**ANNOTATED BIBLIOGRAPHY**

*TOPIC: C14 (myristic) and other short chain fatty acids (caproic, caprylic, capric, lauric) when converted to potassium salts or soap in health and beauty products: properties and potential for skin irritation*

RECENT PEER-REVIEWED RESEARCH

Bulsara, P. A., Varlashkin, P., Dickens, J., Moore, D. J., Rawlings, A. V., & Clarke, M. J. (2017). The rational design of biomimetic skin barrier lipid formulations using biophysical methods. *International Journal of Cosmetic Science*, *39*(2), 206–216.

The authors found that as chain length increased (C14 to C18 to C22) the occlusive/barrier effect of a topical preparation increased.

Prajapati, H.N., Patel, D.P., Patel, N.G., Dalrymple, D.M., & Serajuddin, A.T.M. (2011). Effect of Difference in Fatty Acid Chain Lengths of Medium- Chain Lipids on Lipid/Surfactant/Water Phase Diagrams and Drug Solubility. *Journal of Excipients & Food Chemicals*, *2*(3), 73–88.

This article deals more with solubility for drug application than with cosmetics and soaps, but this may be useful: the authors find that: “… the solubility in C12-fatty acid esters was found to be lower than in C8-fatty acid esters when the lipids were used alone. This difference in solubility due to the difference in fatty acid chain length, practically disappeared when the lipids were combined with the surfactant” (73).

Ren, Q., Deng, C., Meng, L., Chen, Y., Chen, L., Sha, X., & Fang, X. (2014). In Vitro, Ex Vivo, and In Vivo Evaluation of the Effect of Saturated Fat Acid Chain Length on the Transdermal Behavior of Ibuprofen-Loaded Microemulsions. *Journal of Pharmaceutical Sciences*, *103*(6), 1680–1691.

The authors conclude that short chain fatty acids have decreased permeability and long chain fatty acids a higher propensity to irritate skin, therefore recommending medium chain fatty acids in cosmetic product.

Songkro, S. (2009). An overview of skin penetration enhancers: penetration enhancing activity, skin irritation potential and mechanism of action. *Songklanakarin Journal of Science & Technology*, *31*(3), 299–321.

From the article: “This review presents a critical account of the most commonly used chemical penetration enhancers **(fatty acids** and surfactants), and some newer classes of chemical enhancers (terpenes, polymers, monoolein, oxazolidinones), with emphasis on their efficacy, mechanism of action, and **skin irritation** potential” (299). It cites an earlier study (Loftsson et al., 1987) that found an application of 5% oleic acid in propylene glycol caused mild irritation and an application of 20% oleic acid in PG produced severe irritation. Other cited research indicated that of several skin penetration enhancers, fatty acids were found to be the most potentially irritating (306). The author recommends human volunteer studies for safety and efficacy of fatty acids. “Nevertheless, fatty acids have previously been used as stiffening agents in several commercial cosmetics and dermatological preparations (i.e. lipsticks, creams, lotions); products that are not strictly regulated in any country” (306). Also includes a useful table of fatty acid terminology on p. 305.

Tong, P. L., & Chow, E. T. (2017). Isopropyl myristate contact allergy: could your moisturizer be the culprit? *Contact Dermatitis (01051873)*, *77*(3), 184–185.

The authors present two cases (not a study) in which isopropyl myristate is an “underappreciated allergen in atopic patients” (182). (Atopic: genetic/hereditary predisposition.) “The literature reports positive reactions in 2.1–2.3%of patients tested with the cosmetic series” (185).

Wertz, P. W. (2018). Lipids and the Permeability and Antimicrobial Barriers of the Skin. *Journal of Lipids*, 1–7.

Not interesting for cosmetics, but good to know: lauric acid (C12) and sapienic acid (C16) have antimicrobial properties. The author states: “Lauric acid was shown to be a uniquely potent antibacterial against a range of gram positive bacteria but not gram negatives [53]” (citing J.J. Kabara, R. Vrable, and M.S.F. Lie Ken Jie,“Antimicrobial lipids: Natural and synthetic fatty acids and monoglycerides,” *Lipids,* vol.12, no.9, pp.753–759, 1977).

OLDER STUDIES THAT MAY BE RELEVANT

De Haan, P., Heemskerk, A. E. J., Gerritsen, A., & De Boer, E. M. (1993). Comparison of toxicity tests on human skin and epidermoid (A431) cells using free fatty acids as test substances. *Clinical & Experimental Dermatology*, *18*(5), 428–433.

The authors evaluated skin irritancy in humans induced by free fatty acids (chain lengths: C6, C7, C9, C10, C11, C13 and C18) using laser‐Doppler flowmetry (LDF) and visual scoring (VS): “Both methods demonstrated that the toxic effect of free fatty acids determined by LDF and VS increased from C6 through C11 and decreased again for C13 and C18” (428). They found a comparable ranking to Stillman et al., in that C8, C10 an C12 free fatty acids were “significantly more irritating” than those with <8 or >14 carbon atoms (432).

Laube, S., Davies, M. G., Prais, L., & Foulds, I. S. (2002). Allergic contact dermatitis from medium-chain triglycerides in a moisturizing lotion. *Contact Dermatitis (01051873)*, *47*(3), 171-000.

The authors report two cases of patients who developed dermatitis after a reformulation of their usual cucumber face cream, which contained capric/caprylic acid. The authors suggest that the safety of MCTs be reassessed.

Stillman, M. A., Maibach, H. I., & Shalita, A. R. (1975). Relative irritancy of free fatty acids of different chain length. *Contact Dermatitis*, *1*(2), 65–69.

This article discusses fatty acid irritancy after a patch test; almost all resulted in irritancy by the tenth day, especially C8-12; response to other fatty acids (including C14) was negligible. The authors find C8-C14 and a C18 “to be most irritating”. One of many articles from the 1970s on the pathology of acne. Maibach is one of the authors of *Percutaneous Penetration Enhancers* (1995).

RELEVANT REPORTS ON SAFETY ASSESSMENTS

Final Report on the Safety Assessment of Cocoyl Sarcosine, Lauroyl Sarcosine, Myristoyl Sarcosine, Oleoyl Sarcosine, Stearoyl Sarcosine, Sodium Cocoyl Sarcosinate, Sodium Lauroyl Sarcosinate, Sodium Myristoyl Sarcosinate, Ammonium Cocoyl Sarcosinate, and Ammonium Lauroyl Sarcosinate. (2001). *International Journal of Toxicology (Taylor & Francis)*, *20*, 1–14.

Safety assessment of modified fatty acids (sarcosines). The manufacturing process forms a soap through alkaline hydrolysis. Myristoyl sarcosine used mainly in shaving products; chart of sarcosine uses (product formulation data), Table 1 on p. 6, credited to FDA 1998. Section on skin irritation begins p. 9: “Company product information from Geico Chemical Corp. (no date) stated that prolonged contact with acyl sarcosines at high concentrations could cause skin irritation, but the salts were non-irritating. No other details were available.”…“In a primary irritation study (Foo d and Drug Research Laboratories 1989; Technology Sciences Group Inc. 1994c), a formulation containing 30% aqueous Sodium Myristoyl Sarcosinate was not a primary irritant to the skin of six New Zealand white rabbits.”

Johnson, W. (1999). Amended Final Report on the Safety Assessment of Hydroxystearic Acid. *International Journal of Toxicology (Taylor & Francis)*, *18*(Suppl. I):1-10.

The above report references a 1987 report which is not available through the databases: Elder R.L., ed. 1987. Final Report on the Safety Assessment of Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid and Stearic Acid. *Journal of the American College of Toxicology*. 6: 321-401. Relevant material is quoted below:

“In clinical primary and cumulative irritation studies, Oleic, Myristic, and Stearic Acids at concentrations of 100% or 40 to 50%in mineral oil were non-irritating. Mild to intense erythema in single insult occlusive patch tests, soap chamber tests, and 21-day cumulative irritation studies were produced by cosmetic product formulations containing 2-93% Oleic, Palmitic, Myristic, or Stearic Acid and were generally not related to the fatty acid concentrations in the formulations. In clinical repeated insult patch tests, maximization tests, and prophetic patch tests with cosmetic product formulations containing Oleic, Lauric, Palmitic, and Stearic Acids at concentrations ranging from less than1 to 13%, no primary or cumulative irritation or sensitization was reported.”

*Articles were located using Academic Search Complete, Applied Science and Technology Source (EBSCO/Wilson), General Science Full Text (Wilson) and Google Scholar databases with search terms including “potassium myristate”, “myristic acid”, “short chain fatty acids”, “C14” etc., “caproic”, “caprylic”, “capric”, “lauric”, “skin”, “skin irritation”, “potassium salts”, “potassium soaps”, “dermatologic\*”, “cosmetics”, “soap”.*