# Safety Assessment of Chloroxylenol as Used in Cosmetics

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|---|---|
| Status: | Re-Review for Panel Consideration |
| Release Date: | September 1, 2022 |
| Panel Meeting Date: | September 26 – 27, 2022 |

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Priya Cherian, Senior Scientific Analyst/Writer, CIR.


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**Memorandum**

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Cherian, Senior Scientific Analyst/Writer, CIR
Date: September 1, 2022
Subject: Re-Review of the Safety Assessment of Chloroxylenol

The Expert Panel for Cosmetic Ingredient Safety (Panel) first published a review of the safety of Chloroxylenol in 1985 (identified as *originalreport_Chloroxylenol_092022* in the pdf), with the conclusion that this ingredient is safe in the present practices of use, as described in the safety assessment. This conclusion was re-affirmed, as published in 2006 (*rereview2006_Chloroxylenol_092022*).

Because it has been at least 15 years since the previous re-review was published, in accord with Cosmetic Ingredient Review (CIR) Procedures, the Panel should consider whether the safety assessment of Chloroxylenol should be re-opened. An exhaustive search of the world's literature was performed for studies dated 2000 forward. An historical overview, comparison of original and new use data, the search strategy used, and a synopsis of notable new data are enclosed herein (*newdata_Chloroxylenol_092022)*.

New studies were found for several toxicological endpoints (acute dermal, inhalation, and oral toxicity, subchronic and chronic dermal toxicity, DART, genotoxicity, carcinogenicity, dermal irritation, dermal sensitization, and ocular irritation). Of note, are a positive mutagenicity assay and a positive mouse local lymph node assay. In addition, several case reports were found reporting hypersensitization and/or hyper- and depigmentation following exposure to Chloroxylenol.

Also included for your review is a table of current and historical use data (*usetable_Chloroxylenol_092022).* The frequency of Chloroxylenol has slightly increased from 43 to 51 total uses, and the maximum concentration of use has remained the same at 0.5%.

If upon review of the new studies and updated use data the Panel determines that a re-review is warranted, a Draft Amended Report will be presented at an upcoming meeting.

# Re-Review - Chloroxylenol - History and New Data

(Priya Cherian – September 2022 meeting)

| Ingredient (1) | Citation | Conclusion | Use - New Data | Results | Use - Existing Data | Results | Notes |
|---|---|---|---|---|---|---|---|
| **Chloroxylenol** | JACT 4(5):147-169, 1985<br><br>IJT 25(Suppl. 2) :1-89,2006 | safe as used<br><br>not re-opened | frequency of use (2022)<br>conc of use (2022) | 51<br>≤ 0.5% | frequency of use (2002)<br>conc of use (2003) | 43<br>≤ 0.5% | slight increase in frequency of use decreased; no changes in concentration of use |

| NOTABLE NEW DATA | | | |
|---|---|---|---|
| **Publication** | **Study Type** | **Results – Brief Overview** | **Different from Existing Data?** |
| *https://ec.europa.eu/growth/tools-databases/cosing/index.cfm?fuseaction=search.simple* | European Union legislation – CosIng | Chloroxylenol is listed in annex VI of directive 76/768/EEC on Cosmetic Products – maximum concentration in ready for use preparation is 0.5% | EU restrictions not reported in previous report |
| *U.S. Environmental Protection Agency (EPA). 1994. Reregistration Eligibility Decision (RED). Chloroxylenol. EPA 738-R-94-032. September.* | acute dermal toxicity | rats; $LD_{50}$ > 2000 g/kg; no details provided | no |
| *https://echa.europa.eu/da/registration-dossier/-/registered-dossier/26222* | acute dermal toxicity | New Zealand white rabbits (5/sex); Chloroxylenol moistened with physiological saline (2000 mg/kg) applied to shaved skin under occlusive conditions; 24 h exposure; $LD_{50}$ > 2000 mg/kg | acute dermal toxicity data was not provided in previous report |
| *https://echa.europa.eu/da/registration-dossier/-/registered-dossier/26222* | acute oral toxicity | OECD TG 423; Sprague Dawley rats (3/sex); crystalline Chloroxylenol (2000 mg/kg bw) given in arachis oil via gavage; $LD_{50} \geq$ 2000 mg/kg bw | no |
| *U.S. Environmental Protection Agency (EPA). 1994. Reregistration Eligibility Decision (RED). Chloroxylenol. EPA 738-R-94-032. September.* | acute oral toxicity | rats; $LD_{50}$ > 5000 mg/kg; no details provided | higher acute oral $LD_{50}$ than what is currently presented in report |
| *https://echa.europa.eu/da/registration-dossier/-/registered-dossier/26222* | acute inhalation toxicity | Sprague-Dawley rats (5/sex); micronized Chloroxylenol; nose-only, single 4-h exposure; observed for 15 d following exposure; total exposure of 6.29 mg/l; $LC_{50}$ > 6.29 mg/l | acute inhalation toxicity data was not provided in previous report |
| *Yost LJ, Rodricks JD, Turnbull D, DeLeo PC, Nash JF, Quiñones-Rivera A, Carlson PA. Human health risk assessment of chloroxylenol in liquid hand soap and dishwashing soap used by consumers and health-care professionals. Regul Toxicol Pharmacol. 2016 Oct;80:116-24* | subchronic dermal toxicity | CLR:CD-1 (ICB) BR mice (10/sex/group); dermal exposure to 0, 15, 30, and 50% Chloroxylenol in 10 µl acetone (0, 250, 500 and 1000 mg/kg bw/d); no other details on study provided; very slight erythema and edema observed at 350 and 500 mg/kg bw/d dose levels; thickening and scabbing of skin at 1000 mg/kg bw/d dose level | dermal subchronic toxicity studies were not provided in original report |
| *Yost LJ, Rodricks JD, Turnbull D, DeLeo PC, Nash JF, Quiñones-Rivera A, Carlson PA. Human health risk assessment of chloroxylenol in liquid hand soap and dishwashing soap used by consumers and health-care professionals. Regul Toxicol Pharmacol. 2016 Oct;80:116-24* | chronic dermal toxicity | female SlcDddY mice (50/group); 18-mo exposure period; Chloroxylenol applied in 0.025 ml ethanol at 1% and 10%, twice weeks to 1.5 $cm^2$ of dorsal skin; control animals treated with olive oil; no treatment related effects | no dermal chronic toxicity data was provided in the original report |
| *https://echa.europa.eu/da/registration-dossier/-/registered-dossier/26222* | DART | EPA OPP 83-4; powder Chloroxylenol in corn oil (100, 500, and 1000 mg/kg/d) given to Sprague-Dawley female rats (25/group) via gavage during gestation days 6-15; NOAEL for maternal toxicity = 100 mg/kg/d; NOAEL for fetal toxicity and teratogenicity = 1000 mg/kg/d | no DART data was provided in the original report |

| NOTABLE NEW DATA | | | |
|---|---|---|---|
| **Publication** | **Study Type** | **Results – Brief Overview** | **Different from Existing Data?** |
| *El-Naggar DA, El-Zalabany LMA, Shahin DA, Attia AM, El-Mosallamy SA. Testicular Toxicity of Chloroxylenol in Rats: Biochemical, Pathological and Flow Cytometric Study. J Exp Pharmacol. 2022 Jul 13;14:213-220.* | DART | male Sprague-Dawley rats (8-24/group) evaluated for testicular and hormonal toxicity; orally treated with Chloroxylenol in corn oil (100, 200, or 500 mg/kg/d) for 8 wk; treatment with Chloroxylenol resulted in a significant, dose-dependent reduction in testosterone an estradiol levels with marked histopathological alterations affecting testicular tissues | no DART data was provided in the original report |
| *U.S. Environmental Protection Agency (EPA). 1994. Reregistration Eligibility Decision (RED). Chloroxylenol. EPA 738-R-94-032. September.* | genotoxicity – in vitro | unscheduled DNA synthesis in primary rat hepatocytes; non-genotoxic; no details provided | no |
| *https://echa.europa.eu/da/registration-dossier/-/registered-dossier/26222* | genotoxicity – in vitro | OECD TG 473; mammalian chromosome aberration assay; crystalline Chloroxylenol in ethanol (up to 1600 µg.ml) evaluated in human lymphoblastoid cells (TK6) with and without metabolic activation (1 or 2% S9); dose-related, statistically significant increase in cells with aberrations in presence of 2% S9; no clastogenicity observed in presence of 1% metabolic activation | yes; no mutagenicity was observed in an Ames assay in previous report |
| *U.S. Environmental Protection Agency (EPA). 1994. Reregistration Eligibility Decision (RED). Chloroxylenol. EPA 738-R-94-032. September.* | genotoxicity –in vivo | mouse micronucleus assay; non-genotoxic; no details provided | no |
| *Yost LJ, Rodricks JD, Turnbull D, DeLeo PC, Nash JF, Quiñones-Rivera A, Carlson PA. Human health risk assessment of chloroxylenol in liquid hand soap and dishwashing soap used by consumers and health-care professionals. Regul Toxicol Pharmacol. 2016 Oct;80:116-24* | carcinogenicity – dermal | female SlcDddY mice (50/group); 18-mo exposure period; Chloroxylenol applied in 0.025 ml ethanol at 1% and 10%, twice weekly to 1.5 $cm^2$ of dorsal skin; control animals treated with olive oil | no carcinogenicity data was provided in the original report |
| *https://echa.europa.eu/da/registration-dossier/-/registered-dossier/26222* | dermal irritation - animal | OECD TG 404; OECD TG 430; New Zealand white rabbits (n = 6); 0.5 g of Chloroxylenol powder in physiological saline placed on skin; semi-occlusive conditions; 72 h exposure; primary irritation index of 0.3; no corrosion observed; no irritation persisted 72 h post-application | no |
| *https://echa.europa.eu/da/registration-dossier/-/registered-dossier/26222* | skin sensitization – animal | OECD TG 476; mouse local lymph node assay; up to 200 µg/ml Chloroxylenol; test material was shown to be mutagenic to L5178Y cells; classified to have significant skin sensitization potential | yes; skin sensitization was not observed in assays provided in previous report |
| *https://echa.europa.eu/da/registration-dossier/-/registered-dossier/26222* | skin sensitization – animal | EPA test guideline 81-6; Hartley albino guinea pigs (5-10/sex); Chloroxylenol powder (2 cc/site) moistened with 0.9% saline, in a vehicle of acetone; occlusive conditions; 3 total exposures in a 3-wk period; 14-d after last exposure, challenge patch applied; no sensitization | no |
| *Marquardt C, Matuschek E, Bölke E, Gerber PA, Peiper M, V Seydlitz-Kurzbach J, Buhren BA, van Griensven M, Budach W, Hassan M, Kukova G, Mota R, Höfer D, Orth K, Fleischmann W. Evaluation of the tissue toxicity of antiseptics by the hen's egg test on the chorioallantoic membrane (HETCAM). Eur J Med Res. 2010 May 18;15(5):204-9.* | ocular irritation – in vitro | HET-CAM assay; 0.35% Chloroxylenol and 0.8% denatured alcohol; severe irritation | no in vitro ocular irritation assays were provided in the original report |

| NOTABLE NEW DATA | | | |
|---|---|---|---|
| **Publication** | **Study Type** | **Results – Brief Overview** | **Different from Existing Data?** |
| *https://echa.europa.eu/da/registration-dossier/-/registered-dossier/26222* | ocular irritation – animal | OECD TG 405; New Zealand white rabbits (n = 6); 0.1 g powder Chloroxylenol; 24 h exposure; observed for 21 d post-exposure; total irritation scores ranged from 61 to 83/110; test material classified as Toxicity Category 1 | no |
| *U.S. Environmental Protection Agency (EPA). 1994. Reregistration Eligibility Decision (RED). Chloroxylenol. EPA 738-R-94-032. September.* | ocular irritation – animal | rabbits; mild to severe corneal opacity in unwashed eyes, irritation persisted for 14 d; washed eyes had mild to moderate erythema, edema, and discharge | no |
| *Mehrtens SH, Reckling C. Contact urticaria with anaphylaxis caused by chlorocresol, chloroxylenol, and thiourea. Contact Dermatitis. 2019 May;80(5):311-313.* | case report | 41-yr-old woman with 6-mo history of recurrent urticarial, occasionally associated with angioedema after using cleaning products or certain personal care products; patch test positive to chlorocresol, Chloroxylenol, and thiourea; anaphylaxis upon patch testing | no hypersensitivity case reports were provided in the original report |
| *Berthelot C, Zirwas MJ. Allergic contact dermatitis to chloroxylenol. Dermatitis. 2006 Sep;17(3):156-9.* | case report | 39-yr-old restaurant manager with hand dermatitis present for 9 yr; positive patch test reactions Chloroxylenol | no hypersensitivity case reports were provided in the original report |
| *Berthelot C, Zirwas MJ. Allergic contact dermatitis to chloroxylenol. Dermatitis. 2006 Sep;17(3):156-9.* | case report | 50-year-old female with chronic hand dermatitis that worsened for 8 mo. prior; previous work history in janitorial field; positive patch test reaction to Chloroxylenol | no hypersensitivity case reports were provided in the original report |
| *Verma GK, Mahajan VK, Shanker V, Tegta GR, Jindal N, Minhas S. Contact depigmentation following irritant contact dermatitis to chloroxylenol (Dettol). Indian J Dermatol Venereol Leprol. 2011 Sep-Oct;77(5):612-4.* | case report | 65-yr-old male with mild erythema, and scaling, hyperpigmented, and depigmented patches on face, ears, neck, hands, and feet following the use of undiluted Chloroxylenol; patch testing with 1% Chloroxylenol yielded negative results; patch testing with undiluted Chloroxylenol yielded positive results and depigmentation | no hypersensitivity or depigmentation case reports were provided in the original report |
| *Malakar S, Panda S. Post-inflammatory depigmentation following allergic contact dermatitis to chloroxylenol. Br J Dermatol. 2001 Jun;144(6):1275-6.* | case report | 21-yr-old car mechanic reported itching, stinging, burning, erythema, hyperpigmentation, blackening, and depigmentation after taking a bath in an antiseptic containing Chloroxylenol; positive patch test results to 1% Chloroxylenol | no hypersensitivity or depigmentation case reports were provided in the original report |
| *DeKoven, Joel G et al. "North American Contact Dermatitis Group Patch Test Results: 2015–2016." Dermatitis 29.6 (2018): 297–309. Web.* | clinical-multicenter study | positive patch test in 0.6% of 5594 patients with atopic dermatitis from 2015-2016 | no |
| *Jong CT, Statham BN, Green CM, King CM, Gawkrodger DJ, Sansom JE, English JS, Wilkinson SM, Ormerod AD, Chowdhury MM. Contact sensitivity to preservatives in the UK, 2004-2005: results of multicentre study. Contact Dermatitis. 2007 Sep;57(3):165-8.* | clinical-multicenter study | positive patch test in 0.2% of 6958 patients with contact dermatitis from 2004-2005 | no |
| *Nakama A, Funasaka K, Shimizu M. Evaluation of estrogenic activity of organic biocides using ER-binding and YES assay. Food Chem Toxicol. 2007 Sep;45(9):1558-64* | estrogenic activity – in vitro | Chloroxylenol used in estrogen receptor binding assay and yeast estrogen screen assay; with and without metabolic activation; positive results in ER-binding assay; pseudo positive results in YES assay, with and without metabolic activation | no estrogen activity data were provided in original report |

DART = developmental and reproductive toxicity; EPA = Environmental Protection Agency; EU = European Union; ER = estrogen binding; HET-CAM = hen's egg test chorioallantoic membrane; $LC_{50}$ = median lethal concentration; $LD_{50}$ = median lethal dose; OECD TG = Organisation for Economic Co-operation and Development Test Guidelines; YES = yeast estrogen screen

Search (from 2000 on)
PubMed
((("chloroxylenol") OR (88-04-0 [CAS No.])) OR (1321-23-9 [CAS No.])) AND (("2000"[Date - Publication] : "3000"[Date - Publication])) – 121 hits; 27 useful hits

**Current and historical frequency and concentration of use of Chloroxylenol according to duration and exposure**

| | *# of Uses* | | *Max Conc of Use (%)* | |
|---|---|---|---|---|
| | **2022[1]** | **2002[2]** | **2022[3]** | **2003[2]** |
| **Totals*** | **51** | **43** | **0.1 – 0.5** | **0.1 – 5** |
| ***Duration of Use*** | | | | |
| *Leave-On* | *40* | *20* | *0.1 – 0.3* | *0.1 – 0.2* |
| *Rinse-Off* | *10* | *23* | *0.2 – 0.5* | *0.4 – 0.5* |
| *Diluted for (Bath) Use* | *1* | *NR* | *NR* | *NR* |
| ***Exposure Type*** | | | | |
| Eye Area | 8 | 1 | NR | NR |
| Incidental Ingestion | NR | NR | NR | 0.4 |
| Incidental Inhalation-Spray | 20[a]; 5[b] | 7[a]; 2[b] | NR | 0.1[s]; 0.2[b] |
| Incidental Inhalation-Powder | 5[b] | 2[b] | 0.1 – 0.3[c] | 0.2[b]; 0.1[c] |
| Dermal Contact | 40 | 31 | 0.1 – 0.5 | 0.1 – 0.5 |
| Deodorant (underarm) | NR | 1[a] | NR | NR |
| Hair - Non-Coloring | 4 | 12 | 0.3 | NR |
| Hair-Coloring | NR | NR | NR | NR |
| Nail | NR | NR | NR | NR |
| Mucous Membrane | 4 | 12 | 0.2 – 0.5 | 0.4 |
| Baby Products | NR | NR | 0.1 – 0.3 | 0.1 |

*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.
[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[b] 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
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.
NR – not reported

## References

1. US Food and Drug Administration (FDA) Center for Food Safety & Applied Nutrition (CFSAN). 2022. Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients. (Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 4, 2022; received January 11, 2022). College Park, MD.

2. Andersen F.A. (ed). Chloroxylenol. *Int J Toxicol.* 2006;25:21-24.

3. Personal Care Products Council. 2022. Concentration of Use by FDA Product Category: Chloroxylenol. (Unpublished data submitted to Personal Care Products Council on July 7, 2022.)

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# Final Report on the Safety Assessment of Chloroxylenol

**Chloroxylenol is used in cosmetic products as an antimicrobial at concentrations up to 5.0 percent. It is absorbed through the human skin and gastrointestinal tract. Following oral ingestion by a human of a product formulated with Chloroxylenol, both free and conjugated Chloroxylenol were detected in the urine.**

**Chloroxylenol at 100 percent concentration was a moderate irritant to the rabbit eye, whereas a 0.1 percent aqueous Chloroxylenol solution was a nonirritant to rabbit skin.**

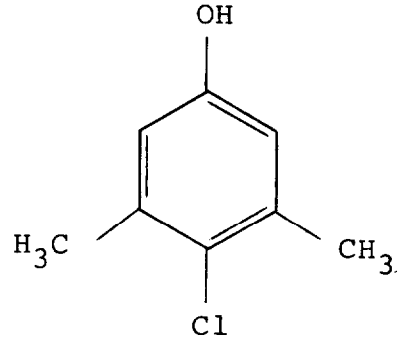
**Chloroxylenol was nonmutagenic in the *Salmonella* mutagenesis assay, both with and without metabolic activation. No carcinogenicity or adequate teratogenicity studies have been reported.**

**In clinical studies, formulations containing up to 1.0 percent Chloroxylenol were nonsensitizing and essentially nonirritating to the skin. The incidence of skin sensitization among 1752 dermatitis patients exposed to 1.0 percent Chloroxylenol was less than 1.0 percent. On the basis of the available information included in this report, it is concluded that Chloroxylenol is safe as a cosmetic ingredient in the present practices of use.**

## CHEMISTRY

### Structure and Properties

Chloroxylenol (CAS No. 88-04-0) is the substituted phenol (4-chloro-3,5-dimethylphenol) that conforms to the formula:[1]



This compound is also known as p-chloro-m-xylenol, parachlorometaxylenol, 4-chloro-3,5-xylenol, 2-chloro-m-xylenol, 2-chloro-5-hydroxy-m-xylene, 2-chloro-5-hydroxy-1,3-dimethylbenzene, 4-chloro-1-hydroxy-3,5-dimethylbenzene, PCMX, Husept Extra Ottasept Extra, RBA 777, and Nipacide MX.[1-6]

Chloroxylenol (molecular weight: 156.6) is a white to off-white crystalline powder having a faint, characteristic phenolic odor. It is soluble in alcohol, ether, benzene, terpenes, fixed oils, and solutions of alkali hydroxides; it is sparingly soluble in water. The boiling point is 246°C and the melting point range, 112 to 117.5°C.[4,5,7-10] Chloroxylenol is volatile with steam and may be isolated by steam distillation.[5,11] When dried, it contains not less than 95 percent $C_8H_9C_{10}$.[12]

The ultraviolet light absorption of Chloroxylenol in ethanol, in 0.1 N hydrochloric acid, and in 0.1 N sodium hydroxide occurs at maxima of 282 nm, 279 nm, and 296 nm respectively.[13] The phenol coefficient as determined by the Rideal-Walker method varies from 40 to 80.[14] A phenol coefficient range of 35.7 to 38 has also been reported.[15] The compound does not readily form insoluble salts[16] and reacts with oxidizing agents.[7]

The binding of Chloroxylenol and various other phenols to human serum, serum albumin and various serum globulins was investigated by Judis.[17] Chloroxylenol had a higher percent binding to whole serum and most of the serum proteins than phenol.

Studies have been conducted on Chloroxylenol to determine its chromatographic behavior, its stability in plastic and glass containers, its corrosive action on various metals, and its spectral and electrocapillary properties.[18-23] Quantitative data on Chloroxylenol, such as dissociation constants, thermodynamic acidity constants, and molecular orbital indices, also have been published.[24-26]

## Method of Manufacture and Impurities

Chloroxylenol may be prepared by treating 3,5-dimethylphenol with $Cl_2$ or $SO_2Cl_2$.[5,7,22,27] The finished product is sold in the form of white or cream colored crystals.[28]

Reported impurities of Chloroxylenol include isomers of 3,5-dimethylphenol, 2,4-dichloro-3,5-dimethylphenol, water (0.5 percent maximum), and varnish makers' and painters' (VMP) naphtha (trace).[7] The supplier of this chemical has indicated that chlorinated dibenzodioxanes do not occur as contaminants or impurities of Chloroxylenol (pharmaceutical grade).[6,29] Upon ignition, Chloroxylenol consists of not more than 0.1 percent nonvolatile sulfates.[8,30]

## Analytical Methods

Reported analytical methods for the identification and determination of Chloroxylenol include potentiometric titration,[31] colorimetric techniques,[12] differential and ultraviolet spectrophotometry,[32-34] partition chromatography,[34,35] gas and gas-liquid chromatography,[36-38] high pressure liquid chromatography,[39] and thin-layer chromatography.[35,40-44]

## Interactions with Cosmetic Ingredients

A number of studies have investigated the interaction of Chloroxylenol with various cosmetic ingredients. Breuninger and Goettsch[45] used an equilibrium dialysis technique to investigate the binding of Chloroxylenol with polyvinylpyrrolidone (PVP), polyethylene glycol 6000 (PEG 6000), polysorbate 80, methylcellulose, and methyl vinyl ether/maleic anhydride (PVM/MA Copolymer). Polysorbate 80 interacted with Chloroxylenol to the greatest degree, whereas binding of the phenolic compound to PVP was relatively small. Possible mechanisms of interaction between Chloroxylenol and the 5 macromolecules were considered.

Ray et al.[46] found that the antimicrobial activity of Chloroxylenol against *Bacillus subtilis, Pseudomonas aeruginosa,* and *Aspergillus niger* was diminished when the phenolic compound was allowed to complex with PEG 6000, methylcellulose, and polysorbate 80. The reduction was considered a direct result of "the molecular interaction with the nonionic macromolecule," thereby diminishing the availability of Chloroxylenol to exert its antimicrobial activity. A loss in the antibacterial activity of Chloroxylenol in the presence of polyethylene glycols and polyethylene glycol stearates also has been reported.[47,48]

McCarthy[20] reported the degradation of Chloroxylenol by PVP in aqueous solutions containing 2.0 percent of the polymer. He suggested that such degradation was ". . . unlikely to be a problem, since the decay losses are similar to those found previously for aqueous solutions of. . . non-phenolic preservatives. . . ."

Interactions of Chloroxylenol with the nonionic surfactants, polyethylene glycol and polyethylene glycol stearate, have been studied.[47-49] Ullmann et al.[47] reported that a hydrogen bond can be formed from the ether oxygen of polyethylene glycol stearate and the hydroxyl group of a phenol. The lipophilic phenol derivative resulting from this complex formation was solubilized by the micellar surfactant. Thoma et al.[49] found that such reactions between phenols and micellar surfactants were reversible.

Mulley and Metcalf[50] reported that the solubility of Chloroxylenol in aqueous solution was augmented by the presence of the nonionic surface-active agent cetomacrogol (ceteth-20). They attributed the increased solubility of this phenolic compound to its incorporation into micelles. Mitchell[51] reported that incorporation of Chloroxylenol into micelles in aqueous solutions of cetomacrogol reduces the compound's bactericidal activity. The binding and solubility of Chloroxylenol with cetomacrogol and sodium lauryl sulfate have also been studied by others.[52-58]

Gucklhorn[28] reported that phenolic materials were incompatible with anionic surfactants, particularly soaps. When gradually increasing amounts of the anionic material were added to a solution containing the phenolic compound, the antimicrobial power was initially increased. However, as the concentration of the anionic surfactant was increased beyond its critical micelle concentration, a progressive inactivation of the phenolic compound took place. Thus, below the critical micelle concentration of the anionic, its presence facilitated the adsorption of the phenolic compound at the cytoplasmic membrane of the microbial cell wall by a reduction in surface tension. Above this anionic surfactant concentration, however, it solubilized the phenol compound and rendered it unavailable to exert its antimicrobial activity. The author also cited several studies

demonstrating inactivation of phenolic compounds by nonionic substances. He noted that phenolics may be inactivated due to hydrogen bonding to the nonionic, thus preventing access of the former to the cytoplasmic membrane of the bacterial cell wall. It was suggested that phenolic compounds are inadequate preservatives "for any of the usual nonionic formulations used in cosmetics," unless the nonionic content is very low (<0.5 percent). Gucklhorn[28] concluded that phenolic compounds are "not very useful for preserving cosmetic products, and should not be used in nonionic or anionic emulsions."

## USE

### Noncosmetic Use

Because of its antibacterial and antifungal properties, Chloroxylenol is widely used as a disinfectant and preservative and as a topical antiseptic for skin and mucous membranes.[3,5,11,59,60] It has been used in liquid powder bases and cleansers for the treatment of acne[61,62] and in dandruff shampoos to prevent secondary infections of scalp sebborrhea.[63]

Federal regulations permit the use of Chloroxylenol as a preservative in adhesive coatings and components that have incidental contact with food. However, no specific concentration limitations for such indirect food additive use have been established.[64] The compound has been suggested for use as an antifungal and antibacterial agent for cheese, paper board, cloth, "solid poster-colors," carbon black, and concrete.[65] A Chloroxylenol/dichlorobenzene combination has been suggested for use as an insecticide and as a mothproofing agent for cloth.[66,67] Chloroxylenol has also been suggested for use as a reagent for standardizing solutions in contact with medical equipment.[68]

An FDA Advisory Review Panel on Over-the-Counter (OTC) drugs determined that there are insufficient data to assess the safety and efficacy of Chloroxylenol as an active ingredient in "antimicrobial soaps," "health-care personnel hand washes," "patient pre-operative skin preparations," "skin antiseptics," "skin wound cleansers," "skin wound protectants," and "surgical hand scrubs."[69-71] The OTC Panel on antimicrobial drug products concluded that Chloroxylenol is safe for topical antifungal use at 0.5 to 3.75 percent concentration but that there are insufficient data available to permit final classification of its effectiveness for use in the treatment of athlete's foot, tinea cruis, and ringworm.[72] It was also concluded that there are insufficient safety and efficacy data to permit use of the compound as an active ingredient in ingrown toenail relief products.[73] Other advisory review panels on OTC drugs have proposed that Chloroxylenol is safe but ineffective in acne or dandruff products at 2 percent concentration.[71] The OTC Advisory Review Panel on topical analgesic, antirheumatic, otic, burn, and sunburn prevention and treatment drug products classified Chloroxylenol as an "inactive ingredient or pharmaceutical necessity" in external analgesics. When used in concentrations at the concentration of or above the minimum effective dose (this dose was not specified), they considered Chloroxylenol an active ingredient.[74]

## Cosmetic Use

Chloroxylenol is used in cosmetic formulations as an antimicrobial compound.[7,75,76] The kinds of products in which this ingredient is used, as well as the concentrations at which it occurs in these products, are presented in Table 1. The information in the table was obtained from FDA's computerized information file containing product formulation data submitted to FDA in 1981 by companies participating in the voluntary cosmetic registration program.[77,78] Chloroxylenol was reported as an ingredient in a total of 93 cosmetic formulations at concentra-

**TABLE 1.** Product Formulation Data[77]

| Product Category | Total No. of Formulations in Category | Total No. Containing Ingredient | No. of Product Formulations Within Each Concentration Range (%)* | | |
|---|---|---|---|---|---|
| | | | >1–5 | >0.1–1 | ≤0.1 |
| Eye makeup remover | 81 | 2 | – | 1 | 1 |
| Fragrance powders (dusting and talcum, excluding aftershave talc) | 483 | 2 | 1 | 1 | – |
| Hair conditioners | 478 | 8 | – | 5 | 3 |
| Hair straighteners | 64 | 4 | – | 4 | – |
| Hair shampoos (noncoloring) | 909 | 29 | 2 | 25 | 2 |
| Tonics, dressings, and other hair grooming aids | 290 | 3 | – | 3 | – |
| Wave sets | 180 | 1 | – | – | 1 |
| Other hair preparations (noncoloring) | 177 | 3 | 2 | – | 1 |
| Hair dyes and colors (all types requiring caution statement and patch test) | 811 | 1 | – | – | 1 |
| Hair rinses (coloring) | 76 | 2 | – | 2 | – |
| Blushers (all types) | 819 | 1 | – | 1 | – |
| Makeup fixatives | 22 | 1 | – | 1 | – |
| Nail basecoats and undercoats | 44 | 1 | – | – | 1 |
| Cuticle softeners | 32 | 1 | – | 1 | – |
| Bath soaps and detergents | 148 | 2 | – | 2 | – |
| Deodorants (underarm) | 239 | 1 | – | 1 | – |
| Feminine hygiene deodorants | 21 | 1 | – | – | 1 |
| Other personal cleanliness products | 227 | 8 | – | 7 | 1 |
| Skin cleansing preparations (cold creams, lotions, liquids, and pads) | 680 | 5 | – | 4 | 1 |
| Depilatories | 32 | 1 | – | 1 | – |
| Face, body, and hand skin care preparations (excluding shaving preparations) | 832 | 7 | – | 2 | 5 |
| Paste masks (mud packs) | 171 | 2 | – | – | 2 |
| Skin fresheners | 260 | 1 | – | – | 1 |
| Other skin care preparations | 349 | 5 | – | 2 | 3 |
| Suntan gels, creams, and liquids | 164 | 1 | – | 1 | – |
| 1981 TOTALS | | 93 | 5 | 64 | 24 |

*Preset product categories and concentration ranges in accordance with federal filing regulations 21 CFR 720.4.

tions of ≤0.1 percent (24 products), >0.1 to 1 percent (64 products), and >1 to 5 percent (5 products). The greatest reported use of the antimicrobial was in non-coloring hair shampoos (29 products).[77]

Voluntary filing of product formulation data with FDA by cosmetic manufacturers and formulators conforms to the prescribed format of preset concentration ranges and product categories as described in Title 21 part 720.4 of the Code of Federal Regulations.[78] Since certain cosmetic ingredients are supplied by the manufacturer at less than 100 percent concentration, the concentration reported by the cosmetic formulator may not necessarily reflect the true, effective concentration found in the finished product. The effective concentration in such a case would be a fraction of that reported to the FDA. The fact that data are only submitted within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lower end of a concentration range is considered the same as one entered at the higher end of that range, thus introducing the possibility of a 2- to 10-fold error in the assumed ingredient concentration.

Cosmetic products containing Chloroxylenol are applied to or come in contact with eyes, skin, nails, hair, and vaginal mucosa (Table 1). Many of these products can be applied as infrequently as once a week to as often as several times a day. These formulations also have the potential to remain in contact with body surfaces for several days and to be applied repeatedly over the course of several years.

Gucklhorn[28] has noted that Chloroxylenol must be solubilized to incorporate "sufficiently effective amounts" in cosmetics, a process that usually inhibits its antimicrobial effectiveness. The author suggests that this problem accounts for the limited use of this compound in cosmetic formulations.

## BIOLOGY

### Antimicrobial Properties

The antimicrobial properties of Chloroxylenol and disinfectant products containing this preservative have been widely studied. Chloroxylenol is purported to be more potent than phenol in terms of antimicrobial activity,[5] and it is reported to retain this activity even at low pH.[16] However, several studies indicate that certain nonionic and anionic materials used in cosmetics, as well as various proteins, can reduce or inactivate these antimicrobial properties.[28,46-48,51,79] It has been suggested that the lethal action of phenolic disinfectants is due to damage of permeability mechanisms, the repair of which is prevented by concomitant inhibition of energy-yielding metabolic reactions.[80]

The use of Chloroxylenol as an antiseptic was first reported by Colebrook and Maxted,[81] who reported that this agent was lethal to hemolytic streptococci and *Escherichia coli*. A number of investigators have since reported that *Pseudomonas* sp. are resistant to Chloroxylenol and Chloroxylenol-based disinfectants.[82-88] However, Hare et al.[89] found that the compound was rapidly lethal to a number of gram-negative and gram-positive bacteria in a dried state, including 14 strains of *P aeruginosa*. Hatch and Cooper[90] reported that acceptable re-

sults for a Chloroxylenol-based disinfectant could be obtained against *P. aeruginosa* if the sequestering agent, sodium hexametaphosphate, was incorporated into such products. Gray and Wilkinson[91] demonstrated that the chelating agent ethylenediaminetetra acetic acid (EDTA) potentiated the activity of Chloroxylenol against *P. aeruginosa*, a finding subsequently confirmed by others.[92-96]

Ray et al.[46] found that the minimum inhibitory concentration (MIC) of Chloroxylenol in nutrient media for *P. aeruginosa, B. subtilis,* and *A. niger* was 0.10, 0.004, and 0.01 percent, respectively. Jacobs et al.[97] reported that the MIC of Chloroxylenol in anionic and nonionic oil-water emulsions was 0.38 to ">0.5" percent for *Candida albicans, P. aeruginosa, Streptococcus faecalis,* and *A. niger.* The MIC in this particular study was defined as the concentration that killed all organisms within 3 days. Meyer-Rohn[98] reported that Chloroxylenol in nutrient media was effective in retarding the growth of the following microbes at the concentrations specified: *Staphylococcus aureus* (500 mcg/ml), *Staphylococcus epidermidis* (500 mcg/ml), *S. faecalis* (500 mcg/ml), *Pseudomonas pyocyanea* (500 mcg/ml), *Proteus vulgaris* (500 mcg/ml), *Bacillus cereus* (250 mcg/ml), *E. coli* (125 mcg/ml), and *Corynebacterium paradiphtheriae* (125 mcg/ml). The preservative was also reported by Gucklhorn[28] to be microbiostatic at the following concentrations: *Bacillus mycoides* (50 ppm), *S. aureus* (100 ppm), *P. aeruginosa* (200 ppm), *P. expansum* (50 ppm), and *A. niger* (50 ppm).

Concentrations of 500, 1000, and 1500 ppm Chloroxylenol added to larval diets of moths were found inadequate in preventing the growth of the mold, *A. niger.*[99] Chloroxylenol (100 μg) was also "relatively ineffective" against the scalp yeast *Pityrosporum ovale,* causing only a 9 percent inhibition of growth as compared to the growth of nontreated control organisms.[100]

Three percent Chloroxylenol in alcohol was microbicidal to *S. aureus* and *P. ovale* and fungistatic to *Microsporum lanosum.*[101] Alcoholic solutions containing 1.44 percent (w/v) Chloroxylenol were effective in controlling *S. aureus, S. faecalis, P. aeruginosa,* and *E. coli* on artificially contaminated skin.[16] Alcoholic solutions containing 1.2 percent (w/v) Chloroxylenol together with 1.65 percent (w/v) EDTA were also found effective in controlling the growth of *S. aureus* and various gram-negative bacilli isolated from the skin flora of hospital staff.[102]

Koda et al.[103] tested the antibacterial activity of Chloroxylenol against 6 strains of *Corynebacterium acnes* in the presence and absence of synthetic sebum using an agar plate diffusion method. The test compound was solubilized in a vehicle consisting of approximately 10 percent acetone, 40 percent alcohol, and 50 percent water. Chloroxylenol concentrations of 0.03 to 1.0 percent (w/v) were bacteriostatic to all 6 strains in both the presence and absence of 0.25 percent (w/v) sebum, although the zones of inhibition were decreased somewhat in the presence of the sebum. The effect of the vehicle on the bacteria was not reported.

Menczel and Mel[104] conducted stability and bacteriostatic tests to determine the "optimal" concentration of Chloroxylenol in cold creams. A concentration of 2 percent was bacteriostatically effective and yet within the range of concentrations compatible with the stability of the cold cream formulations tested.

Yambor and Boyk[60] found that protein hair conditioners can be preserved adequately "for over one year" against contaminating *Aspergillus* fungi and *Pseudomonas* bacteria by the incorporation of 0.25 percent Chloroxylenol. The com-

pound at a concentration of 0.075 percent by total weight (or 0.5 percent by weight of solids) was effective in preserving aqueous starch solutions against unspecified fungal and bacterial growth. The same authors also reported that concentrations of 0.1 percent Chloroxylenol in silicone emulsion inhibited the growth of *Micrococcus pyrogenes, E. coli* and *A. niger,* and 0.1, 0.5, and 1.0 percent of the preservative in cosmetic gel products inhibited the growth of *S. aureus, E. coli, P. aeruginosa,* and *C. albicans.*

In tests designed to evaluate the efficacy of Chloroxylenol in various cosmetic products, Cowen[105] found that little correlation existed between the antimicrobial activity of Chloroxylenol under actual use conditions and its activity in the laboratory. Data relating to the effects of this agent on *P. aeruginosa, S. aureus,* and *Staphylococcus albus* were presented to support this claim.

Jacobs et al.[97,106] studied the influence of pH, emulsifier, and accelerated aging on preservative requirements of oil-water emulsions. They recommended Chloroxylenol for use in anionic-alkaline lotions at a concentration of 0.38 percent, the MIC to microbes, but they did not recommend it for use in nonionic (acidic or alkaline) or anionic-acidic lotions where the MIC was >0.5 percent. It was suggested that adequate preservation was more easily accomplished by Chloroxylenol in anionic systems.

Mitchell[51] reported that the bactericidal activity of Chloroxylenol in water and in solutions of the nonionic surfactant cetomacrogol was related to the degree of saturation of the system, expressed as the saturation ratio, which was defined as the amount of Chloroxylenol present to its solubility. A saturated solution of Chloroxylenol in water had the same bactericidal activity as saturated surfactant solutions containing up to 100 times as much Chloroxylenol. It was suggested that the bactericidal activity depended on the amount of Chloroxylenol in the true aqueous phase and not on the total amount of bactericidal agent present. It also was observed that the bactericidal activity of undersaturated solutions of Chloroxylenol in cetomacrogol fell as the saturation ratio was reduced. This reduction was attributed to the incorporation of Chloroxylenol into micelles, where the preservative was unavailable to exert its bactericidal activity.

### Absorption, Metabolism, Excretion, and Storage

Roberts et al.[107] examined the permeability of human abdominal skin samples to various phenolic compounds in vitro. The permeability coefficient (Kp)* for Chloroxylenol was $9.84 \times 10^4$ cm/minutes. No "threshold concentration for damage" (the aqueous concentration at which the Kp value begins to increase) was observed for any concentration of Chloroxylenol "up to saturation." The authors noted that the phenolic compound produced little or no damage to the skin.

Zondek[108] reported that Chloroxylenol was "particularly well absorbed" by the mucous membranes, the vulva, and the palms of the hands. He noted that absorption was "somewhat less" on the arms, legs, abdomen, and back.

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*Kp, permeability coefficient = DK/h = Js/Cv, where D is the diffusion coefficient of the solute in the stratum corneum of thickness h, K is the solute's stratum corneum/vehicle partition coefficient, Js is the molecular flux of the solute, and Cv is the concentration of the solute in the vehicle.

Joubert et al.[109] described a case of intentional ingestion of 350 ml of Dettol disinfectant* containing 16.8 g of Chloroxylenol. "Large amounts" of conjugated Chloroxylenol and "minute amounts" of free Chloroxylenol were found in the urine, whereas phenolic compounds presumed to be metabolites and conjugation products were present in the blood. It was the authors' opinion that the body has very efficient mechanisms for rapidly metabolizing and eliminating Chloroxylenol.

The studies by Reckitt and Colman[111] described partially the metabolism and excretion of Chloroxylenol. The C-14 compound was synthesized and was administered to rats as a Dettol formulation, which omitted burnt sugar, the coloring agent. Both studies on the excretion of radioactivity and the metabolism of Chloroxylenol were performed. The extent of metabolism was assessed with thin-layer chromatographic techniques, and identification of metabolites was performed by enzymatic digestion and GC-mass spectrometry. The specially formulated Dettol was diluted 1:4, and the solution was administered at doses of 4 ml/kg and 1 ml/kg to the rats and dogs, respectively. Dosing was by either the oral route or applied with a lint dressing to the abraded skin. Chloroxylenol was well absorbed after oral dosing, and virtually all of the radioactivity was excreted in the urine by 24 hours in both dogs and rats. Absorption from the skin was approximately half of that observed with oral administration. Only small amounts of radioactivity were found in the feces. Peak blood concentrations of Chloroxylenol were achieved in 30 minutes after oral administration and in 2 hours after application to the skin of the rat. In dogs, peak blood concentrations of Chloroxylenol were observed 45 to 60 minutes after oral dosing and 60 minutes after application to the skin. After oral dosing, the plasma half-life of total radioactivity was assessed at approximately 60 minutes in both species. Both species metabolized Chloroxylenol extensively. All plasma radioactivity was accounted for as polar metabolites, primarily conjugates. Tissue distribution studies indicated that the highest concentration of radioactivity was found in the kidney, whereas relatively little was observed in the brain. Hydrolysis of conjugates under acidic conditions was complete. After hydrolysis, the major radioactive species was Chloroxylenol, and the minor metabolite was a hydroxylated derivative of Chloroxylenol. Both sulfate and glucuronide conjugates were found, and the glucuronide predominated in a ratio of approximately 6:1.

In a companion study[112] a number of metabolic studies were performed using the Gunn rat. The Wistar rat was used for control studies. Results indicated the presence of glucuronide conjugates in the urine despite the deficiency of glucuronyl transferase in this strain of rat. The authors noted that this probably was related to the impurity of the enzymes used in the digestion of the conjugates, suggesting the possibility that the major conjugate was the sulfate. Sulfate conjugates were found as were nonconjugated, polar metabolites.

It appears that Chloroxylenol in the rat and the dog is metabolized extensively. Both the hydroxylated metabolite and Chloroxylenol have sulfate and glucuronide conjugates. Data presently available do not allow a clear delineation

*Dettol is composed of isopropyl alcohol, essential pine oils, castor oil, soap, burnt sugar, and 4.8 percent Chloroxylenol as the active ingredient.[110]

of which metabolic pathway is the predominant one except that conjugation predominates over hydroxylation. Distribution of radioactivity indicated a large accumulation in the kidney, the primary route of excretion, but no effort has been made to identify which metabolite accumulated in the organ. Furthermore, the organ responsible for metabolism has not been identified.

## Animal Toxicology

### Acute Oral Toxicity

The acute oral toxicity of Chloroxylenol was examined in fasted, Dublin strain male albino rats. The preservative was administered by stomach tube as a 25.0 percent (w/v) suspension in corn oil. Six groups of 5 rats were given the test suspension in doses of either 1.00, 1.47, 2.15, 3.16, 4.64, or 6.81 g/kg, respectively. With the exception of diarrhea noted in a few rats on the day of dosing, animals in the 1.00 and 1.47 g/kg groups had essentially normal behavior and appearance throughout the 14-day observation period. No deaths occurred within these 2 treatment groups. In the 2.15 and 3.16 g/kg groups, diarrhea, mild depression, and emaciation were observed. In addition, 2 rats of the 3.16 g/kg group developed transient salivation. Normal behavior and appearance were observed in these 2 dosage groups (2.15 and 3.16 g/kg) from Day 2 through 14 postdosing. Rats exposed to the 4.64 g/kg dose developed diarrhea, depression, depressed righting, placement, pain, and corneal reflexes, ataxia, excessive salivation, piloerection, and emaciation. Prior to death, 1 rat of this group (4.64 g/kg) was comatose. Four of five rats did not survive the 4.64 g/kg dose. Within 15 to 30 minutes following administration of the Chloroxylenol-corn oil suspension, 3 rats of the 6.81 g/kg group developed depression, depressed righting and placement reflexes, ataxia, excessive salivation, and a comatose condition. In addition, the 2 other rats of this group also developed depressed respiration, absent pain reflex, and diarrhea during the day of dosing. All 5 rats of the 6.81 g/kg group were dead within 24 hours. The average body weight gains over the 14-day observation period for rats of each dosage group were within normal limits for rats of the age, sex, and strain used in the study. In rats that died, congested lungs, gastrointestinal irritation, darkened livers, congested adrenals, and hemorrhagic kidneys were detected. Surviving animals at termination had no significant gross lesions. The acute oral $LD_{50}$ of the 25 percent Chloroxylenol-corn oil suspension was 3.83 g/kg.[113]

### Intraperitoneal Toxicity

Aqueous suspensions containing 2.0 to 4.0 g of Chloroxylenol were given by intraperitoneal injection to 5 groups of mice (6 animals per group). Animals were examined daily for 5 days. The $LD_{50}$ was 2.88 g per 25 g mouse. The investigator concluded that Chloroxylenol possesses "low toxicity" when injected intraperitoneally.[14]

### Eye Irritation

A modification of the procedure described by Draize[114] was used to evaluate the eye-irritating potential of 100 percent Chloroxylenol. A single 0.1 ml* application of the test material was made into the conjunctival sac of 1 eye of each of 6 albino rabbits; the untreated eye of each animal served as a control. (It was not specified whether or not the treated eyes received a water rinse following instillation of the test substance.) Average conjunctival irritation scores were 28, 31, 30, 28, and 34 on Days 1, 2, 3, 4, and 7, respectively (maximum score, 110). Chloroxylenol was considered a "moderate" eye irritant under conditions of this test.[116]

Thirty percent (w/v) Chloroxylenol in propylene glycol also was tested for eye irritation. The test material was instilled in a single 0.1 ml dose into 1 eye of each of 6 albino rabbits; the untreated eye served as a control. Ocular responses were graded according to the procedures described by Draize.[114] Twenty-four hours following treatment, marked corneal opacity, iritis, and conjunctivitis were observed. Eye irritation was characterized by erythema, edema, and discharge. In the majority of rabbits, these signs did not subside appreciably over the 72-hour observation period.[117]

When tested by the same procedures, a foot powder containing 0.25 percent Chloroxylenol was a "mild" ocular irritant. Average irritation scores were 2, 6, and 0 on Days 1, 2, and 3, respectively.[118]

### Primary Skin Irritation

The skin-irritating effect of a 1.0 percent Chloroxylenol aqueous solution was evaluated on 9 albino rabbits. One tenth of a milliliter of the test material was applied to a filter disc and held in contact with the intact, shaved skin of each animal under occlusion. The disc was removed after 24 hours, and the test sites were graded for irritation and edema; no skin reactions were observed.[119]

A foot powder containing 0.25 percent Chloroxylenol was also tested for primary skin irritation on 9 albino rabbits. A 50 percent aqueous solution of the product (0.1 ml) was applied to the shaved skin by "gentle induction" under nonocclusive conditions (actual Chloroxylenol concentration: 0.25 percent $\times$ 0.5 = 0.125 percent). Application of the test material was made daily for 4 consecutive days. Test sites were graded for irritation 24 hours after each application. A PII of 1.0 on a scale of 0 to 4 was determined from the results taken from the day when the greatest irritation response was noted. The investigator considered the aqueous solution containing 0.125 percent Chloroxylenol a slight skin irritant.[120]

### Acute Percutaneous Toxicity

In a series of immersion studies, rats were exposed to Dettol solution or Dettol base (containing no Chloroxylenol) for 30 minutes. The $LD_{50}$ for the Dettol solution and Dettol base were 3.0 and 11.0 percent v/v, respectively.[112]

*For solids in flake, granule, or powder form, the amount that has a volume of 0.1 ml is used whenever this volume weighs less than 100 mg. In such a case, the weight of 0.1 ml test dose is recorded.[115]

### Subchronic and Chronic Toxicity

In a subchronic oral study, 4 groups of 30 CFY rats were orally given Dettol as an emulsion in water 7 days a week for 13 weeks. Each group of 30 rats (15 males and 15 females per group) received 1 of the following Dettol doses: 0, 0.5 ml/kg per day of a 5 percent emulsion, 5.0 ml/kg per day of a 25 percent emulsion, or 5.0 ml/kg per day of a 50 percent emulsion. No deaths were attributed to Dettol administration during the 13-week study. However, 1 rat in the middose group (25 percent emulsion) and 2 rats in the high-dose group (50 percent emulsion) died as a result of intubation errors or "possible" intubation errors. In rats of the high-dose group (50 percent emulsion), salivation was observed for approximately 5 minutes following dosing. During Week 12 of treatment, males of the high-dose group excreted a greater volume of dilute urine than did the control animals. This was likely a result of the marginally higher water intake of this treatment group. Lower packed cell volume and hemoglobin values and higher total leukocyte and lymphocyte counts were found among male rats of the high-dose group. Also observed in the high-dose group were increased absolute and relative liver weights in both sexes and increased kidney weights among males. In the middose group (25 percent emulsion), salivation was observed in a few rats following dosing, and increased absolute and relative liver and kidney weights were observed among males. The male rats of the low-dose group (5 percent emulsion) had increased absolute and relative liver weights. No other differences between control and treatment groups were observed with respect to organ weights, ocular lesions, urinalysis, or various hematological and blood chemistry parameters. No macroscopic or histopathological changes were seen in any treated animals that could be attributed to Dettol administration. Tissues and organs examined microscopically included lungs, liver, thyroid, heart, pancreas, kidneys, adrenals, aorta, brain, colon, cecum, duodenum, eye, femur, ileum, jejunum, lymph nodes, mammary gland, esophagus, ovaries, pancreas, pituitary, prostate, salivary glands, sciatic nerve, seminal vesicles, skeletal muscle, skin, spleen, stomach, testes, thymus, tongue, trachea, urinary bladder, and uterus.[121]

Dettol was administered by gavage to 24 beagle dogs in a second subchronic study. For 13 weeks, 4 groups of 6 dogs received doses of Dettol of either 0, 0.5 ml/kg per day of a 25 percent solution, 5 ml/kg per day of a 25 percent solution, or 5 ml/kg per day of a 50 percent solution. No deaths were observed during the study. However, vomiting was sometimes noted in both 5 ml/kg per day groups. No adverse effects were noted with respect to body weight, water consumption, or food consumption. No ocular changes and no hematological or biochemical changes were observed. Hematological and biochemical parameters measured included erythrocyte sedimentation rate, packed cell volume, hemoglobin concentration, red cell count, reticulocyte count, mean corpuscular hemoglobin concentration, total and differential white cell count, platelet count, prothrombin index, plasma urea, plasma glucose, total serum proteins, serum alkaline phosphatase, serum glutamic-pyruvic transaminase, and serum bilirubin. In the urinalysis conducted after 4, 8, and 12 weeks, a positive reaction for total reducing substances was found in all animals receiving 5.0 ml/kg per day of the 25 and 50 percent solution. This was probably due to the presence of a metabolite. No gross lesions were observed at necropsy. Although most individual organ weights

were within normal ranges, the mean liver weights for dosed groups were significantly greater than the control values; the differences were dose related. Organs weighed included brain, pituitary, heart, lungs, liver, spleen, pancreas, thymus, prostate, uterus, kidneys, thyroids, adrenals, and gonads. No lesions were observed in the aforementioned organs or in the following tissues: aorta, trachea, lymph nodes, gallbladder, urinary bladder, salivary gland, tongue, esophagus, stomach, duodenum, jejunum, ileum, colon, skin, mammary gland, skeletal muscle, bone marrow, peripheral nerve, eye and optic nerve, and spinal cord.[122]

A subchronic oral toxicity study was conducted using 6 pure-bred beagle dogs (3M, 3F). The animals were given Dettol by gavage in the following dose regimen: (1) 2 dogs: 2 ml/kg per day of undiluted solution for 4 weeks, (2) 2 dogs: 4 ml/kg per day of undiluted solution for 4 weeks followed by 5 ml/kg per day of a 50 percent solution for 4 weeks, and (3) 2 dogs: 8 ml/kg per day of undiluted solution "for up to 3½ weeks." Vomiting was sometimes observed up to 2 hours after dosing in all groups, with the exception of the group given 5 ml/kg per day of a 50 percent solution. Suppression of appetite and loss of weight were observed within 1 week in animals receiving 8 ml/kg per day. At necropsy, edema of the pancreas and congestion of the kidneys were found in 1 animal receiving 8 ml/kg per day. The thymus of both animals receiving 8 ml/kg per day and both the splenic and pancreatic weights of 1 of these animals were lower than normal. No abnormalities were observed in the remaining dogs.[123]

A subchronic cutaneous toxicity study was conducted with an unspecified test material containing 0.25 percent Chloroxylenol. A 2000 mg/kg dose of the test substance was applied under occlusion to the shaved skin of each of 10 (5F, 5M) albino rabbits for 6 to 8 hours. After this period, each test site was "thoroughly" rinsed with water and patted dry. This application procedure was repeated 5 days a week for 4 weeks (20 applications). Two males and two females received the test material on abraded skin. No deaths, skin irritation, or "untoward behavioral or systemic reactions" were observed. Losses in body weight were noted in 2 of 10 rabbits in the untreated control group and in 2 rabbits in the test group. Results of urine analyses (glucose, albumin, microscopic elements, pH) were comparable for both control and test groups. Exposed and control animals were also comparable with respect to hematological parameters (erythrocyte count, hemoglobin concentration, hematocrit value, total leukocyte count, differential leukocyte count) and clinical blood chemistries (blood urea nitrogen, serum alkaline phosphatase activity, serum glutamic-pyruvic transaminase activity, fasting blood glucose concentration). The skin of treated animals had no significant gross alterations; microscopic changes included acanthosis and hyperkeratosis in 2 of the treated rabbits. It was not specified if these reactions were observed in the rabbits with abraded or nonabraded skin.[124]

The systemic toxicity of Chloroxylenol in propylene glycol by percutaneous absorption was evaluated in a subchronic and chronic study using 27 albino rabbits. The animals were divided into 3 groups consisting of 9 rabbits for each study. The skin of 3 rabbits from each group was abraded; the skin of the remaining 6 rabbits was left intact. One of the three groups served as the vehicle control group. This group received propylene glycol at a dose of 1.0 ml/kg per day. One treatment group was administered 1.8 percent (w/v) Chloroxylenol in propylene

glycol at a dose of 1.0 ml/kg per day (18 mg of Chloroxylenol/kg per day), whereas the second treatment group received 18 percent Chloroxylenol in propylene glycol at a dose of 1.0 ml/kg per day (180 mg of Chloroxylenol/kg per day). The propylene glycol vehicle and Chloroxylenol in propylene glycol were applied daily to clipped, abraded skin of the back 15 times over a 3-week period and daily to clipped intact skin of the back 65 times over a 13-week period. All rabbits exposed to Chloroxylenol survived the study and had normal behavior and appearance. Rabbits in the high-dose group (180 mg/kg per day) had moderate to extreme skin irritation. Erythema, desquamation, and fissuring were observed at treated skin sites. Both the low-dose group (18 mg/kg per day) and vehicle control group had little or no skin irritation. Within each treatment group, abraded and intact skin responses were essentially the same. No differences were observed between control and treated groups with respect to growth (body weight gain), urinalysis, hematological values, and gross and microscopic examination of various organs and tissues. Urinalysis included monitoring of color/appearance, pH, specific gravity, sugar, protein, acetone, bilirubin, and occult blood. Hematological parameters measured included hemoglobin, hematocrit, total and differential leukocyte count, and red blood cell count. Organs and tissues macroscopically and/or microscopically examined included skin, heart, liver, lungs, kidney, spleen, adrenals, stomach, small and large intestines, bone marrow, urinary bladder, testes, ovaries, and uterus.[125]

## Mutagenesis

Chloroxylenol at a concentration of 0.2 to 1.0 μg/plate was nonmutagenic in the *Salmonella* mutagenesis assay, both in the presence and absence of metabolic activation. Results with positive control substances (MNNG and 9-aminoacridine) indicated that all bacterial strains tested (TA1535, TA1537, TA1538, TA1978, TA98, and TA100) were reverting properly. Results with 2-aminofluorene confirmed that the S-9 liver fraction isolated from Aroclor 1254-induced rats was active. Bacteria exposed to the solvent control (DMSO) had normal values for spontaneous revertants. There was no evidence that the liver preparation used metabolized Chloroxylenol to mutagenic derivatives. In fact, there was an indication that the liver enzymes decreased the high degree of bacterial toxicity associated with this compound. The investigators emphasized that extreme caution should be exercised in any extrapolation of these in vitro assay results to projections of in vivo activity. They noted that false positive and false negative results are known to occur with compounds of known toxicity.[126]

## Teratogenesis

Chicken eggs were dipped once or twice into a 1.0 percent antiseptic solution (Dettol) containing an unspecified amount of Chloroxylenol. The eggs were then immediately removed from the test solution. At the end of the incubation period, the embryos were removed and inspected for developmental malformations. No teratogenic effects were observed.[127] The CIR Panel believes this study is inadequate for assessing the teratogenicity of Chloroxylenol.

## Clinical Assessment of Safety

### Skin Irritation and Sensitization

Reference to the skin-irritating ability of Chloroxylenol has been made in several standard texts. Sax[4] describes the preservative as a moderate skin irritant under acute conditions, whereas Gosselin et al.[2] report that no "cutaneous irritation" results from concentrations of 5 percent Chloroxylenol. Procedures used to obtain these observations were not detailed.

A 24-hour patch test was conducted on 18 subjects to determine the skin-irritating effects of a foot powder containing 0.25 percent Chloroxylenol. An aqueous paste of the product was applied to the volar surface of the forearm or inner aspect of the upper arm of each individual. No primary skin irritation was observed.[128]

A modification of the repeated insult patch test procedure described by Draize[114] was used to evaluate the skin irritation and sensitization potential of a deodorant foot powder containing 0.25 percent Chloroxylenol. Potential test subjects were screened in order to exclude those with a history of diabetes, psoriasis, or chronic skin conditions. The test population consisted of 154 women and 42 men between the ages of 16 and 60. A 24-hour patch containing an aqueous paste of the test material was applied to the back of each of the 196 panelists every other day for 3 successive weeks (9 induction applications). A 48-hour challenge patch was applied to the original induction site and to an untreated site 2 weeks after the final induction application. No evidence of skin irritation or sensitization was observed.[129]

A repeated insult patch test was conducted on 25 subjects to assess the skin-irritating and sensitizing ability of 1.0, 0.1, and 0.01 percent Chloroxylenol in corn oil. Patches containing the 3 test materials were applied to the upper arms of each panelist on Monday, Wednesday, and Friday for 3 consecutive weeks. Similar applications were made with the corn oil vehicle control. Patches were removed 24 hours after application. Challenge applications to original and adjacent sites were made 2 weeks after the final serial application. One subject developed a single minimal erythema reaction following the seventh induction application. No other skin irritation or sensitization reactions were observed.[130]

The skin-sensitizing effects of Chloroxylenol were tested by means of the Draize method[114] on groups of 208, 66, and 110 males aged 21 to 50 years. The test population was approximately 82 percent Caucasian, 13 percent black, and 5 percent Native American/Mexican. Chloroxylenol (0.5 g) in petrolatum was applied to the upper arm and covered with an occlusive patch for 48 or 72 hours. Ten successive induction applications were made to the same site over a 3- to 5-week period. Following a 2-week nontreatment period, a challenge patch was applied for 72 hours. Challenge was always done with a nonirritant concentration of the test material. No evidence of skin sensitization was observed in the 3 test groups at the concentrations tested (Table 2).[131,132]

Calnan[133] reported that Chloroxylenol was the second highest cause of medicinal contact allergic dermatitis in the United Kingdom. Of 220 reported cases of allergic skin sensitivity to antibacterial agents (excluding antibiotics), 53 were caused by Chloroxylenol. Other case reports of skin sensitivity to Chloroxylenol or products containing the preservative have been documented.[134-138] It has

**TABLE 2.** Skin Sensitization[131,132]

| *Induction Concentration (%)* | *Challenge Concentration (%)* | *No. Sensitized* |
|---|---|---|
| 5 | 5 | 0/208 |
| 10 | 5 | 0/66 |
| 20 | 10 | 0/110 |

been suggested that individuals sensitive to Chloroxylenol may cross-react to chlorocresol, a structurally related compound used in cosmetics.[135,139] Burry et al.[140] reported that 13 subjects suspected of skin sensitivity to chlorocresol had positive patch tests to Chloroxylenol.

The North American Contact Dermatitis Group[141] reported that the incidence of skin sensitization among 1752 dermatitis patients exposed to 1 percent Chloroxylenol was less than 1.0 percent (13 reactors).

## SUMMARY

Chloroxylenol is a crystalline powder having a characteristic phenolic odor. Impurities include isomers of 3,5-dimethylphenol, 2,4-dichloro-3,5-dimethylphenol, water, and varnish makers' and painters' naphtha. One supplier reported that Chloroxylenol contains no chlorinated dibenzodioxanes. Chloroxylenol binds or complexes with a number of cosmetic materials including PVP, polyethylene glycol, polysorbate, methylcellulose, and methyl vinyl ether/maleic anhydride. In the presence of nonionic and anionic surfactants, Chloroxylenol forms micelles. Diminished antimicrobial activity may result from the interaction of Chloroxylenol with various cosmetic materials.

Noncosmetic applications of Chloroxylenol include use as a disinfectant, preservative, and topical antiseptic. Chloroxylenol is used in a number of over-the-counter drug preparations, such as antimicrobial soaps, hand washes, surgical scrubs, wound cleansers, ingrown toenail products, acne and dandruff products, tinea cruis and athlete's foot formulations, and external analgesics. In cosmetics, Chloroxylenol is used as an antimicrobial. Cosmetic firms participating in the FDA voluntary cosmetic registration program reported in 1981 that Chloroxylenol was used as an ingredient in 93 cosmetic products at concentrations of $\leq$0.1 percent (24 products), $>$0.1 to 1.0 percent (64 products), and $>$1.0 to 5.0 percent (5 products). Cosmetic products containing Chloroxylenol included eye products, fragrances, hair preparations, blushers, makeup preparations, nail products, deodorants, bath soaps, and feminine hygiene deodorants. The greatest reported use of the antimicrobial was in noncoloring hair shampoos (29 products). Cosmetic products formulated with Chloroxylenol are intentionally applied to or may incidentally come in contact with eyes, skin, nails, hair (scalp), and vaginal mucosa.

Numerous studies have been published regarding the antimicrobial activity of Chloroxylenol against yeast, fungi, and various gram-negative and gram-posi-

tive bacteria. The antimicrobial potency of Chloroxylenol is purported to be greater than that of phenol.

An early report suggested that Chloroxylenol is readily absorbed by palms of the hands, the vulva, and mucous membranes. A more recent study indicated that the compound is absorbed by human abdominal skin in vitro. Chloroxylenol may also be absorbed by the gastrointestinal tract. Following oral ingestion by a human of a product formulated with Chloroxylenol, conjugated Chloroxylenol and free Chloroxylenol were detected in the urine. Phenolic compounds presumed to be metabolites and conjugation products were also detected in the blood.

Studies with rats and dogs indicated that Chloroxylenol is metabolized extensively. Virtually all of the C-14 compound was excreted in the urine within 24 hours following oral administration. Absorption from the skin in rats and dogs was approximately half that observed after oral administration. Peak blood concentrations of C-14 Chloroxylenol were achieved in 2 hours after application to rat skin and in 1 hour after application to dog skin. All plasma radioactivity was accounted for as polar metabolites, primarily conjugates. Tissue distribution studies indicated a large accumulation of Chloroxylenol in the kidney, the primary route of excretion. The organ responsible for metabolism of Chloroxylenol in the rat and dog was not identified.

The oral $LD_{50}$ in rats of a 25 percent Chloroxylenol-corn oil suspension was 3.83 g/kg. In mice, the intraperitoneal $LD_{50}$ of Chloroxylenol was 2.88 g "per 25 gram mouse." Chloroxylenol (100 percent) was a moderate irritant to the rabbit eye, whereas a 0.1 percent aqueous Chloroxylenol solution was a nonirritant to rabbit skin.

The subchronic and chronic toxicity of Chloroxylenol and a Chloroxylenol-based product, Dettol, was assessed in rats, dogs, and rabbits. (Dettol is composed of isopropyl alcohol, essential pine oils, castor oil, soap, burnt sugar, and 4.8 percent Chloroxylenol). Rats administered a 25 or 50 percent aqueous Dettol solution in an oral dose of 5.0 ml/kg per day for 13 weeks had increased salivation, hematological changes, and increased liver and kidney weights. Dogs given a 0.5 or 5.0 ml/kg per day oral dose of a 25 or 50 percent Dettol solution sometimes vomited and had a dose-related increase in liver weight. Dogs given undiluted Dettol in an oral dose of 8 ml/kg per day of undiluted Dettol for 3½ weeks sometimes vomited and had weight loss, edema of the pancreas, congestion of the kidneys, and increased thymic, splenic, and pancreatic weights. A 2000 mg/kg dose of an unspecified product containing 0.25 percent Chloroxylenol caused acanthosis and hyperkeratosis when applied to the skin of rabbits for 4 weeks. Rabbits exposed by skin application to 180 mg of Chloroxylenol/kg per day for either 3 or 13 weeks had irritation, erythema, desquamation, and fissuring of the skin.

Chloroxylenol was nonmutagenic in the *Salmonella* mutagenesis assay, both in the presence and absence of microsomal preparations from rat liver. No carcinogenicity or adequate teratogenicity studies were reported.

In clinical studies, foot powders containing 0.25 percent Chloroxylenol and corn oil containing 1.0, 0.1, and 0.01 percent Chloroxylenol were nonsensitizing and essentially nonirritating to the skin. The preservative was also nonsensitizing to human skin when tested at challenge concentrations of 5 and 10 percent. The

North American Contact Dermatitis Group observed that the incidence of skin sensitization among 1752 dermatitis patients exposed to 1.0 percent Chloroxylenol was less than 1.0 percent (13 reactors). It was reported that individuals sensitive to Chloroxylenol may cross-react to chlorocresol, a structurally related compound used in cosmetics.

## CONCLUSION

On the basis of the information presented in this report, the CIR Expert Panel concludes that Chloroxylenol is safe as a cosmetic ingredient in the present practices of use.

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## CHOLESTEROL

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

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

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

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

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## CHLOROXYLENOL

A safety assessment of Chloroxylenol was published in 1985 with the conclusion that this ingredient was safe as a cosmetic ingredient in the practices of use at that time (Elder 1985). New studies, along with the updated information below regarding types and concentrations of use, were considered by the CIR Expert Panel. The Panel determined not to reopen this safety assessment.

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

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

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

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

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## DIISOPROPANOLAMINE, ISOPROPANOLAMINE, TRIISOPROPANOLAMINE, AND MIXED ISOPROPANOLAMINES

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

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

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

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

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

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

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

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

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