated by consumer, scientific and medical groups, government agencies, and industry. The Food and Drug Administration, the Consumer Federation of America, and the Personal Care Products Council provide nonvoting liaisons to the Expert Panel who are actively involved in the comment and discussion process. Final decisions rendered by the Expert Panel are published in the peer-reviewed journal *International Journal of Toxicology*.

This anniversary edition includes an overview of CIR that provides a broader discussion of the infrastructure, the Expert Panel's decision-making process, and approaches to modern challenges, such as the review of botanical ingredients and safety evaluations using nonanimal data. Included in this edition are the full safety assessments of crosslinked alkyl acrylates and of diethanolamine and its salts as used in cosmetics.

Also included are 18 rereview summaries. Rereviews are performed 15 years after a safety assessment was published, and the process is intended to uncover any new data that have become available for an ingredient (or ingredient group) since safety was last evaluated. 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 Expert Panel decides to not reopen a safety assessment, thereby reaffirming the original conclusion, 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 the assessment, this Annual Review of Cosmetic Ingredient Safety Assessments is prepared.

A list of reference sources is provided as part of a rereview summary; this listing indicates the update to the available published literature and includes any unpublished data made available since the previous safety assessment. The rereview also captures information on the industry's current practices of ingredient use. Although these rereview summaries provide the opinion of the Expert Panel regarding the new data that have become available, it does not constitute a full safety review.

The Expert Panel has assessed the safety of over 4,500 cosmetic ingredients since its inception in 1976. These safety assessments have been published in the *Journal of Environmental Pathology and Toxicology* (1980), the *Journal of the American College of Toxicology* (1982 to 1996), and the *International Journal of Toxicology* (1997 to current).

The ingredients the Expert Panel reconsidered during the 2011 to 2015 period and did not reopen are:

1. Alpha hydroxyl acids (AHA)
2. 2-Amino-6-chloro-4-nitrophenol
3. Bisabolol
4. 4-Chlororesorcinol
5. Glutaral
6. HC Orange No. 1
7. HC Red No. 1
8. HC Yellow No. 4
9. Isostearamidopropyl morpholine lactate
10. Iodopropynyl butylcarbamate
11. Methyldibromo glutaronitrile
12. m-Phenylenediamine and m-phenylenediamine sulfate
13. Dibutyl, diethyl, and dimethyl phthalate
14. Polyvinyl alcohol
15. Polyvinyl acetate
16. PVP (also known as polyvinylpyrrolidone)
17. Quaternium-15
18. Retinyl palmitate and retinol

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Alpha Hydroxy Acids

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Keywords
cosmetics, safety, alpha hydroxy acids

Conclusion

In a 1998 safety assessment, the Cosmetic Ingredient Review Expert Panel (Panel) concluded that glycolic and lactic acid, their common salts, and their simple esters (referred to as alpha hydroxy acids [AHA] ingredients) are safe for use in cosmetic products at concentrations $\leq$10%, at final formulation pH $\geq$3.5, when formulated to avoid increasing sun sensitivity or when directions for use include the daily use of sun protection. These ingredients are safe for use in salon products at concentrations $\leq$30%, at final formulation pH $\geq$3.0, in products designed for brief discontinuous use followed by thorough rinsing from the skin, when applied by trained professionals, and when application is accompanied by directions for the daily use of sun protection.[1]

The Panel reviewed newly available studies since that assessment, along with updated information regarding types and concentrations of use (Tables 1 and 2).[2-41] The Panel determined to not reopen this safety assessment. Therefore, the Panel confirmed the original conclusion as stated above.

Discussion

The use of AHAs has increased considerably since the original assessment. Glycolic acid had been used in 42 cosmetic formulations in 1997, and lactic acid was reported to be used in 342 cosmetic formulations. In 2014, the US Food and Drug Administration (FDA) reported that glycolic acid is used in 339 formulations and lactic acid is used in 1092 cosmetic formulations. A survey of current use concentrations conducted by industry reported that leave-on use concentrations of glycolic and lactic acid are similar to those reported in the 1998 assessment; however, the highest maximum use concentrations in rinse-off products have increased.[10]

The Panel acknowledged the FDA's "Guidance for Industry: Labeling for Cosmetics Containing Alpha Hydroxy Acids" that was issued in 2005, which also addressed the use of sun protection with AHA products. The FDA recommended that the labeling of a cosmetic product that contains an AHA ingredient and that is topically applied to the skin or mucous membrane bear a statement, prominently and conspicuously placed on the cosmetic product, which conveys the following information:

> Sunburn Alert: This product contains an AHA that may increase your skin's sensitivity to the sun and particularly the possibility of sunburn. Use a sunscreen, wear protective clothing, and limit sun exposure while using this product and for a week afterwards.

The FDA guidance does not apply to drug–cosmetic products that contain an AHA as an ingredient and are labeled to contain a sunscreen for sun protection.

Although AHA ingredients are in products for consumer, salon, and medical use, the Panel stated that this safety assessment does not address the medical use of AHA ingredients; it addresses only the consumer and salon use, that is, those products available to the general public and those applied by trained estheticians, respectively.

Finally, the Panel reviewed the photocarcinogenicity studies that have been published since the original safety assessment.[8,26] In these studies, the dermal application of glycolic acid to mouse skin did not increase the incidence of skin tumors in mice. The Panel stated these studies provided additional evidence to confirm the safety of AHAs for use in cosmetic formulations.

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Table 1. Current and Historical Frequency and Concentration of Use of AHAs According to Duration and Exposure.

	Number of uses		Max conc. of use (%)		Number of uses		Max conc. of use (%)	
	2014[5]	1997[1]	2013[10]	1995[1]	2014[5]	1997[1]	2013[10]	1995[1]
	Glycolic acid				Ammonium glycolate			
Totals[a]	339	42	0.0005-50	<1-20[b]	44	19	NR	NR[c]
Duration of use								
Leave-on	239	31	0.0005-10	<1-20[b]	30	11	NR	NR[c]
Rinse-off	99	11	0.0008-50	≤7.8-9.8[b]	14	8	NR	NR[c]
Diluted for (bath) use	1	NR	NR	NR[b]	NR	NR	NR	NR[c]
Exposure type								
Eye area	8	NR	0.035-0.49	NR[b]	1	NR	NR	NR[c]
Incidental ingestion	NR	NR	NR	7.04-14.29[b] (70% aq; pH 3.89-4.01)	NR	NR	NR	NR[c]
Incidental inhalation—spray	2; 76[d]; 88[e]	21[d,e]	aerosol: 0.0005; pump: 0.05; 0.12-0.6[d]	NR[b]	12[d]; 7[e]	7[d,e]	NR	NR[c]
Incidental inhalation—powder	1; 88[e]	11[e,f]	NR	NR[b]	7[e]	3[e,f]	NR	NR[c]
Dermal contact	307	30	0.012-50	<1-20[b]	41	16	NR	NR[c]
Deodorant (underarm)	NR	NR	NR	NR[b]	NR	NR	NR	NR[c]
Hair—noncoloring	30	2	0.0005-4.5	≤8[b]	2	2	NR	NR[c]
Hair-coloring	NR	NR	0.0008-4	NR[b]	NR	NR	NR	NR[c]
Nail	2	2	4.1	≤8[b]	1	1	NR	NR[c]
Mucous membrane	10	NR	0.06	≤8[b]	NR	NR	NR	NR[c]
Baby products	NR	NR	NR	NR[b]	NR	NR	NR	NR[c]
	Sodium Glycolate				Lactic Acid			
Totals[a]	23	1	0.0002 -1.9	NR[c]	1092	342	0.000023-30	0.1-11.8[b]
Duration of use								
Leave-on	5	1	0.0002	NR[c]	656	177	0.000023-10.1	0.1-11.8[b]
Rinse-off	18	NR	0.005-0.25	NR[c]	425	162	0.000081-6.1	0.7-2[b]
Diluted for (bath) use	NR	NR	1.9	NR[c]	11	3	0.085-30	≤6[b]
Exposure type								
Eye area	1	NR	NR	NR[c]	17	1	0.000023-0.2	0.12-3.53[b] (85% aq.)
Incidental ingestion	NR	NR	NR	NR[c]	2	NR	0.0023-0.085	NR[b]
Incidental inhalation—spray	1[d]; 2[e]	NR	NR	NR[c]	283[d]; 173[e]	9	0.00063-0.21; aerosol: 0.0002; pump: 0.17-5.8; 0.00321.1[d]	NR[b]
Incidental inhalation—powder	2[e]	NR	NR	NR[c]	2[f]; 173[e]	NR	0.000023	NR[b]
Dermal contact	14	1	0.01-1.9	NR[c]	695	229	0.000023-10	0.1-11.8[b] (85% aq.)
Deodorant (underarm)	NR	NR	NR	NR[c]	3[d]	NR	0.05-1.7	NR[b]
Hair—noncoloring	9	NR	0.0002-0.25	NR[c]	379	144	0.000081-5.8	0.1-5[b]
Hair-coloring	NR	NR	NR	NR[c]	11	46	0.014-5	≤1[b]
Nail	NR	NR	NR	NR[c]	3	7	0.0006-10.1	≤10[b]
Mucous membrane	6	NR	0.01-1.9	NR[c]	70	3	0.01-30	≤6[b]
Baby products	NR	NR	NR	NR[c]	2	1	NR	NR[b]

(continued)

Table 1. (continued)

	Number of uses		Max conc. of use (%)		Number of uses		Max conc. of use (%)	
	2014[5]	1997[1]	2013[10]	1995[1]	2014[5]	1997[1]	2013[10]	1995[1]
	Ammonium lactate				Calcium lactate			
Totals[a]	21	NR	0.0003-0.06	NR	11	NR	0.072-1.5	NR
Duration of use								
Leave-on	15	NR	0.0003-0.06	NR	3	NR	0.072-1	NR
Rinse-off	6	NR	0.0064-0.032	NR	7	NR	0.3-1.5	NR
Diluted for (bath) use	NR	NR	NR	NR	1	NR	NR	NR
Exposure type								
Eye area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental ingestion	NR	NR	0.0003	NR	5	NR	1	NR
Incidental inhalation—spray	8[d]; 4[e]	NR	pump: 0.0064; 0.023-0.06[d]	NR	NR	NR	0.3[d]	NR
Incidental inhalation—powder	4[e]	NR	NR	NR	NR	NR	NR	NR
Dermal contact	20	NR	0.0004-0.06	NR	6	NR	0.072	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair—noncoloring	1	NR	0.0064-0.032	NR	NR	NR	NR	NR
Hair-coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous membrane	NR	NR	0.0003	NR	6	NR	0.3-1.5	NR
Baby products	NR	NR	NR	NR	3	NR	NR	NR
	Potassium lactate				Sodium lactate			
Totals[a]	29	3	0.0004-0.92	NR	385	93	0.0002-8	<0.1-50[c]
Duration of use								
Leave-on	16	3	0.92	NR	290	66	0.0002-8	<0.1-10[c]
Rinse-off	13	NR	0.0004	NR	94	26	0.0002-7.6	<0.1-50[c]
Diluted for (bath) use	NR	NR	NR	NR	1	1	NR	NR[c]
Exposure type								
Eye area	NR	NR	NR	NR	20	NR	0.02-0.6	NR[c]
Incidental ingestion	NR	NR	NR	NR	1	NR	0.0018-0.1	NR[c]
Incidental inhalation—spray	6[d]; 3[e]	NR	NR	NR	1; 119[d]; 107[e]	NR	0.075-1.3; aerosol: 0.012-0.013; pump: 0.035-0.06; 0.0002[d]; -0.63[e]	NR[c]
Incidental inhalation—powder	3[e]	NR	NR	NR	2; 1[f]; 107[e]	NR	0.03; -0.63[e]	NR[c]
Dermal contact	27	3	0.0004-0.92	NR	356	71	0.0002-8	<0.1-50[c]
Deodorant (underarm)	NR	NR	NR	NR	1[d]	1	0.01-0.075	NR[c]
Hair—noncoloring	2	NR	NR	NR	23	20	0.0002	0.1-1[c]
Hair-coloring	NR	NR	NR	NR	1	NR	0.07	NR[c]
Nail	NR	NR	NR	NR	3	NR	NR	NR[c]
Mucous membrane	8	NR	NR	NR	26	1	0.0002-1.2	0.1-50[c]
Baby products	NR	R	NR	NR	2	NR	NR	NR[c]

(continued)

Table 1. (continued)

	Number of uses		Max conc. of use (%)		Number of uses		Max conc. of use (%)	
	2014[5]	1997[1]	2013[10]	1995[1]	2014[5]	1997[1]	2013[10]	1995[1]
	TEA-lactate				Butyl lactate			
Totals[a]	18	13	0.06-0.07 (≤0.1[c])	≤0.1[c]	NR	NR	1	NR
Duration of use								
Leave-on	17	7	0.06-0.07 (≤0.1[c])	≤0.1[c]	NR	NR	1	NR
Rinse-off	1	6	NR	NR[c]	NR	NR	NR	NR
Diluted for (bath) use	NR	NR	NR	NR[c]	NR	NR	NR	NR
Exposure type								
Eye area	1	NR	NR	NR[c]	NR	NR	NR	NR
Incidental ingestion	NR	1	NR	NR[c]	NR	NR	NR	NR
Incidental inhalation—spray	5[d]; 5[e]	NR	NR	NR[c]	NR	NR	NR	NR
Incidental inhalation—powder	5[e]	NR	NR	NR[c]	NR	NR	NR	NR
Dermal contact	17	84	0.06-0.07 (≤0.1[c])	≤0.1[c]	NR	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR[c]	NR	NR	NR	NR
Hair—noncoloring	NR	NR	NR	NR[c]	NR	NR	NR	NR
Hair-coloring	NR	4	NR	NR[c]	NR	NR	NR	NR
Nail	1	NR	NR	NR[c]	NR	NR	1	NR
Mucous membrane	NR	1	NR	NR[c]	NR	NR	NR	NR
Baby products	NR	NR	NR	NR[c]	NR	NR	NR	NR
	Cetyl lactate				Ethyl lactate			
Totals[a]	49	38	0.015-10.2	0.5-9[b]	5	3	0.15-95	50[b] (NR[c])
Duration of use								
Leave-on	47	36	0.5-10.2	0.5-9[b]	2	3	95	50[b] (NR[c])
Rinse-off	2	2	0.015-1.2	1[b]	3	NR	0.15-49	NR[c]
Diluted for (bath) use	NR	NR	NR	NR[b]	NR	NR	NR	NR[c]
Exposure type								
Eye area	NR	1	1.5-10	0.5-2[b]	1	NR	NR	NR[c]
Incidental ingestion	23	29	2-9	3-9[b]	NR	NR	NR	NR[c]
Incidental inhalation—spray	16[d]; 2[e]	4	NR	NR[b]	NR	NR	NR	NR[c]
Incidental inhalation—powder	1[f]; 2[e]	4	NR	NR[b]	NR	NR	NR	NR[c]
Dermal contact	25	9	0.5-10.2	0.5-5[b]	2	NR	0.15	NR[c]
Deodorant (underarm)	NR	NR	NR	NR[b]	NR	NR	NR	NR[c]
Hair—noncoloring	1	NR	0.015	NR[b]	NR	NR	NR	NR[c]
Hair—coloring	NR	NR	NR	NR[b]	NR	NR	NR	NR[c]
Nail	NR	NR	NR	NR[b]	3	3	49-95	50[b]
Mucous membrane	23	NR	0.55-9	3-9[b]	NR	NR	NR	NR[c]
Baby products	1	1	NR	NR[b]	NR	NR	NR	NR[c]
	Lauryl lactate				Methyl lactate			
Totals[a]	22	13	0.14-10	0.1-5[b] (≤0.1-25[c])	NR	NR	0.038-0.75	NR
Duration of use								
Leave-on	20	9	0.14-10	0.15[b] (0.1-25[c])	NR	NR	0.038-0.75	NR
Rinse-off	2	4	0.5-1	≤0.1-5[b,c]	NR	NR	NR	NR
Diluted for (bath) use	NR	NR	NR	NR[b,c]	NR	NR	NR	NR

(continued)

Table 1. (continued)

	Number of uses		Max conc. of use (%)		Number of uses		Max conc. of use (%)	
	2014[5]	1997[1]	2013[10]	1995[1]	2014[5]	1997[1]	2013[10]	1995[1]
Exposure type								
Eye area	1	NR	1	0.1[b]	NR	NR	NR	NR
Incidental ingestion	NR	NR	1	1-25[c]	NR	NR	NR	NR
Incidental inhalation—spray	6[d]; 10[e]	NR	0.14-2[d]	NR[c]	NR	NR	NR	NR
Incidental inhalation—powder	10[e]	4	NR	NR[c]	NR	NR	NR	NR
Dermal contact	21	13	0.5-10	0.1-5[b]; 1-25[c]	NR	NR	0.038-0.75	NR
Deodorant (underarm)	2[d]	1	NR	NR[c]	NR	NR	Aerosol: 0.038	NR
Hair—noncoloring	1	NR	0.14	≤0.1[c]	NR	NR	NR	NR
Hair-coloring	NR	NR	NR	NR[c]	NR	NR	NR	NR
Nail	NR	NR	1	NR[c]	NR	NR	NR	NR
Mucous membrane	1	1	0.5	1-25[c]	NR	NR	NR	NR
Baby products	NR	NR	NR	NR[c]	NR	NR	NR	NR
	Myristyl lactate							
Totals[a]	214	195	0.01-13.2	>1.5-15[b] (0.1-50[c])				
Duration of use								
Leave-on	208	187	0.01-13.2	>1.5-1[b] (0.1-50[c])				
Rinse-off	6	8	0.79-11.2	0.1-1[c]				
Diluted for (bath) use	NR	NR	NR	0.1-1[c]				
Exposure type								
Eye area	97	105	3.5-7.2	5-15[b] (0.1-25[c])				
Incidental ingestion	62	53	6.3-13.2	11.54[b] (0.1-50[c])				
Incidental inhalation—spray	11[d]; 15[e]	NR	1.5-5.7[d]	0.1-50[c]				
Incidental inhalation—powder	2; 15[e]	1	NR	NR[c]				
Dermal contact	151	140	0.01-11.2	>1.5-15[b] (0.1-50[c])				
Deodorant (underarm)	1[d]	NR	NR	NR[c]				
Hair—noncoloring	1	2	NR	0.1-1[c]				
Hair-coloring	NR	NR	NR	NR[c]				
Nail	NR	NR	NR	NR[c]				
Mucous membrane	64	53	6.3-13.2	11.54[b] (0.1-50[c])				
Baby products	NR	NR	NR	NR[c]				

Abbreviations: FDA, Food and Drug Administration; NR, no reported use.

[a]Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

[b]Some concentration of use data were reported.

[c]At the time of the 1998 safety assessment, concentration of use data were not reported by the FDA; 1984 data were presented.

[d]It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

[e]Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

[f]It is possible these products are powders, but it is not specified whether the reported uses are powders.

Table 2. AHAs Not in Current Use According to VCRP and Council Survey Data.

Butyl glycolate
Calcium glycolate[a]
Ethyl glycolate[a]
Methyl glycolate[a]
Potassium glycolate[a]
Propyl glycolate[a]
Isopropyl lactate[a]

Abbreviation: AHA, alpha hydroxy acid; VCRP, Voluntary Cosmetic Registration Program.
[a]These ingredients were included in the original 1998 safety assessment, but they are not listed in the *International Cosmetic Ingredient Dictionary* as cosmetic ingredients.

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2-Amno-6-Chloro-4-Nitrophenol

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Keywords
cosmetics, safety, 2-amino-6-chloro-4-nitrophenol

Conclusion

In a 1997 safety assessment of 2-amino-6-chloro-4-nitrophenol, the Cosmetic Ingredient Review (CIR) Expert Panel (Panel) stated that 2-amino-6-chloro-4-nitrophenol and its hydrochloride salt are safe for use in hair dye formulations at concentrations up to 2.0%.[1] The Panel reviewed newly available studies since that assessment,[2-11] along with updated information regarding types and concentrations of use and did not reopen this safety assessment. The Panel confirmed that 2-amino-6-chloro-4-nitrophenol and its hydrochloride salt are safe for use in hair dye formulations at concentrations up to 2.0%.

Discussion

A new margin of safety calculation, published in the opinion on 2-amino-6-chloro-4-nitrophenol released by the European Commission's Scientific Committee on Consumer Products (SCCP) in 2006,[2] concluded that a maximum use concentration of 2% in the finished product does not pose a risk to the health of the consumer, although the SCCP did note that this ingredient is a known sensitizer. According to the European Commission Health and Consumers Cosmetics CosIng database, 2-amino-6-chloro-4-nitrophenol has a maximum authorized concentration of 2.0% in nonoxidative hair dye products. In oxidative hair dye products, the maximum concentration applied to hair after mixing under oxidative conditions must not exceed 2.0%.[3] Appropriate labeling must be used.

Information supplied to the US Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP)[5] indicates that 2-amino-6-chloro-4-nitrophenol was not reported to be used and 2-amino-6-chloro-4-nitrophenol hydrochloride was used in a total of 15 hair-coloring products in 1997.[1] The VCRP data provided by FDA in 2012 indicated 2-amino-6-chloro-4-nitrophenol was being used in 62 hair dyes and colors requiring caution statements, although no uses were reported for the hydrochloride salt. The results of a 2012 industry survey[7] indicated that 2-amino-6-chloro-4-nitrophenol was being used in hair dyes and colors (all types requiring caution statements and patch tests) at a maximum concentration of 1.5%, and 0.4% in coloring hair rinses. These concentrations are lower than the maximum concentration allowed in the original CIR safety assessment[1] and that allowed by the European Commission.

The Panel recognized that carcinogenicity data were not available. However, 2-amino-6-chloro-4-nitrophenol is not significantly absorbed through the skin and it is not genotoxic.[2]

The CIR Expert Panel noted that hair dyes containing coal tar derivatives are exempt from certain adulteration and color additive provisions of the US 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. Although there has been recent concern expressed in Europe regarding the potential induction of sensitization that may result from the currently recommended self-test procedure for hair dyes,[9-11] the Panel agreed that there was not a sufficient basis for changing the advice to consumers at this time.

The Panel concluded that the available epidemiology studies are insufficient to conclude there is a causal relationship between hair dye use and cancer or other toxicologic end points, based on lack of strength of the associations and inconsistency of findings. Use of direct hair dyes, while not the focus in all investigations, appears to have little evidence of any association with adverse events as reported in epidemiology studies. A detailed summary of the available hair dye epidemiology data is available at http://www.cir-safety.org/cir-findings.

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Bisabolol

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Keywords
bisabolol, safety, cosmetics

Table 1. Current and Historical Frequency and Concentration of Use of Bisabolol According to Duration and Exposure.

	No. of uses		Max concentration of use (%)	
	2015[13]	1997[1]	2014[14]	1995[1]
Totals[a]	999	184	0.00002-1	0.001-1
Duration of use				
Leave on	774	142	0.00002-1	0.001-1
Rinse off	215	41	0.00002-0.5	0.01-0.02
Diluted for (bath) use	10	1	NR	0.25
Exposure type				
Eye area	90	11	0.01-0.5	<0.1
Incidental ingestion	31	2	0.15-1	0.001-0.2
Incidental inhalation spray	Spray: 10 Possible: 209[b]; 185[c]	Spray: 3 Possible: 37[b]; 33[c]	Spray: 0.001-0.2 Possible: 0.000-0.1[b]	Spray: 0.01 Possible: 0.01-0.02[b]; 0.01-1[c]
Incidental inhalation powder	Powder: 9 Possible: 185[c]; 5[d]	Possible: 33[c]; 3[d]	Powder: 0.1-0.2 Possible: 0.01-1[d]	Possible: 0.01-1[c]
Dermal contact	912	176	0.00002-1	0.01-1
Deodorant (underarm)	34[b]	4[b]	Not spray: 0.1; aerosol: 0.11-0.3; pump spray: 0.2	1[b]
Hair—noncoloring	35	1	0.00002-0.5	NR
Hair coloring	5	1	0.1	NR
Nail	3	2	0.01-0.09	0.05
Mucous membrane	86	6	0.0001-1	0.001-0.25
Baby products	9	3	NR	NR

Abbreviation: NR, no reported use.
[a]Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[b]Includes products that can be sprayed, but it is not known whether the reported uses are sprays.
[c]Not specified whether this product is a spray or a powder or neither, but it is possible it may be a spray or a powder, so this information is captured for both categories of incidental inhalation.
[d]Includes products that can be powders, but it is not known whether the reported uses are powders.

Conclusion

In a 1999 safety assessment of bisabolol, the Cosmetic Ingredient Review (CIR) Expert Panel (Panel) concluded that this ingredient was safe as used in cosmetic products.[1] The Panel reviewed studies newly available since that assessment,[2-12] along with updated frequency and concentration of use information.[13,14] The Panel reaffirmed the original conclusion that bisabolol is safe as a cosmetic ingredient in the practices of use and concentration as given in Table 1.

Discussion

Information supplied to the US Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Ingredient Reporting Program indicates that use of bisabolol has increased since the time of the original review but that there is no increase in the concentration of use. Voluntary Cosmetic Ingredient Reporting Program data provided by FDA in 1997 indicated 184 uses, which is fewer than the 999 uses reported in 2015. The results of the 2015 industry survey indicated that bisabolol is used at up to 1% in leave-on formulations.

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The Panel noted in the 1999 review[1] that bisabolol is well absorbed following dermal application and can be a penetration enhancer. Because these ingredients are used in baby products, the Panel reiterated their caution to formulators of the possibility of increased absorption of other ingredients, especially those ingredients for which safety was based on their lack of dermal absorption. The Panel also noted a study that reported a possible lightening of the skin after induction of pigmentation by ultraviolet light (0.5% bisabolol topical daily for 8 weeks); however, they determined that this study did not warrant a change in the conclusion of the original (1999) report.

The Panel determined to not reopen this safety assessment and confirmed that bisabolol is safe as a cosmetic ingredient in the current practices of use and concentration (Table 1).

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4-Chlororesorcinol

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Keywords
cosmetics, safety, 4-chlororesorcinol

Conclusion

In a 1996 safety assessment of 4-chlororesorcinol, the Cosmetic Ingredient Review (CIR) Expert Panel stated that this ingredient is safe as used in hair dye formulations.[1] The Expert Panel reviewed newly available studies since that assessment along with updated frequency and concentration of use information (Table 1).[2-5] The Expert Panel determined to not reopen this safety assessment and confirmed that 4-chlororesorcinol is safe in the present practices of use and concentration in hair dye formulations.

Discussion

The Expert Panel reviewed new data that were published in the opinion released by the European Commission's Scientific Committee on Consumer Safety (SCCS) in 2010, which determined that this ingredient was not a health risk, apart from sensitization, at a maximum concentration of 2.5%.[2] The Expert Panel noted that use of 4-chlororesorcinol in hair dyes has increased from 33 uses to 210 and that the current use concentration is up to 2%, which is higher than the 1% concentration previously reported on but below the SCCS limit.[3,4]

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 or other toxicologic end points, based on lack of strength of the associations and inconsistency of findings. Use of direct hair dyes, while not the focus in all investigations, appears to have little evidence of any association with adverse events as reported in epidemiology studies. A detailed summary of the available hair dye epidemiology data is available at http://www.cir-safety.org/findings.shtml.

Table 1. Historic and Current Uses and Concentrations of 4-Chlororesorcinol.[1,3,4]

	No. of uses		Concentration of use (%)	
	4-chlororesorcinol			
Data Year	1996	2011	1996	2011
Totals[a]	33	210	≤1	0.005-2
Duration of use				
Leave on	NR	NR	NR	NR
Rinse off	33	210	<1	0.005-2
Exposure type				
Eye area	NR	NR	NR	NR
Possible ingestion	NR	NR	NR	NR
Inhalation	NR	NR	NR	NR
Dermal contact	NR	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR
Hair—noncoloring	NR	NR	NR	NR
Hair coloring	33	210	≤1	0.005-2
Nail	NR	NR	NR	NR
Mucous membrane	NR	NR	NR	NR
Bath products	NR	NR	NR	NR
Baby products	NR	NR	NR	NR

Abbreviation: NR, not reported.
[a]Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses. Totals = rinse off + leave on product uses.

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Glutaral

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Keywords
cosmetics, safety, glutaral

Table 1. Historic and Current Uses and Concentrations of Glutaral.[1,14,28]

	Number of uses		Concentration of use (%)	
	Glutaral			
	1996	2011	1996	2011
Exposure type[a]				
Eye area	2	NR	[b]	NR
Incidental ingestion	NR	NR	[b]	NR
Incidental inhalation—sprays	1	1	[b]	NR
Incidental inhalation—powders	NR	NR	[b]	NR
Dermal contact	19	7	[b]	NR
Deodorant (underarm)	NR	NR	[b]	NR
Hair—Noncoloring	41	6	[b]	6×10^{-6}[c]
Hair-coloring	NR	NR	[b]	NR
Nail	NR	NR	[b]	NR
Mucous membrane	NR	1	[b]	NR
Baby products	NR	NR	[b]	NR
Duration of use				
Leave-on	18	8	[b]	6×10^{-6}[c]
Rinse-off	42	5	[b]	6×10^{-6}[c]
Diluted for (bath) use	NR	NR	[b]	NR
Totals[d]	60	13	≤ 1[b]	6×10^{-6}[c]

Abbreviation: NR, not reported.
[a]Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum of total uses.
[b]Breakdown is not available.
[c]Calculated concentration of incidental glutaral in the finished product. Glutaral is included at low concentrations in a raw material added to the final product. It is not functional in the final product.
[d]Totals = rinse-off + leave-on product uses.

Conclusion

In the 1996 safety assessment of glutaral, the Cosmetic Ingredient Review Expert Panel (Panel) stated that this ingredient is safe for use at concentrations up to 0.5% in rinse-off products. There were insufficient data to determine the safety of glutaral in leave-on products, and this ingredient should not be used in aerosolized products.[1] The Panel reviewed newly available studies since that assessment along with updated frequency and concentration of use information (Table 1).[2-46] The Panel determined to not reopen this safety assessment and confirmed the original conclusion of glutaral.

Discussion

Since the original conclusion, numerous studies have been published, including a 2-year National Toxicology Program (NTP) study on inhalation. Although the number of uses for glutaral has decreased from 60 to 13, this ingredient is currently being used in an aerosol product and in leave-on products. The current concentration of use is 6×10^{-6}% in noncoloring hair products. The Panel received clarification that this concentration of glutaral is incidental and that glutaral is not added to the products for functional use. Additionally, although glutaral did not cause cancerous lesions in the 2-year NTP study, several

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studies have found that this ingredient does cause damage to the upper respiratory tract in animals.[6,16,25,38,45,46]

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HC Orange No. 1

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cosmetics, HC Orange No. 1, safety

Conclusion

In the 1998 safety assessment of HC Orange No. 1, the Cosmetic Ingredient Review Expert Panel concluded that this ingredient was safe as a cosmetic ingredient at concentrations ≤3%.[1] The Expert Panel reviewed newly available studies since that assessment along with updated frequency and concentration of use information.[2-4] The Expert Panel reaffirmed the original conclusion that HC Orange No. 1 is safe as a hair dye at concentrations ≤3%.

Discussion

This ingredient was used in 95 hair dyes and colors and no hair tints in 1996, based on the voluntary reports submitted to the US Food and Drug Administration by the industry, with concentrations of use up to 0.15% in semipermanent hair colors.[1]

In 2013, HC Orange No. 1 was reportedly used in 15 hair dyes and colors and 1 hair tint.[2] Data from an industry survey in 2013 indicate that concentrations of use have increased from 0.15% in 1998 to 0.55% and that this ingredient is only used in hair dyes and colors up to 0.55%.[3] The Expert Panel noted that these hair dyes should be formulated to be nonirritating, although the increased concentration is still well below the maximum concentration of 3%.

The Expert Panel recognized that HC Orange No. 1 can be considered a coal tar hair dye. Accordingly, products containing this ingredient are exempt from certain adulteration and color additive provisions of the Federal Food, Drug, and Cosmetic Act, when the product label bears a caution statement and patch test instructions for determining whether the product causes skin irritation. The Expert Panel considered concerns about such self-testing but agreed that following this procedure enables consumers to determine, prospectively, whether they will have an irritation/sensitization reaction and allow them to avoid subsequent significant exposures. The results of ongoing studies to evaluate the risks and benefits of consumer self-testing will be considered in the future.

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HC Red No. 1

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Keywords
cosmetics, safety, HC Red No. 1

Conclusion

In a 1996 safety assessment of HC Red No. 1, the Cosmetic Ingredient Review Expert Panel stated that this ingredient is safe as used in hair dye formulations at concentrations of ≤0.5%.[1] The Expert Panel reviewed newly available studies since that assessment along with updated information regarding types and concentration of use.[2-8] The Expert Panel confirmed that HC Red No. 1 is safe as a hair dye ingredient at concentrations of ≤0.5%, as given in Table 1 and did not reopen this safety assessment.

Discussion

HC Red No. 1 is a direct hair dye reported used in 47 hair-coloring products in 1996, based on voluntary reports[1] submitted to the US Food and Drug Administration by the industry, with concentrations of use ≤0.5%.[6] In 2011, HC Red No. 1 was reportedly used in 9 cosmetic products.[4] Data from an industry survey in 2011 indicated that this ingredient was used at 0.07%.[6]

Table 1. Historic and Current Uses and Concentrations of HC Red No.1.[1,4,6]

	HC Red No. 1			
	No. of uses		Concentration of use, %	
Data year	1996	2011	1996	2011
Totals	47	9	<0.5	0.07
Duration of use				
Leave-on	NR	NR	NR	NR
Rinse-off	47	9	≤0.5	0.07
Exposure type				
Eye area	NR	NR	NR	NR
Possible ingestion	NR	NR	NR	NR
Inhalation	NR	NR	NR	NR
Dermal contact	NR	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR
Hair—noncoloring	NR	NR	NR	NR
Hair-coloring	47	9	≤0.5	0.07
Nail	NR	NR	NR	NR
Mucous membrane	NR	NR	NR	NR
Bath products	NR	NR	NR	NR
Baby products	NR	NR	NR	NR

Abbreviation: NR, not reported.

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HC Yellow No. 4

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cosmetics, safety, HC Yellow No. 4

Conclusion

In the 1998 safety assessment of HC Yellow No. 4, the Cosmetic Ingredient Review Expert Panel stated that this ingredient was safe as used in hair dyes.[1] The Expert Panel reviewed newly available studies since that assessment along with updated information regarding types and concentrations of use.[2-6] The Expert Panel determined to not reopen this safety assessment. Therefore, the Expert Panel confirmed the original conclusion that HC Yellow No. 4 is safe for use in hair dyes.

Discussion

HC Yellow No. 4 had been used in 78 hair dyes and colors and 3 hair tints.[1] Use concentrations were reported to be up to 3.0% in oxidative and semipermanent hair colors according to a 1998 industry survey.[1] The US Food and Drug Administration reported that HC Yellow No. 4 is used in 18 hair dyes and colors, 1 hair tint, and 1 hair shampoo (coloring),[6] at a reported concentration range of 0.04% to 0.75% in hair dyes and colors[2] according to survey data. No concentration of use was reported for hair tints and hair shampoo (coloring).

The Expert Panel cautioned that HC Yellow No. 4 should not be used in formulations where N-nitroso compounds may be formed. The Expert Panel considered study results that indicate reproductive effects to rats and noted that these were all oral studies and at concentrations much higher than the reported concentration of use of 0.75%.[3] These new reproductive toxicity data, therefore, do not suggest a concern for use of HC Yellow No. 4 in hair coloring.

The Expert Panel recognized that HC Yellow No. 4 can be considered a coal tar hair dye. Accordingly, products containing this ingredient are exempt from certain adulteration and color additive provisions of the Federal Food, Drug, and Cosmetic Act, when the product label bears a caution statement and patch test instructions for determining whether the product causes skin irritation. The Expert Panel has considered concerns about such self-testing but agreed that following this procedure enables consumers to determine, prospectively, whether they will have an irritation/sensitization reaction and allow them to avoid subsequent significant exposures. In the future, the Expert Panel will consider the results of ongoing studies by the industry to evaluate the risks and benefits of consumer self-testing.

Declaration of Conflicting Interests

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Isostearamidopropyl Morpholine Lactate

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Conclusion

In the 1999 safety assessment of isostearamidopropyl morpholine lactate, the Cosmetic Ingredient Review (CIR) Expert Panel (Panel) concluded that this ingredient was safe for use as a cosmetic ingredient in rinse-off formulations in the (then) present concentrations and practices of use.[1] The Panel also concluded the data were insufficient to support the safety of leave-on formulations and stated that the following data were needed to support the safety of leave-on products:

1. skin penetration; if there is significant skin penetration, then both a 28-day dermal toxicity study and reproductive and developmental toxicity study are needed;
2. a genotoxicity study in a mammalian system; if positive, a 2-year dermal carcinogenicity study using National Toxicology Program methods may be needed; and
3. inhalation toxicity data.

No new data were found in the published literature that would result in any new information. The Panel reaffirmed that isostearamidopropyl morpholine lactate is safe for use in cosmetics in rinse-off formulations in the practices of use and concentration as given in Table 1, and that the data are insufficient to support the safe use in leave-on formulations.

Table 1. Current and Historical Frequency and Concentration of Use of Bisabolol According to Duration and Exposure.

	Number of Uses		Maximum Concentration of Use, %	
	2015[2]	1996[1]	2014[3]	1995[1]
Totals[a]	283	20	0.13-5	1-5
Duration of use				
Leave-on	1	5	NR	[b]
Rinse-off	276	15	0.13-5	[b]
Diluted for (Bath) use	6	NR	NR	NR
Exposure type				
Eye area	NR	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR
Incidental inhalation-spray	1[c]	NR	NR	[b]
Incidental inhalation-powder	1[c]	NR	NR	NR
Dermal contact	242	4	0.13-0.2	NR
Deodorant (underarm)	NR	NR	NR	NR
Hair–noncoloring	39	16	0.25-5	[b]
Hair-coloring	2	NR	0.38	[b]
Nail	NR	NR	NR	NR
Mucous membrane	238	1	0.13-0.2	NR
Baby products	NR	1	NR	NR

Abbreviation: NR = no reported use.
[a]Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[b]Concentration of use of 1-5% in hair preparations was reported, but the types of hair preparations were not specified; therefore it is not known if the products were leave-on or rinse-off, non-coloring or coloring, or sprays.
[c]Not specified whether this product is a spray or a powder or neither, but it is possible it may be a spray or a powder, so this information is caputured for both categories of incidental inhalation.

Discussion

Current and historical usage and use concentration data are presented in Table 1. In 1996, it was reported to the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) that isostearamidopropyl morpholine lactate was used in 20-product formulations; no use concentration data were reported by industry survey. The FDA data indicate 283 uses in 2015, and the ingredient is still reported to be used in 1 leave-on formulation. According to CIR procedures, ingredients deemed to have an insufficient data conclusion but are reported to be in use according to the VCRP, will be recategorized to have a conclusion of "Use Not Supported" if the data needed are not provided within 2 years. Therefore, if no data are submitted in response to these data needs by June 2017, the conclusion will be reclassified to Use Not Supported for leave-on use.

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Iodopropynyl Butylcarbamate

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Table 1. Historic and Current Uses and Concentrations.[1,5,6,a,b]

	No. of uses		Maximum concentration of use (%)	
	Iodopropynyl butylcarbamate			
Data year	1996	2013	1995	2013
Totals	122	942	0.005-0.0125	0.00012-0.05
Duration of use				
Leave-on	44	564	0.005-0.0125	0.001-0.05
Rinse-off	78	364	0.0125	0.00012-0.05
Diluted for (bath) use	NR	14	NR	0.015
Exposure type				
Eye area	NR	45	NR	0.009-0.023
Incidental ingestion	NR	NR	NR	NR
Incidental inhalation—sprays	9	48	0.01-0.0125	0.001-0.02
Incidental inhalation—powders	NR	1	NR	0.02
Dermal contact	38	548	0.005-0.0125	0.002-0.05
Deodorant (underarm)	NR	NR	NR	0.0075-0.02
Hair—noncoloring	73	374	NR	0.00012-0.05
Hair coloring	10	14	NR	0.0078-0.011
Nail	1	1	NR	0.03
Mucous membrane	NR	102	NR	0.015-0.05
Baby products	NR	14	NR	NR

Abbreviation: NR, not reported.
[a]Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not be equal to the sum of total uses.
[b]Totals = Rinse-off + leave-on product uses.

Conclusion

In the 1998 safety assessment of iodopropynyl butylcarbamate (IPBC), the Cosmetic Ingredient Review Expert Panel (Panel) stated that IPBC is safe as a cosmetic ingredient at concentrations $\leq 0.1\%$ and should not be used in products intended to be aerosolized.[1] Since that assessment, the Panel reviewed additional studies along with updated frequency and concentration of use information (Table 1).[2-21] At the September 2013 meeting, the Panel determined that this safety assessment should not be reopened.

Discussion

During the Panel discussion, the European Union's (EU) 0.1% concentration limit on IPBC in cosmetics was noted. Currently, the following 3 maximum concentrations of this ingredient, which are authorized for use in cosmetics, are in effect in the EU, each of which is lower than the 0.1% limit previously determined: (1) rinse-off products (0.02%), (2) leave-on products (0.01%, except deodorants/antiperspirants), and (3) deodorants/antiperspirants (0.0075%). Furthermore, this ingredient is not to be used in oral hygiene and lip care products, and the following warning must be displayed on the label of rinse-off and leave-on cosmetic products that contain IPBC: not to be used for children aged younger than 3 years. Using the Scientific Committee on Cosmetic Products and Non-food Product's opinion on IPBC as the basis for the EU's limitations,

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the Panel noted that these limitations are based on concerns relating to potential iodine release from this ingredient and subsequent overdose. However, the Panel agreed that it is not likely that iodine release from IPBC would be significant enough at use concentrations to affect thyroid function or produce iodine overload, particularly after considering that effects on the thyroid gland were not reported in a 104-week, chronic oral toxicity study on this ingredient (up to 80 mg/kg/d) involving rats.[1] The absence of evidence that IPBC causes thyroid toxicity in this study was also considered along with the absence of evidence that this ingredient can be dehalogenated to produce free iodine in animals or in humans. The Panel also noted that the available irritation and sensitization data do not suggest that IPBC is unsafe for use in cosmetic products at concentrations up to 0.05%, the highest maximum use concentration reported in a survey of ingredient use concentrations.[1,10-20]

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Methyldibromo Glutaronitrile

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Table 1. Historic and Current Uses and Concentrations of Methyldibromo Glutaronitrile.[1,37,38]

	No. of uses[a]		Maximum concentration of use, %	
	Methyldibromo glutaronitrile			
Data year	1996	2011	1996	2011
Totals[b]	35	36	0.0075-0.06[c]	0.005-0.04
Duration of use				
Leave-on	23	22	[c]	0.012
Rinse-off	12	11	[c]	0.04
Diluted for (bath) use	NR	3	[c]	NR
Exposure type				
Eye area	5	NR	[c]	NR
Incidental ingestion	NR	NR	[c]	NR
Incidental inhalation—sprays	4	NR	[c]	0.01
Incidental inhalation—powders	5	NR	[c]	NR
Dermal contact	22	22	[c]	0.04
Deodorant (underarm)	NR	NR	[c]	NR
Hair—Noncoloring	12	14	[c]	0.016
Hair-coloring	NR	NR	[c]	NR
Nail	1	NR	[c]	NR
Mucous membrane	NR	9	[c]	NR
Baby products	NR	NR	[c]	NR

Abbreviation: NR, not reported.
[a]Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum of total uses.
[b]Totals = rinse-off + leave-on product uses.
[c]Breakdown is not available.

Conclusion

In the1996 safety assessment of methyldibromo glutaronitrile, the Cosmetic Ingredient Review Expert Panel stated that this ingredient is safe as used in rinse-off products and safe at ≤0.025% in leave-on products.[1] The Expert Panel reviewed newly available studies since that assessment along with updated frequency and concentration of use information and did not reopen this safety assessment.[2-65] The Expert Panel confirmed that methyldibromo glutaronitrile is safe as used in rinse-off products and safe at ≤0.025% in leave-on products (Table 1).

Discussion

Information supplied to the US Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Ingredient Reporting Program indicates that in 1996, methyldibromo glutaronitrile was being used in 35 cosmetic formulations at concentrations up to and including 0.06%. Use of this ingredient in 36 product formulations in specific product categories was reported to FDA in 2011, and an industry survey produced use concentrations up to 0.04%. The European Commission had banned the ingredient from use in both leave-on and rinse-off products due to increased reports of sensitivity. However, the Expert Panel opined that many, if not most, reports of sensitization in patch test studies likely are due to testing at high concentrations such that the reactions observed are actually irritation responses.

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m-Phenylenediamine and m-Phenylenediamine Sulfate

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Keywords
safety, cosmetics, m-phenylenediamine, m-phenylenediamine sulfate

Table 1. Historic and Current Uses and Concentrations of m-Phenylenediamine and m-Phenylenediamine Sulfate.[1,8,9,a,b]

	No. of Uses		Maximum Concentration of Use (%)	
	m-Phenylenediamine (P) and m-Phenylenediamine Sulfate (S)			
Data Year	1995	2012	1995	2012
Totals	162 (P); 28 (S)	46 (P); 19 (S)	3 (P); 3 (S)	0.01-0.2 (P); 1 (S)
Duration of use				
Leave-on	NR	NR	NR	NR
Rinse-off	162 (P); 28 (S)	46 (P); 19 (S)	3 (P); 3 (S)	0.01-0.2 (P); 1 (S)
Diluted for (bath) use	NR	NR	NR	NR
Exposure type				
Eye area	NR	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR
Incidental inhalation—sprays	NR	NR	NR	NR
Incidental inhalation—powders	NR	NR	NR	NR
Dermal contact	NR	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR
Hair—noncoloring	NR	NR	NR	NR
Hair—coloring	162 (P); 28 (S)	46 (P); 19 (S)	3 (P); 3 (S)	0.01-0.2 (P); 1 (S)
Nail	NR	NR	NR	NR
Mucous membrane	NR	NR	NR	NR
Baby products	NR	NR	NR	NR

Abbreviation: NR, not reported.
[a]Totals = rinse-off + leave-on product uses.
[b]Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

Conclusion

In the 1997 safety assessment of m-phenylenediamine and m-phenylenediamine sulfate, the Cosmetic Ingredient Review Expert Panel stated that these ingredients are safe for use in hair dyes at concentrations up to 10%.[1]

The Expert Panel reviewed newly available studies since that assessment along with updated frequency and concentration of use information.[2-29] The Expert Panel determined to not reopen this safety assessment and confirmed the original conclusion of m-phenylenediamine and m-phenylenediamine sulfate.

Discussion

The Expert Panel reviewed mostly genotoxicity data and, also, limited skin sensitization and cross-sensitization data. The Panel noted that, according to the European Union Cosmetics Directive, m-phenylenediamine and its salts are among the substances that must not form part of the composition of cosmetic products marketed in the European Union. The Personal Care Products Council explained that this is a natural consequence of an industry decision to not support the safety of m-phenylenediamine and m-phenylenediamine sulfate as hair dye ingredients in Europe. The Panel acknowledged that the 10% concentration limit is higher than the maximum use concentration recently provided by the

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cosmetics industry, from 0.01% to 0.2% for m-phenylenediamine and 1% for m-phenylenediamine sulfate. However, the Expert Panel noted that the 10% limit was based on skin irritation and sensitization test data and does not need to be changed.

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Dibutyl, Dimethyl, and Diethyl Phthalate and Butyl Benzyl Phthalate

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Keywords
phthalates, safety, cosmetics

Conclusion

In a 1985 safety assessment of dibutyl, diethyl, and dimethyl phthalate, the Cosmetic Ingredient Review Expert Panel stated that these ingredients are safe for use in cosmetics in the present practice of use and concentration.[1] Subsequently, in 2005, the Panel conducted an extensive rereview of the newly available studies since that assessment, confirmed the decision, and determined to not reopen that report.[2] In 1992, butyl benzyl phthalate was found safe in the present practice of use and concentration.[3] The Panel reviewed studies performed since that assessment as well as updated the use and concentration data in 2007 and confirmed that conclusion.[4] In 2012, the Panel reviewed 3 new studies on phthalates published in 2012 and confirmed that dibutyl, dimethyl, and diethyl phthalate and butyl benzyl phthalate are safe in cosmetics in the present practices of use and concentration. The Panel did not reopen the safety assessment.

Discussion

The Panel reviewed new studies that focused on the potential for endocrine disruption/reproductive and developmental toxicity on dibutyl, dimethyl, and diethyl phthalate and butyl benzyl phthalate. One study of children aged 5 to 9, who were part of a Manhattan-Bronx cohort, revealed detectable, although varied, levels of phthalates in the urine of all 244 study participants.[5] Higher levels of both diethyl phthalate and butyl benzyl phthalate were associated with airway inflammation.

Two studies addressed diabetes and phthalates. In 1 study, there were 1,015 men and women 70 years of age from Uppsala, Sweden.[6] One sample per participant was collected from 2001 to 2004 and analyzed 5 to 8 years later. In this study, blood levels for dimethyl phthalate, diethyl phthalate, diisobutyl phthalate, and diethylhexyl phthalate were measured and correlated with measures of insulin resistance and poor insulin secretion in nondiabetic participants.

In the second study, urinary concentrations of phthalate metabolites measured by the Centers for Disease Control and Prevention and self-reported diabetes in 2,350 women aged 20 to <80 participating in the National Health and Nutrition Examination Survey (NHANES) (2001-2008) were used.[7] The odds ratio for diabetes in women with higher levels of n-butyl phthalate, isobutyl phthalate, benzyl phthalate, 3-carboxypropyl phthalate, and the sum of diethylhexyl phthalate metabolites was greater than the odds ratio for women with the lowest concentrations of these phthalates.

The Panel noted that all of these studies identified associations between phthalate metabolites and either diabetes or airway inflammation. Such studies did not suggest a causal link between phthalates and any adverse outcome. The possibility that phthalate metabolites may impact peroxisome proliferation pathways was suggested in the diabetes studies, but that mechanism is not established as a mode of action. The Panel agreed that that there is a need for further study of the reported association between phthalates exposures and diabetes and to investigate possible causal links.

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Polyvinyl Alcohol

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Keywords
polyvinyl alcohol, safety, cosmetics

Table 1. Historical and Current Use and Concentration of Use Data for Polyvinyl Alcohol.[1,11,12]

	No. of uses		Maximum concentration of use (%)	
	Polyvinyl alcohol			
Data year	1998	2014	1998	2014
Totals[a]	37	212	2-≤25[b]	0.0035-15[c]
Duration of use				
Leave-on	23	186	2-3	0.1-15[c]
Rinse-off	14	25	3-10	0.0035-14
Diluted for (bath) use	NR	1	NR	NR
Exposure type				
Eye area	7	103	3	0.1-5.5
Incidental ingestion	NR	NR	NR	1
Incidental inhalation—spray?[d,e]	4	57	NR	1.6-3
Reported spray[f]	NR	NR	NR	NR
Incidental inhalation—Powder?[e,g]	3	55	NR	0.1
Reported powder[h]	NR	NR	NR	NR
Dermal contact	23	139	2-10	0.0035-15[c]
Deodorant (underarm)—spray?[d]	NR	3	NR	NR
Reported spray[f]	NR	NR	NR	NR
Reported as not spray[f]	NR	NR	NR	NR
Hair—noncoloring	1	3	NR	1-3
Hair coloring	NR	NR	NR	NR
Nail	8	1	NR	0.18
Mucous membrane	NR	1	NR	0.0035-1
Baby products	NR	NR	NR	NR

Abbreviation: NR, not reported.
[a]Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[b]Use concentrations not well detailed in 1998, a general maximum use concentration was reported to be ≤25% for all product uses. Specific use concentration data were provided for a few specific product categories.
[c]Fifteen percent reported in other skin care preparations, specifically a pull-off skin strip.
[d]It is possible these products *may* be sprays, but it is not specified whether the reported uses are sprays.
[e]Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.
[f]Use in a spray product has been reported in response to a survey conducted by the Council.
[g]It is possible these products *may* be powders, but it is not specified whether the reported uses are powders.
[h]Use in a powder product has been reported in response to a survey conducted by the Council.

Conclusion

In the 1998 safety assessment of polyvinyl alcohol, the Cosmetic Ingredient Review Expert Panel concluded that this ingredient was safe as used in cosmetic products.[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 reaffirmed the original conclusion that polyvinyl alcohol is safe as a cosmetic ingredient in the practices of use and concentration as given in Table 1 and did not reopen the safety assessment.

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Discussion

Polyvinyl alcohol is listed in the *International Cosmetic Ingredient Dictionary and Handbook* as a cosmetic ingredient and is described to function as a binder, film former, and viscosity-increasing agent in cosmetic products.[2]

Polyvinyl alcohol was reported to be used in eye makeup and skin care products.[11] The US Food and Drug Administration in 2014 reported that there were 212 total cosmetic uses, which is an increase from 37 uses reported in 1998. The maximum use concentration in 1998 was reported to be ≤25%.[1] A survey of use concentrations conducted by the Personal Care Products Council in 2014 reported maximum concentration of use ranges of 0.0035% to 15%, with the 15% reported to be used in a pull-off skin strip.[12]

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Polyvinyl Acetate

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Keywords
polyvinyl acetate, safety, cosmetics

Table 1. Historic and Current Uses and Concentrations of Polyvinyl Acetate.[1,6,10]

	Number of uses		Maximum concentrations of use, %	
	Polyvinyl acetate			
Data year	1996	2011	1996	2011
Totals[a]	7[c]	50	<25[c]	0.4-47
Duration of use[b]				
Leave-on	[c]	49	[c]	0.4-47
Rinse-off	[c]	1	[c]	11
Diluted for (bath) use	NR	NR		NR
Exposure type				
Eye area	7	49	[c]	2-47
Incidental ingestion	NR	NR	[c]	NR
Incidental inhalation—sprays	NR	NR	[c]	NR
Incidental inhalation—powders	NR	NR	[c]	NR
Dermal contact	[c]	7	[c]	0.4-15
Deodorant (underarm)	NR	NR	[c]	NR
Hair—noncoloring	NR	NR	[c]	NR
Hair-coloring	NR	NR	[c]	NR
Nail	NR	NR	[c]	NR
Mucous membrane	NR	NR	[c]	11
Baby products	NR	NR	[c]	NR

Abbreviation: NR, not reported.
[a]Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum of total uses.
[b]Totals = rinse-off + leave-on product uses.
[c]Breakdown is not available.

Conclusion

In the1996 amended safety assessment of polyvinyl acetate, the Cosmetic Ingredient Review Expert Panel stated that this ingredient is safe as a cosmetic ingredient in the present practices of use.[1] The Expert Panel reviewed newly available studies since that assessment along with updated frequency and concentration of use information.[2-11] The Expert Panel confirmed that polyvinyl acetate is safe in the present practices of use and concentration given in Table 1 and did not reopen this safety assessment.

Discussion

Polyvinyl acetate was used in 7 products in 1996, based on voluntary reports provided to the US Food and Drug Administration (FDA) by industry, at concentrations <25%.[1] Data provided to FDA in 2011 indicated that polyvinyl acetate was being used in 50 products.[6] Current use concentration data from a cosmetics industry survey indicated that the ingredient was being used in cosmetics at concentrations ranging from 0.4% to 47%.[10] Although concentration of use for polyvinyl acetate had increased since the original safety assessment, the 1996 safety assessment detailed a human repeat insult patch study in which polyvinyl acetate was tested at a concentration of 50% with no allergic or irritation responses.[1]

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PVP (Polyvinylpyrrolidone)

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Keywords
polyvinylpyrrolidone, safety, cosmetics, PVP

Conclusion

In the 1998 safety assessment of polyvinylpyrrolidone (PVP), the Cosmetic Ingredient Review (CIR) Expert Panel (Panel) concluded that this ingredient was safe as used in cosmetic products.[1] The Panel reviewed newly available studies since that assessment, along with updated information regarding types and concentration of use.[2-26] The Panel confirmed that PVP is safe as a cosmetic ingredient in the practices of use and concentration as given in Table 1 and did not reopen the safety assessment.

Discussion

Polyvinylpyrrolidone was reported to have use in a total of 395 products at concentrations from 0.15% up to 35%. The US Food and Drug Administration (FDA) in 2013 reported that there were 799 total cosmetic uses.[6] An industry survey[20,21] of current use concentrations found use concentrations between 0.0005% and 12%. Table 1 presents the available use and concentration of use data.

Polyvinylpyrrolidone-iodine, a complex of PVP and iodine,[8] is listed in the *International Cosmetic Ingredient Dictionary and Handbook* as a cosmetic ingredient. The Panel acknowledged that data on this ingredient were incorporated in the 1998 safety assessment on PVP because of the similarities in chemical properties and structure to PVP. Although PVP-iodine could be added to the PVP safety assessment, the Panel stated that it is an approved drug used as an active ingredient in such antiseptics as Betadine and would be reviewed under the jurisdiction of FDA. The Panel determined to not add PVP-iodine to this safety assessment. There are currently no reported uses of PVP-iodine in cosmetics.

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Table 1. Historical and Current Use and Concentration of Use Data for PVP.[1,6,20,21]

	Number of uses		Max conc. of use, %	
	PVP			
Data year	1998	2013	1998	2013
Totals[a]	395	799	0.15-35	0.0005-12
Duration of use				
Leave-on	283	675	0.15-35	0.002-12
Rinse-off	112	123	0.5-2	0.0005-10.5
Diluted for (Bath) use	NR	1	NR	NR
Exposure type				
Eye area	129	222	2-10	0.05-12
Incidental ingestion	2	35	0.5-7.5	0.1-10.5
Incidental inhalation—spray	23	22	0.15-5	0.002-5[b]
Incidental inhalation—powder	NR	NR	NR	NR
Dermal contact	87	186	1-35	0.0005-12
Deodorant (underarm)	NR	NR	NR	0.5
Hair—noncoloring	205	423	0.15-5	0.0005-10.5
Hair-coloring	5	7	NR	1.6-3.3
Nail	NR	1	NR	0.3-5
Mucous membrane	7	37	0.5-7.5	0.1-10.5
Baby products	1	1	0.5	NR

Abbreviations: NR, not reported; PVP, polyvinylpyrrolidone.
[a]Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[b]0.1% to 3.5% reported in aerosol hair sprays; 0.02% to 5% reported in pump hair sprays; 3% reported in an aerosol hair tonic, dressing, or other hair grooming aid; 0.5% to 3% reported in a pump hair tonic, dressing, or other hair grooming aid; 0.42% reported in a body spray.

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Quaternium-15

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Keywords
safety, cosmetics, quaternium-15

Conclusion

In a 2010 amended safety assessment of quaternium-15, the Cosmetic Ingredient Review Expert Panel stated that this ingredient is safe as a cosmetic ingredient in the practices of use in this safety assessment at concentrations not to exceed 0.2%.[1] The conclusion also stated that quaternium-15 is not a formaldehyde releaser. The Expert Panel reviewed newly available studies on quaternium-15 since that assessment.[2-10] While acknowledging the release of formaldehyde from quaternium-15, the Expert Panel confirmed that the ingredient is safe in the present practices of use and concentration and did not reopen this safety assessment.

Discussion

The Expert Panel reviewed new data on quaternium-15 because they were concerned about the evidence that indicated a potential release of formaldehyde. Because of improved detection methodology, published reports indicate that quaternium-15 is a formaldehyde releaser.[2-10]

The Panel noted that because the use of quaternium-15 was restricted to 0.2% in cosmetic products, the amount of formaldehyde that could be released from a formulation with this amount of quaternium-15 would be 0.003% to 0.005% (300 and 500 ppm, respectively), which is well below the amount of formaldehyde currently allowed in a cosmetic formulation (0.2%).

The Expert Panel recognizes concerns about the potential release of formaldehyde with the use of quaternium-15 in aerosolized products, such as hair spray. However, at the current limit of quaternium-15 used in cosmetic formulation, the amount of formaldehyde which could be released in an aerosol is sufficiently low as to not present a safety concern.

Declaration of Conflicting Interests

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Retinol and Retinyl Palmitate

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Keywords
safety, cosmetics, retinol, retinyl palmitate

Table 1. Historic and Current Uses and Concentrations.[1,17,18,a]

	No. of uses		Maximum concentration of use (%)	
	Retinyl palmitate and retinol			
Data year	1981	2013	1981	2013
Totals	131 (R) 101 (P)	188 (R) 2161 (P)	0.1-5 (R) 0.1-5 (P)	0.0005-1 (R) 0.0000002-1.97 (P)
Duration of use				
Leave-on	107 (R) 93 (P)	173 (R) 1763 (P)	0.1-5 (R) 0.1-5 (P)	0.0005-1 (R) 0.0001-1.97 (P)
Rinse-off	25 (R) 6 (P)	11 (R) 383 (P)	0.1-1 (R) 0.1-1 (P)	0.0005-0.1 (R) 0.00001-1 (P)
Diluted for (bath) use	NR (R) 2 (P)	4 (R) 15 (P)	NR (R) 0.1 (P)	NR (R) 0.0000001 (P)
Exposure type				
Eye area	1 (R) 4 (P)	18 (R) 182 (P)	0.1 (R) 1 (P)	0.0005-0.1 (R) 0.01-0.5 (P)
Incidental ingestion	5 (R) 14 (P)	12 (R) 232 (P)	NR (R) 1 (P)	0.15 (R) 0.006-0.28 (P)
Incidental inhalation—sprays	1 (R) 1 (P)	NR (R) 85 (P)	0.1 (R) 1 (P)	NR (R) 0.0006-0.18 (P)
Incidental inhalation—powders	2 (R) 1 (P)	1 (R) 53 (P)	1 (R) 0.1 (P)	NR (R) 0.01-1 (P)
Dermal contact	70 (R) 81 (P)	169 (R) 1609 (P)	5 (R) 0.1-5 (P)	0.0005-1 (R) 0.0000002-1.97 (P)
Deodorant (underarm)	NR	1 (P)	NR	NR
Hair—noncoloring	15 (R) 4 (P)	3 (R) 264 (P)	0.1-1 (R) 0.1-1 (P)	0.1 (R) 0.0001-0.5 (P)
Hair—coloring	NR	NR (R) 6 (P)	NR	NR (R) 0.0011-0.02 (P)
Nail	2 (R) 2 (P)	4 (R) 32 (P)	0.1 (R) 0.1 (P)	0.01 (R) 0.01-0.1 (P)
Mucous membrane	6 (R) 16 (P)	22 (R) 351 (P)	NR (R) 0.1-1 (P)	0.15 (R) 0.0000002-0.28 (P)
Baby products	1 (R)	1 (R) 4 (P)	1 (R)	NR

Abbreviations: NR, not reported; (P), retinyl palmitate; (R), retinol; totals = rinse-off + leave-on product uses.
[a]Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

Conclusion

In a 1987 safety assessment of retinyl palmitate and retinol, the Cosmetic Ingredient Review Expert Panel stated that these ingredients are safe as cosmetic ingredients in the present practices of use and concentration.[1] The Panel reviewed newly available studies since that assessment along with updated information regarding types and concentration of use[2-152] and did not reopen this safety assessment (Table 1). The Expert Panel confirmed that retinyl palmitate and retinol are safe as cosmetic ingredients in the present practices of use and concentration and recommended monitoring the progress of a new, ongoing National Toxicology Program (NTP) photococarcinogenesis study on retinyl palmitate and retinoic acid.

Discussion

The Panel thoroughly reviewed a 2012 NTP photococarcinogenicity study on retinyl palmitate and retinoic acid, including an expert panel's review of the study findings. The Panel noted the methodological flaws and, on that basis, determined that the findings could not be properly interpreted to suggest additional risks associated with these ingredients. A second NTP photococarcinogenesis study to address flaws in the original study may be considered when the new study is completed.

New toxicity data on retinol and retinyl palmitate and data on retinoic acid, retinyl acetate, and retinyl propionate that became available since the final safety assessment was issued were reviewed. The Panel recommended that data on residual levels of retinyl palmitate and retinol that remain in the

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epidermis following ingredient application in the presence of UV light be included when the second NTP study data are reviewed and that retinoic acid be removed from the report because it is a US Food and Drug Administration–approved drug.

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