

Product Name: FSS Hemp Oil Liposome PF
Code: FSS61005PF
INCI Name: Water & Phospholipids & Cannabis Sativa Flower/Leaf/Stem Extract

FSS Hemp Oil Liposome PF is manufactured by cleaning plant matter *Cannabis sativa* (Hemp) to remove unnecessary material by mechanical means only, processing (mechanical grinding/milling) of the flowers leaves & stems followed by collection of the oily fraction. The oily fraction is then dispersed with Phospholipids at a specific pH, temperature and time followed by homogenizing to form entrapped liposomes. FSS Hemp Oil Liposome PF was tested using *in vitro* dermal and ocular irritation models, including phototoxicity irritation (EpiDerm™ EPI-200-SIT). This product was found to be non-irritating in all models, including non-phototoxic for the *in vitro* dermal model.

A *Salmonella typhimurium* reverse mutation standard plate incorporation study was conducted to evaluate whether FSS Hemp Oil Liposome PF would cause mutagenic changes in the average number of revertants for histidine-dependent *Salmonella typhimurium* strains in the presence and absence of S9 metabolic activation. This study was conducted to satisfy, in part, the Genotoxicity requirement of the International Organization for Standardization: Biological Evaluation of Medical Devices, Part 3: Tests for Genotoxicity, Carcinogenicity and Reproductive Toxicity. FSS Hemp Oil Liposome PF was considered to be nonmutagenic to the *Salmonella typhimurium* tester strains under the conditions of this assay.

FSS Hemp Oil Liposome PF was also tested via the OECD TG 442C Direct Peptide Reactivity and OECD TG 442D In Vitro Skin Sensitization Assays in accordance with the EURL ECVAM and UN GHS guidelines. This product was determined to be a non-skin sensitizer in both *in chemico* and *in vitro* models.

FSS Hemp Oil Liposome PF was also assessed for ready biodegradability in an aerobic aqueous medium via the OECD 301 B Ready Biodegradability: CO₂ Evolution (Modified Sturm Test). FSS Hemp Oil Liposome PF achieved 92.1% biodegradation after 28 days of testing, indicating that the product meets method requirements for the Ready Biodegradable classifications.

The full reports for each safety study analyzing FSS Hemp Oil Liposome PF are available upon request.

Due to the restriction placed on animal testing of cosmetic raw materials, and Formulator Sample Shop's internal non-animal testing policy, this product was not tested for NOAEL. However, there is substantial amounts of published data for Phospholipids and Hemp that provides useful information to determine approximate NOAEL and demonstrate the non-cytotoxic effects of FSS Hemp Oil Liposome PF. Investigation of the following data for Phospholipids and Hemp along with US Food and Drug Administration guidelines¹ has allowed us to estimate FSS Hemp Oil Liposome PF exposure based off dosage in topical form, with an approximate NOAEL of 88 mg/kg/day (average of published NOAEL for Phospholipids and Hemp^{2,3}

At an average 2% use level in 1 oz (or 28 g) finished product per day on a person averaging a 65 kg body weight, a daily exposure of 8.62 mg/kg FSS Hemp Oil Liposome PF is expected ($28 \text{ g} \times 2\% = 0.56 \text{ g}$ or 560 mg; $560 \text{ mg} / 65 \text{ kg}$). It is expected that FSS Hemp Oil Liposome PF has an estimated average NOAEL of 88 mg/kg/day $[(\text{NOAEL Phospholipids} + \text{NOAEL Hemp})/4 \text{ or } (160 + 16)/2]$ ^{2,3}. When FSS Hemp Oil Liposome PF is used at approximately 2% in a finished formula sample, we do not expect exposure to exceed 8.62 mg/kg daily, which is well under the conservative average NOAEL estimate of 88 mg/kg/day.

In a 2009 published toxicity study on soy-derived Phospholipids, the NOAEL in rats was considered to be 1,000 mg/kg/day.² When converting from animal to human equivalent doses (i.e. from rats to humans) a general conversion factor of 0.16 can be used.⁴ Therefore the human equivalent NOAEL for Phospholipids is expected to be 160 mg/kg/day (rat NOAEL x 0.16).

In a Journal of Toxicology paper on the potential toxicity of *Cannabis sativa*, the NOAEL for hemp extract used in rats was considered to be 100 mg/kg bw/day for males and 360 mg/kg bw/day for females, or 16 mg/kg/day and 57.6 mg/kg/day human equivalents.³ The Cannabis Sativa Flower/Leaf/Stem Extract used to manufacture FSS Hemp Oil Liposome PF is rich in Cannabidiol (CBD), but is not test on every lot at this time. A Center for Drug Evaluation and Research paper concluded that the NOAEL for mice exposed to CBD was 400 mg/kg/day for males and 550 mg/kg/day for females.⁵ Which equates to approximately 64 mg/kg/day and 88 mg/kg/day in respective human equivalents.

Additionally, Phospholipids and Hemp based products are commonly used in the food and nutraceutical industries. Lecithin, a mixture of various phospholipids has been affirmed as Generally Recognized as Safe (GRAS).^{2,6,7,8} Since these materials are intentionally used in food, mixtures of them such as FSS Hemp Oil Liposome PF may be classified as GRAS according to the FDA's Federal Food, Drug and Cosmetic Act.⁷

The act states:

Any substance that is intentionally added to food is a food additive, that is subject to premarket review and approval by FDA, unless the substance is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use, or unless the use of the substance is otherwise excluded from the definition of a food additive.⁹

The Cosmetic Ingredient Review (CIR) also published a report assessing the safety of various types of plant-derived fatty acid oils, including hydrogenated soybean oil. The report concluded that all types of soybean oil forms are safe for use in cosmetic preparations.⁸ Allergic reactions to Phospholipids derived from hydrogenated soybean oil are very rare, but are possible. Those with known allergies or sensitivities to soy should avoid products containing it.¹⁰ Several, published data sets exist to support the safety of FSS Hemp Oil Liposome PF. Additionally, it is presented in an aqueous carrier, all but eliminating its risk for inhalation. Toxicological, irritation, and sensitization assays have all been performed with favorable results for each. This knowledge combined with the tested and published toxicity assays allows us to support the safety of FSS Hemp Oil Liposome PF in cosmetic applications.

It is logically concluded that of FSS Hemp Oil Liposome PF is safe in cosmetic applications at use levels of 1.00 – 10.00%. No further testing is required at this time.

1. U.S. Food and Drug Administration (FDA) – Assessing Safety When Toxicity Data are Limited. <https://pdfs.semanticscholar.org/presentation/a8c3/4a1ed34f929156bbc3d8db6693b6f22c8f9b.pdf>
2. Assessment report on Glycine max (L.) Merr., lecithin - https://www.ema.europa.eu/documents/herbal-report/draft-assessment-report-glycine-max-l-merr-lecithin_en.pdf
3. Tennille K. Marx, Robin Reddeman, Amy E. Clewell, et al., "An Assessment of the Genotoxicity and Subchronic Toxicity of a Supercritical Fluid Extract of the Aerial Parts of Hemp," Journal of Toxicology, vol. 2018, Article ID 8143582, 26 pages, 2018 - <https://www.hindawi.com/journals/jt/2018/8143582/>
4. Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers - <https://www.fda.gov/downloads/Drugs/Guidances/UCM078932.pdf%23search=%27guidekines+for+industry+sfe+starting%27>
5. Department of Health and Human Services Public Health Service Food and Drug Administration Center for Drug Evaluation and Research. PCannabidiol 100mg/mL oral solution, 2017 - https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000PharmR.pdf
6. Code of Regulations Title 21 – Sec. 184.1400 Lecithin - <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=184.1400>
7. Federal Food, Drug and Cosmetic Act. U.S Food and Drug Administration. www.fda.gov.
8. Industrial Hemp and Cannabidiol (CBD) in Food Products – CDPH Food and Drug Branch, 2018. <https://www.cdph.ca.gov/Programs/CEH/DFDCS/CDPH%20Document%20Library/FDB/FoodSafetyProgram/HEMP/Web%20template%20for%20FSS%20Rounded%20-%20Final.pdf>
9. "Final Report of Plant-Derived Fatty Acid Oils as Used in Cosmetics." Cosmetic Ingredient Review. <http://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR577.pdf>
10. "Soy Allergy". Mayo Clinic. <http://www.mayoclinic.org/diseases-conditions/soy-allergy/basics/prevention/con-20031370>