Walker Downey & Associates, Inc

Chronic Health Effects Assessment of Spike Lavender Oil

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This EXPERT OPINION reflects Walker Downey & Associates, Inc. assessment of all relevant evidential chronic health effects data for the product under review. When requested by the client, Walker Downey & Associates, Inc. will submit this EXPERT OPINION for additional external peer-review, or make it available for public review. Final responsibility for the contents and views expressed in this EXPERT OPINION resides with Walker Downey & Associates, Inc.

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Executive Summary

Evidential data are supportive that **Spike Lavender Oil** would not cause a chronic health effect with acute or prolonged dermal or inhalation exposure. The potential for idiosyncratic allergenicity may exist and should be forewarned, but this effect would be readily identified and reversible. It is not proposed as a label caution. Adverse effects during pregnancy are unknown but assumed minimal given the history of product use. It is not proposed as a label caution.

Background

The Art Tree LLC (Madison, WI) commissioned Walker Downey & Associates, Inc. (Verona, WI), an evidence-based product safety and development consultancy, to review their product **Spike Lavender Oil** (*Lavandula latifolia*, CAS RN 8016-78-2, EINECS 284-290-6) for conformance to ASTM D4236 – 94 (2005) – Standard practice for labeling art materials for chronic health hazards. A chronic health hazard is defined herein to mean a health risk to humans, resultant from exposure to a substance that may cause a chronic adverse health effect.[1] Similarly, a chronic adverse health effect(s) is a persistent toxic effect(s) that develops over time from a single, prolonged, or repeated exposure to a substance. This effect may result from exposure(s) to a substance that can, in humans, cause sterility, birth defects, harm to a developing fetus or to a nursing infant, cancer, allergenic sensitization, damage to the nervous system, or a persistent adverse effect to any other organ system. [2] Accordingly, available evidential scientific literature for Spike Lavender Oil (hereafter, *Lavandula latifolia*) were reviewed and summarized for conformance to the subject standard, particularly as it would relate to ASTM D4236 – 94 (2005), §3.1 – 5.11. Noteworthy, this review attempts to address all Chronic Hazard Statements as described in ASTM D4236 – 94 (2005), §A1, and the Precautionary Statements (for MSDS use) as described in ASTM D4236 – 94 (2005), §A2. Exemption is claimed for ASTM D4236 – 94 (2005), §X1 – Guidelines for a certifying organization, as this is currently nonmandatory information. Nevertheless, Walker Downey & Associates, Inc. is considered qualified by education, training, experience, and certification (see Appendix 1) to facilitate this conformance statement.

Introduction

Lavender oil is an essential oil [3] obtained by distillation from the flower spikes of certain species of lavender.[4] Two forms are distinguished, *lavender flower oil* (a colorless oil, insoluble in water, having a density of 0.885 g/mL), not a subject of this review; and, as the subject of the current review, *lavender spike oil* (a distillate from the herb *Lavandula latifolia*, having density 0.905 g/mL). Like all essential oils, *Lavandula latifolia* (Figure 1) is not a pure compound; rather, it is a complex mixture of naturally occurring photochemicals, including linalool (~50%), eucalyptol (~26%), camphor (~13%),

[1] ASTM D4236 – 94 (2005), §2.1.5

[2] ASTM D4236 – 94 (2005), §2.1.4

[3] An essential oil is a concentrated, hydrophobic liquid containing volatile aroma compounds from plants. They are also known as volatile or ethereal oils, or simply as the "oil of" the plant material from which they were extracted, such as *oil of clove*. An oil is "essential" in the sense that it carries a distinctive scent, or essence, of the plant. Essential oils do not need to have any specific chemical properties in common, beyond conveying characteristic fragrances.

[4] Lavender is an evergreen woody shrub about 36-inches high, with gray-green narrow linear leaves and purple-blue flowers perched on a long stem. A few varieties of it grow wild in the Mediterranean region, but the main producer is France. The name is derived from the Latin word 'lavera' which means 'to wash' and the Romans (and later the English) used it frequently in their bath routine (i.e., historical dermal exposure).

monoterpenols (< 4%), sesquiterpenes (< 3%), and monoterpenes (~2%). Primary uses include perfume fragrance and aromatherapy.

As a prelude to the following product safety discussion it is worth noting that the **history of** perfume is thousands of years old - the word "perfume" comes from the Latin per fume "through smoke" (for current use, exposure by inhalation). One of the oldest uses of perfumes comes from the burning of incense and aromatic herbs used in religious services, often the aromatic gums, frankincense and myrrh, gathered from trees. However, lavender, eucalyptol and camphor are also widely referenced in this history. [5]

In a similar manner, **aromatherapy** also dates back at least to 4000 BC, although the term "aromatherapy" was first used in the 1920s by the French chemist René Maurice Gattefossé who accidentally discovered that **lavender oil** relieves pain and assists to slight burns healing. The word "aromatherapy" is a compound Greek word made up by the word fragrance (aroma) and the word treatment (therapy, including dermal and inhalation exposures from scented massage oils). [6]

Figure 1 - **Lavandula latifolia**

Lavandula latifolia is an aromatic shrub cultivated worldwide for the production of essential oils. As discussed, the major constituents of these oils are monoterpenes which are obtained from isopentenyl diphosphate and dimethylallyl diphosphate precursors through the plastidial methylerythritol phosphate (MEP) pathway and/or the cytosolic mevalonate pathway. Transgenic plants have been developed and accumulate significantly more essential oils compared to controls (from 101.5% to 359.0% and from 12.2% to 74.1% yield increase compared to controls in leaves and flowers, respectively).

Human Exposure Potential

Spike Lavender Oil is intended as a replacement for turpentine and would most commonly be used in very small amounts (2-4 drops with a tablespoon of paint) as a medium or diluent for oil paints from the tube. Routes of potential human exposure are both dermal and inhalation. However, owing to its chemical volatility **Spike Lavender Oil** should remained bottle-capped when not in use, thereby further restricting vapor inhalation exposure potential.

[5] Accessed online at http://inventors.about.com/gi/dynamic/offsite.htm?site=http://www.healthy.net/asp/templates/article.asp%3FPageType=article%26ID=1712

[6] Accessed online at http://www.aromatherapypoint.com/history-of-aromatherapy/

Evidential Literature Review

GRAS Status

In accordance with Title 21 – Food and Drugs, Chapter I – Food and Drug Administration (FDA), Department of Health and Human Services, Part 182 – **SUBSTANCES GENERALLY RECOGNIZED AS SAFE (GRAS)**, Subpart A – Sec. 182.20 General Provisions: Essential oils, oleoresins (solvent-free), and natural extractives (including distillates) that are **GENERALLY RECOGNIZED AS SAFE** for their intended use, within the meaning of section 409 of the Act, includes Lavender, spike (*Lavandula latifolia* Vill.). Importantly, **GENERALLY RECOGNIZED AS SAFE** (**GRAS**) is a USFDA designation that a chemical or substance added to food (i.e., food additive) is considered safe by experts, and so is exempted from the usual Federal Food, Drug, and Cosmetic Act (FFDCA, the Act) food additive tolerance requirements. **GRAS** exemptions are granted for substances that are generally recognized, among experts qualified by scientific training and experience to evaluate their safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or through experience based on common use in food) to be safe under the conditions of their intended use. The substance must be shown to be "generally recognized" as safe under the conditions of its intended use.

The term “food additive” is defined in section 201(s) of the Act. The first part of that section states that a food additive is any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food including any substance intended for use in packing, packaging, producing, manufacturing, processing, preparing, treating, transporting, or holding food; and including any source of radiation intended for any such use. However, Section 201(s) goes on to expressly exempt from the definition of food additive certain categories of substances, including substances that are **GENERALLY RECOGNIZED AS SAFE** or **GRAS** for the intended use. A partial list of substances recognized by FDA as **GRAS** may be found in 21 CFR Part 182 (as noted previously, *Lavandula latifolia* is included here), and a list of substances affirmed by FDA as GRAS appears in 21 CFR Part 184. These lists may include substances which are GRAS for use as antimicrobial agents.

Published Reviews

Basch et al [7] have published an evidence-based systematic review of *sp. Lavandula angustifolia* (Note – not *latifolia)* including scientific evidence, expert opinion, folkloric precedent, history, pharmacology, kinetics/dynamics, interactions, adverse effects, toxicology, and dosing. Similarly, Cavanagh and Wilkinson [8] conducted a review which included *Lavandula latifolia.* Importantly, both reviews note that essential oils distilled from members of the genus Lavandula have been used both cosmetically and therapeutically for centuries with the most commonly used species being *L. angustifolia*, ***L. latifolia***, L. *stoechas* and *L. x intermedia*. These reviews also note that although there is considerable anecdotal information about the biological activity of these oils, much of this has not been substantiated by scientific or clinical evidence. Among the claims made for lavender oil are that is it antibacterial, antifungal, carminative (smooth muscle relaxing), sedative, anti-depressive and effective for burns and insect bites. According to these authors, although the data are still inconclusive and often controversial,

[7] Basch E, Foppa I, Liebowitz R, Nelson J, Smith M, Sollars D, Ulbricht C (2004) Lavender (Lavandula angustifolia Miller). J Herb Pharmacother 4(2): 63-78.

[8] Cavanagh HM, Wilkinson JM (2002) Biological activities of lavender essential oil. Phytother Res. 16(4): 301-8.

there does seem to be both scientific and clinical data that support the traditional uses of **lavender**. On the other hand, methodological and oil identification problems have been viewed to have severely hampered the evaluation of the therapeutic significance of much of the research on Lavandula spp. Some recent research is discussed below.

Evidence-Based Hazard Evaluation

Based on the proposed use, exposure potentials would be greatest by dermal and inhalation routes; thus, these routes of exposure are reviewed separately below.

Dermal Sensitization/Allergenicity

Brandão [9] reported on the occupational allergy to lavender oil more than two decades ago, and research in this area is still quite active. For example, in 2008 Hagvall et al [10] reported the effect of air oxidation on the skin sensitizing potency of the monoterpenes linalyl acetate, linalool and beta-caryophyllene, the main constituents of lavender oil. The aim of their study was to investigate if the autoxidation observed for the single synthetic terpenes, resulting in strong contact allergens, will take place also in lavender oil. Accordingly, lavender oil was exposed to air and the autoxidation was followed by chemical analysis. The sensitizing potency before and after air exposure was investigated in mice using the local lymph node assay. Also, patients with patch test reactions to oxidized linalool were tested to investigate if air-exposed lavender oil could elicit dermatitis in these individuals. Results showed that terpenes oxidized in air-exposed lavender oil at the same rates as the pure compounds exposed to air, and the same oxidation products were identified. The sensitizing potency of lavender oil increased accordingly on air exposure. Patch testing showed positive reactions to air-exposed lavender oil and also to oxidized linalyl acetate in patients with contact allergy to oxidized linalool. The authors concluded that lavender oil lacks natural protection against autoxidation, and that air-exposed lavender oil can be an important source of exposure to allergenic hydroperoxides.

Similarly, Sköld et al [11] reported that fragrances are among the most common causes of allergic contact dermatitis. They had previously shown that linalool autoxidizes on air exposure forming allergenic oxidation products, and that oxidized linalool was found to be a frequent cause of contact allergy in a patch test study on consecutive dermatitis patients. Because of structural similarities, they theorized that linalyl acetate should also be susceptible to oxidation on air exposure, forming similar oxidation products as linalool. Subsequently, they investigated the autoxidation of linalyl acetate and the influence of oxidation on its sensitizing potency. In their current study, analyses were performed using gas chromatography, nuclear magnetic resonance spectrometry and mass spectrometry. Sensitizing potencies of compounds were determined using the local lymph node assay (LLNA) in mice. Analyses showed that the content of linalyl acetate decreased over time on air exposure and other compounds were formed. Hydroperoxides, an epoxide and an alcohol were identified as oxidation products from linalyl acetate. In the LLNA, linalyl acetate of high purity showed a weak sensitizing potency (EC3 25%). Autoxidation increased the sensitizing potency of linalyl acetate, and a 10 weeks oxidized sample gave an EC3 value of 3.6%. As for linalool, the hydroperoxides were shown to be the oxidation products with

[9] Brandão FM (1986) Occupational allergy to lavender oil. Contact Dermatitis 15(4): 249-50.

[10] Hagvall L, Sköld M, Bråred-Christensson J, Börje A, Karlberg AT (2008) Lavender oil lacks natural protection against autoxidation, forming strong contact allergens on air exposure. Contact Dermatitis, 59(3): 143-50.

[11] Sköld M, Hagvall L, Karlberg AT (2008) Autoxidation of linalyl acetate, the main component of lavender oil, creates potent contact allergens. Contact Dermatitis. 58(1): 9-14.

the highest sensitizing potency. The authors concluded that autoxidation of the weakly allergenic linalyl acetate leads to formation of allergenic oxidation products.

Sugiura et al [12] reported the annual results of patch testing with lavender oil for a 9-year period from 1990 to 1998 in Japan. Using Finn Chambers and Scanpor tape, they performed 2-day closed patch testing with lavender oil on the upper back of each patient suspected of having cosmetic contact dermatitis. They compared the frequency of positive patch tests to lavender oil each year with those to other fragrances. Finally, they diagnosed contact allergy when patch test reactions were + or <+ at 1 day after removal. The positivity rate of lavender oil was 3.7% (0-13.9%) during the 9-year period from 1990 to 1998. Interestingly, the positivity rate of lavender oil increased suddenly in 1997. To this point, the authors noted that recently, in Japan, there has been a trend for aromatherapy using lavender oil. With this trend, placing dried lavender flowers in pillows, drawers, cabinets, or rooms has become a new fashion. Consequently, the investigators asked patients who showed a positive reaction to lavender oil about their use of dried lavender flowers. They confirmed the use of dried lavender flowers in 5 cases out of 11 positive cases in 1997 and 8 out of 15 positive cases in 1998. The authors concluded that the increase in patch test positivity rates to lavender oil in 1997 and 1998 was due to the above fashion, rather than due to fragrances in cosmetic products.

Preclinically, Kim and Cho [13] studied the effects of lavender oil on mast cell-mediated immediate-type allergic reactions in mice and rats. Lavender oil (1:500, 1:100, 1:10, 1:1, 1:0) inhibited concentration-dependently mast cell-dependent ear swelling response induced by compound 48/80 in mice by both topical and intradermal application. Lavender oil (1:500, 1:100, 1:10, 1:1, 1:0) inhibited concentration-dependently passive cutaneous anaphylaxis induced by anti-dinitrophenyl (DNP) IgE in rats by both topical and intradermal application. Lavender oil (1:500, 1:100, 1:10, 1:1, 1:0) also inhibited concentration-dependently the histamine release from the peritoneal mast cells by compound 48/80 or anti-DNP IgE. Moreover, lavender oil (1:1000, 1:100, 1:10, 1:0) had a significant inhibitory effect on anti-DNP IgE-induced tumor necrosis factor-alpha secretion from peritoneal mast cells. These results indicate that lavender oil inhibits immediate-type allergic reactions by inhibition of mast cell degranulation in-vivo and in-vitro.

In summary, based on the foregoing, a sensitization/allergenicity potential for *Lavandula latifolia* would appear to exist, albeit evidentially idiosyncratic. This is important because the population-base exposed to *Lavandula latifolia*, through aromatherapy and massage oils, for example, has grown dramatically in the last decade or so, without a correlative increase in reported sensitizations. The evidence is fairly strong that oxidized product is more allergenic. Sensitization/allergenicity potential is not a chronic hazard potential as removal of the offending agent will typically alleviate symptoms. Caution is advised that the agent may invoke sensitization/allergenicity in a small subset of persons and that product exposure to air may increase potency of the reaction. Some of the more common symptoms of allergy are shown in Table 1.

[12] Sugiura M, Hayakawa R, Kato Y, Sugiura K, Hashimoto R (2000) Results of patch testing with lavender oil in Japan. Contact Dermatitis 43(3): 157-60.

[13] Kim HM, Cho SH (1999) Lavender oil inhibits immediate-type allergic reaction in mice and rats. J Pharm Pharmacol. 51(2): 221-6.

Table 1 – Common symptoms of allergy

Affected organ	Symptom
Nose	Swelling of the nasal mucosa (allergic rhinitis)
Sinuses	Allergic sinusitis
Eyes	Redness and itching of the conjunctiva (allergic conjunctivitis)
Airways	Sneezing, coughing, bronchoconstriction, wheezing and dyspnea, sometimes outright attacks of asthma, in severe cases the airway constricts due to swelling known as angioedema
Ears	Feeling of fullness, possibly pain, and impaired hearing due to the lack of eustachian tube drainage.
Skin	Rashes, such as eczema and hives (urticaria)
GI tract	Abdominal pain, bloating, vomiting, diarrhea

Other Topical Effects

Essential lavender oil has a long tradition as a mild sedative in herbal medicine. Relaxing effects after inhalation have also been demonstrated for one of its main constituents, (-)-linalool. Heuberger et al [14] studied the effects of this monoterpenoid alcohol on human physiological parameters (blood oxygen saturation, breathing rate, eye-blink rate, pulse rate, skin conductance, skin temperature, surface electromyogram as well as systolic and diastolic blood pressure) and assessments of subjective well-being. (-)-Linalool was applied to 14 healthy subjects by percutaneous administration. Inhalation of the fragrance was prevented by means of breathing masks. (-)-Linalool induced deactivation with respect to physiology, that is, a decrease of systolic blood pressure and a smaller decrease of skin temperature, compared to a corresponding control group receiving a placebo, but had no effects on subjective evaluation of well-being.

In aromatherapy, essential oils are used as anti-inflammatory remedies, but experimental studies on their action mechanisms are very limited. To assess their anti-inflammatory activities, effects of essential oils on neutrophil activation were examined by Abe et al [15] *in vitro*. Neutrophil activation was measured by tumor necrosis factor-alpha (TNF-alpha)-induced adherence reaction of human peripheral neutrophils. All essential oils tested at 0.1% concentration suppressed TNF-alpha-induced neutrophil adherence, and, in particular, lemongrass, geranium and spearmint oils clearly lowered the reaction even at 0.0125%. Similar inhibitory activities for the neutrophil adherence were obtained by their major constituent terpenoids: citral, geraniol, citronellol and carvone. In contrast, very popular essential oils, tea tree oil and **lavender oil**, did not display the inhibitory activity at the concentration. Thus, while some essential oils used as anti-inflammatory remedies suppress neutrophil activation by TNF-alpha at a low concentration (0.0125-0.025 %) *in vitro*, **lavender oil** apparently does not.

Lavender (Lavandula angustifolia, P. Miller) is used in aromatherapy as a holistic relaxant and is said to have carminative, anti-flatulence and anticolic properties. Its sedative nature, on inhalation, has been shown both in animals and man. Lavender has a spasmolytic activity on guinea pig ileum and rat uterus *in vitro* and it also decreases the tone in the skeletal muscle preparation of the phrenic nerve-diaphragm of rats. As the mechanism of action had not been studied previously, the spasmolytic activity was

[14] Heuberger E, Redhammer S, Buchbauer G (2004) Transdermal absorption of (-)-linalool induces autonomic deactivation but has no impact on ratings of well-being in humans. Neuropsychopharmacology 29(10): 1925-32.

[15] Abe S, Maruyama N, Hayama K, Ishibashi H, Inoue S, Oshima H, Yamaguchi H (2003) Suppression of tumor necrosis factor-alpha-induced neutrophil adherence responses by essential oils. Mediators Inflamm. 12(6): 323-8.

studied by Lis-Balchin and Hart [16] *in vitro* using a guinea pig ileum smooth muscle preparation. The mechanism of action was postsynaptic and not atropine-like. The spasmolytic effect of lavender oil was considered most likely to be mediated through cAMP, and not through cGMP. The mode of action of linalool, one of lavender's major components, reflected that of the whole oil. The mode of action of lavender oil resembled that of geranium and peppermint oils.

Lavender oil has recently been implicated in gynecomastia, the abnormal development of breasts in young boys. As most cases of male prepubertal gynecomastia are classified as idiopathic, Henley et al [17] investigated possible causes of gynecomastia in three prepubertal boys who were otherwise healthy and had normal serum concentrations of endogenous steroids. In all three boys, gynecomastia coincided with the topical application of products that contained **lavender** and tea tree oils. Gynecomastia resolved in each patient shortly after the use of products containing these oils was discontinued. Since studies in human cell lines indicated that the two oils had estrogenic and anti-androgenic activities, the authors concluded that repeated topical exposure to **lavender** and tea tree oils probably caused prepubertal gynecomastia in these boys. The conclusion that the gynecomastia was actually caused by the essential oils in the products used by the three boys is currently being disputed by the Natural Artisan Perfumers Guild and Cropwatch due to insufficient evidence.

No chronic hazardous effects are expected from the foregoing.

Inhalation

Preclinically, Lim et al [18] investigated the stimulative or sedative effects of inhaling fragrant essential oils (EOs) by using a forced swimming test (FST) with mice. This behavioral test is commonly used to measure the effects of antidepressant drugs. The inhalation by mice of EOs, such as ginger oil ($p<0.05$), thyme oil ($p<0.05$), peppermint oil ($p<0.05$), and cypress oil ($p<0.01$) resulted in 5% to 22% reduction of immobility. The same results were achieved when over-agitation was artificially induced in the mice by an intraperitoneal injection of caffeine (a psycho-stimulant). In contrast, inhalation of some EOs by the mice resulted in increased immobility. To evaluate more correctly the sedative effects of EOs, the immobility of over-agitated mice induced with caffeine was ascertained after the inhalation of various EOs. Inhalation of lavender oil ($p<0.01$) and hyssop oil ($p<0.01$) increased the immobile state in mice that were treated with caffeine. The results of this study indicate that the inhalation of essential oils may induce stimulative or sedative effects in mice.

Similarly, Shimizu et al [19] examined the effects of odors on sustained attention during a vigilance task. Two essential oils (lavender and eucalyptus) and two materials (l-menthol and linalyl acetate) were compared with a control. The increase in reaction time was significantly lower with lavender than with the control. The results suggest that the administration of lavender helped to maintain sustained attention during the long-term task.

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[16] Lis-Balchin M, Hart S (1999) Studies on the mode of action of the essential oil of lavender (Lavandula angustifolia P. Miller). Phytother Res. 13(6): 540-2.

[17] Henley DV, Lipson N, Korach KS, Bloch CA (2007) Prepubertal gynecomastia linked to lavender and tea tree oils. N Engl J Med. 356(5): 479-85.

[18] Lim WC, Seo JM, Lee CI, Pyo HB, Lee BC (2005) Stimulative and sedative effects of essential oils upon inhalation in mice. Arch Pharm Res. 28(7): 770-4.

[19] Shimizu K, Gyokusen M, Kitamura S, Kawabe T, Kozaki T, Ishibashi K, Izumi R, Mizunoya W, Ohnuki K, Kondo R (2008) Essential oil of lavender inhibited the decreased attention during a long-term task in humans. Biosci Biotechnol Biochem. 72(7): 1944-7.

The sedative properties of the essential oil of Lavender (Lavandula angustifolia Miller) and of its main constituents – linalool and linalyl acetate – were investigated by Buchbauer et al [20] in mice in a series of experimental procedures. The significant decrease in the motility of female and male laboratory animals observed under standardized experimental conditions was found to be closely dependent on the exposure time to the drugs. Nevertheless after an injection of caffeine into mice, hyperactivity was observed which was reduced to nearly a normal motility only by inhalation of the fragrance drugs. In particular the correlation of the motility of the animals to linalool in serum was experimentally proven. The authors conclude that these experiments furnish evidence of the aroma-therapeutical use of herbal pillows employed in folk medicine in order to facilitate falling asleep or to minimize stressful situations of man.

In a study by Barocelli et al [21], the antinociceptive and the gastroprotective effects of orally administered or inhaled Lavandula hybrida Reverchon "Grosso" essential oil, and its principal constituents linalool and linalyl acetate were evaluated in rodents. Either when orally administered (100 mg/kg) or inhaled for 60 min lavender essential oil significantly reduced the acetic acid-writhing response in a naloxone-sensitive manner. In the hot plate test, analgesic activity observed after oil inhalation was inhibited by naloxone, atropine, mecamylamine pretreatment suggesting the involvement of opioidergic as well as cholinergic pathways. Regardless of the administration route and the experimental model used both linalool and linalyl acetate did not produce significant analgesic response. Oral or inhalatory treatment with analgesic doses of essential oil did not affect mice spontaneous locomotor activity. Concerning the gastric effects, lavender oil, linalool and linalyl acetate oral administration protected against acute ethanol-induced gastric ulcers but did not prevent indomethacin-induced lesions indicating no interference with arachidonic acid metabolic cascade. The authors concluded that, besides this gastroprotection, lavender oil reveals an interesting analgesic activity mainly relevant after inhalation, at doses devoid of sedative side effect, suggesting the interest for potential application of this oil in aromatherapy.

Moss et al [22] assessed the olfactory impact of the essential oils of lavender (Lavandula angustifolia) and rosemary (Rosmarlnus officinalis) on cognitive performance and mood in healthy volunteers. One hundred and forty-four participants were randomly assigned to one of three independent groups, and subsequently performed the Cognitive Drug Research (CDR) computerized cognitive assessment battery in a cubicle containing either one of the two odors or no odor (control). Visual analogue mood questionnaires were completed prior to exposure to the odor, and subsequently after completion of the test battery. The participants were deceived as to the genuine aim of the study until the completion of testing to prevent expectancy effects from possibly influencing the data. The outcome variables from the nine tasks that constitute the CDR core battery feed into six factors that represent different aspects of cognitive functioning. Analysis of performance revealed that lavender produced a significant decrement in performance of working memory, and impaired reaction times for both memory and attention based tasks compared to controls. In contrast, rosemary produced a significant enhancement of performance for overall quality of memory and secondary memory factors, but also produced an

[20] Buchbauer G, Jirovetz L, Jäger W, Dietrich H, Plank C (1991) Aromatherapy: evidence for sedative effects of the essential oil of lavender after inhalation. Z Naturforsch [C]. 46(11-12): 1067-72.

[21] Barocelli E, Calcina F, Chiavarini M, Impicciatore M, Bruni R, Bianchi A, Ballabeni V (2004) Antinociceptive and gastroprotective effects of inhaled and orally administered Lavandula hybrida Reverchon "Grosso" essential oil. Life Sci. 76(2): 213-23.

[22] Moss M, Cook J, Wesnes K, Duckett P (2003) Aromas of rosemary and lavender essential oils differentially affect cognition and mood in healthy adults. Int J Neurosci. 113(1): 15-38.

impairment of speed of memory compared to controls. With regard to mood, comparisons of the change in ratings from baseline to post-test revealed that following the completion of the cognitive assessment battery, both the control and lavender groups were significantly less alert than the rosemary condition; however, the control group was significantly less content than both rosemary and lavender conditions. These findings indicate that the olfactory properties of these essential oils can produce objective effects on cognitive performance, as well as subjective effects on mood.

No chronic hazardous effects are expected from the foregoing.

Oral Effects

A paucity of literature was available for oral exposure. In one study, the pharmacological effects of lavender oil were investigated by Umezu et al [23] using two conflict tests in ICR mice, and then the active constituents were identified. Lavender oil produced significant anticonflict effects at 800 and 1600 (oral) mg/kg in the Geller conflict test and at 800 mg/kg in the Vogel conflict test, suggesting that the oil has an anti-anxiety effect. Analysis using GC/MS revealed that lavender oil contains 26 constituents, among which alpha-pinene (ratio, 0.22%), camphene (0.06%), beta-myrcene (5.33%), p-cymene (0.3%), limonene (1.06%), cineol (0.51%), linalool (26.12%), borneol (1.21%), terpinene-4-ol (4.64%), linalyl acetate (26.32%), geranyl acetate (2.14%) and caryophyllene (7.55%) were identified. The authors examined the effects of linalool, linalyl acetate, borneol, camphene, cineol, terpinen-4-ol, alpha-pinene and beta-myrcene using the Geller and Vogel conflict tests in ICR mice. Cineol, terpinen-4-ol, alpha-pinene and beta-myrcene did not produce any significant anticonflict effects in the Geller test. Linalyl acetate did not produce any significant anticonflict effects in either test. Both borneol and camphene at 800 mg/kg produced significant anticonflict effects in the Geller, but not in the Vogel conflict test. Linalool, a major constituent of lavender oil, produced significant anticonflict effects at 600 and 400 mg/kg in the Geller and Vogel tests, respectively, findings that were similar to those of lavender oil. The authors concluded that linalool is the major pharmacologically active constituent involved in the anti-anxiety effect of lavender oil.

An LD50 Oral-Rat has been reported as 3.8 g/kg [24] which would translate to a “moderately toxic” material by US Environmental Protection Agency ranking and a “slightly toxic” material by World Health Organization ranking (e.g., probable oral lethal dose for average 150-pound adult is between 1 ounce – 1 pint for moderately toxic, and 1 pint – 1 quart for slightly toxic).

No chronic hazardous effects are expected from the foregoing.

Pesticidal Activity

In Argentina, field populations of the head louse Pediculus humanus capitis De Geer (Phthiraptera: Pediculidae) have developed resistance to permethrin and other pyrethroids. Consequently, Gonzalez et al [25] developed a lotion containing essential oils from plants and an alcoholic coadjuvant to improve biological effect. Ethanol + isopropanol (1 + 1 in volume) 50% in water and ethanol 96% were taken as bases for preparation of experimental lotions containing essential oils from plants. They found that

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[23] Umezu T, Nagano K, Ito H, Kosakai K, Sakaniwa M, Morita M (2006) Anticonflict effects of lavender oil and identification of its active constituents. Pharmacol Biochem Behav. 85(4): 713-21.

[24] Food and Chemical Toxicology, 14: 453, 1976 (data unsubstantiated).

[25] Gonzalez Audino P, Vassena C, Zerba E, Picollo M (2007) Effectiveness of lotions based on essential oils from aromatic plants against permethrin resistant Pediculus humanus capitis. Arch Dermatol Res. 299(8): 389-92.

experimental lotions containing **lavender**, peppermint and eucalyptus oils in a 5% composition and the combination of eucalyptus and peppermint in a total concentration of 10%, dissolved in 50% ethanol + isopropanol (1 + 1) in water, showed the best knockdown effect. On the other hand, lotion containing peppermint oil and eucalyptus oil (1 + 1) 10%, dissolved in ethanol 96%, showed to be as effective as the best commercial lotion now available in Argentina. Furthermore, addition of 1-dodecanol in all cases increased the effectiveness of all the experimental lotions. The authors conclude that this difference is important for 1-dodecanol concentration of 10%, reaching a toxic activity compared to the best commercial lotion available in the market.

Managing the poultry red mite, Dermanyssusgallinae (De Geer) by conventional means (i.e., synthetic acaricides) has become increasingly problematic. As a possible alternative, research has identified several plant essential oils that are toxic to D. gallinae. However, essential oils are highly volatile and any acaricidal effect they exert could be short-lived in practice. George et al [26] investigated the short-lived toxicity of six lavender essential oils to D. gallinae. In sealed Petri-dishes, mites were exposed to filter papers impregnated with essential oil at a concentration of 0.14mg/cm(3). When filter papers were used immediately after impregnation, 66-90% D. gallinae mortality was observed after 24h, depending upon the essential oil used. If impregnated filter papers were left in a fume cupboard for 24h prior to use, mortality rates of D.gallinae fell to 11% or less.

The antifungal activity of the essential oil of Lavandula angustifolia Mill. (lavender oil) and its main components, linalool and linalyl acetate, was investigated by D'Auria et al [27] against 50 clinical isolates of Candida albicans (28 oropharyngeal strains, 22 vaginal strains) and C. albicans ATCC 3153. Growth inhibition, killing time and inhibition of germ tube formation were evaluated. The chemical composition of the essential oil was determined by gas chromatography and mass spectrometry. Lavender oil inhibited C. albicans growth: mean minimum inhibitory concentration (MIC) of 0.69% (vol./vol.) (vaginal strains) and 1.04% (oropharyngeal strains); mean MFC of 1.1% (vaginal strains) and 1.8% (oropharyngeal strains). Linalool was more effective than essential oil: mean MIC of 0.09% (vaginal strains) and 0.29% (oropharyngeal strains); mean MFC of 0.1% (vaginal strains) and 0.3% (oropharyngeal strains). Linalyl acetate was almost ineffective. Lavender oil (2%) killed 100% of the C. albicans ATCC 3153 cells within 15 min; linalool (0.5%) killed 100% of the cells within 30 s. The essential oil inhibited germ tube formation (mean MIC of 0.09%), as did the main components (MIC of 0.11% for linalool and 0.08% for linalyl acetate). Both the essential oil and its main components inhibited hyphal elongation of C. albicans ATCC 3153 (about 50% inhibition at 0.016% with each substance). According to these authors, lavender oil shows both fungistatic and fungicidal activity against C. albicans strains. At lower concentrations, it inhibits germ tube formation and hyphal elongation, indicating that it is effective against C. albicans dimorphism and may thus reduce fungal progression and the spread of infection in host tissues.

Bactericidal Effects

Patchouli, tea tree, geranium, **lavender** essential oils and Citricidal (grapefruit seed extract) were used by Edwards-Jones et al [28] singly and in combination to assess their anti-bacterial activity against three

[26] George DR, Callaghan K, Guy JH, Sparagano OA (2008) Lack of prolonged activity of lavender essential oils as acaricides against the poultry red mite (Dermanyssusgallinae) under laboratory conditions. Res Vet Sci. 85(3): 540-2.

[27] D'Auria FD, Tecca M, Strippoli V, Salvatore G, Battinelli L, Mazzanti G (2006) Antifungal activity of Lavandula angustifolia essential oil against Candida albicans yeast and mycelial form. Med Mycol. 43(5): 391-6.

[28] Edwards-Jones V, Buck R, Shawcross SG, Dawson MM, Dunn K (2004) The effect of essential oils on methicillin-resistant Staphylococcus aureus using a dressing model. Burns 30(8): 772-7.

strains of Staphylococcus aureus: Oxford S. aureus NCTC 6571 (Oxford strain), Epidemic methicillin-resistant S. aureus (EMRSA 15) and MRSA (untypable). The individual essential oils, extracts and combinations were impregnated into filter paper discs and placed on the surface of agar plates, pre-seeded with the appropriate strain of Staphylococcus. The effects of the vapors of the oils and oil combinations were also assessed using impregnated filter paper discs that were placed on the underside of the Petri dish lid at a distance of 8mm from the bacteria. The most inhibitory combinations of oils for each strain were used in a dressing model constructed using a four layers of dressings: the primary layer consisted of either Jelonet or TelfaClear with or without Flamazine; the second was a layer of gauze, the third a layer of Gamgee and the final layer was Crepe bandage. The oil combinations were placed in either the gauze or the Gamgee layer. This four-layered dressing was placed over the seeded agar plate, incubated for 24h at 37 degrees C and the zones of inhibition measured. All experiments were repeated on three separate occasions. No anti-bacterial effects were observed when Flamazine was smeared on the gauze in the dressing model. When Telfaclear was used as the primary layer in the dressing model compared to Jelonet, greater zones of inhibition were observed. A combination of Citricidal and geranium oil showed the greatest-anti-bacterial effects against MRSA, whilst a combination of geranium and tea tree oil was most active against the methicillin-sensitive S. aureus (Oxford strain). This study demonstrated the potential of essential oils and essential oil vapors as antibacterial agents and for use in the treatment of MRSA infection.

The minimum inhibitory doses (MIDs) of essential oils by vapor contact to inhibit the growth of Trichophyton mentagrophytes and Trichophyton rubrum on agar medium were determined by Inouye et al [29] using airtight boxes. Among seven essential oils examined, cinnamon bark oil showed the least MID, followed by lemongrass, thyme and perilla oils. Lavender and tea tree oils showed moderate MID, and citron oil showed the highest MID, being 320 times higher than that of cinnamon bark oil. The MID values were less than the minimum inhibitory concentration (MIC) values determined by agar dilution assay. Furthermore, the minimum agar concentration (MAC) of essential oils absorbed from vapor was determined at the time of MID determination as the second antifungal measure. The MAC value by vapor contact was 1.4 to 4.7 times less than the MAC remaining in the agar at the time of MIC determination by agar dilution assay. Using selected essential oils, the anti-Trichophyton activity by vapor contact was examined in more detail. Lemongrass, thyme and perilla oils killed the conidia, inhibited germination and hyphal elongation at 1-4 micrograms ml-1 air, whereas lavender oil was effective at 40-160 micrograms ml-1 air. The in-vivo efficacy of thyme and perilla oils by vapor contact was shown against an experimental tinea pedis in guinea pigs infected with T. mentagrophytes. These results indicated potent anti-Trichophyton action of essential oils by vapor contact.

Cytotoxicity

Prashar et al [30] demonstrated that lavender oil (in this experiment *Lavandula angustifolia*) is cytotoxic to human skin cells in vitro (endothelial cells and fibroblasts) at a concentration of 0.25% (v/v) in all cell types tested (HMEC-1, HNDF and 153BR). The major components of the oil, linalyl acetate and linalool, were also assayed under similar conditions for their cytotoxicity. The activity of linalool reflected that of the whole oil, indicating that linalool may be the active component of lavender oil. Linalyl acetate

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[29] Inouye S, Uchida K, Yamaguchi H (2001) In vitro and in vivo anti-Trichophyton activity of essential oils by vapor contact. Mycoses 44(3-4): 99-107.

[30] Prashar A, Locke IC, Evans CS (2004) Cytotoxicity of lavender oil and its major components to human skin cells. Cell Prolif. 37(3): 221-9.

cytotoxicity was higher than that of the oil itself, suggesting suppression of its activity by an unknown factor in the oil. Membrane damage is proposed as the possible mechanism of action.

Mutagenicity

Evandri et al [31] report that Essential oils from Melaleuca alternifolia (tea-tree oil) and Lavandula angustifolia (lavender oil) are commonly used to treat minor health problems. Tea-tree oil possesses broad-spectrum antimicrobial activity, and is increasingly used for skin problems. Lavender oil, traditionally used as an antiseptic agent, is now predominantly used as a relaxant, carminative, and sedative in aromatherapy. Despite their growing use no data are available on their mutagenic potential. In their study, after determining the chemical composition of tea-tree oil and lavender oil, by gas-chromatography and mass spectrometry, they investigated the mutagenic and antimutagenic activities by the bacterial reverse mutation assay in Salmonella typhimurium TA98 and TA100 strains and in Escherichia coli WP2 uvrA strain, with and without an extrinsic metabolic activation system. Neither essential oil had mutagenic activity on the two tested Salmonella strains or on E. coli, with or without the metabolic activation system. Conversely, **lavender** oil exerted strong antimutagenic activity, reducing mutant colonies in the TA98 strain exposed to the direct mutagen 2-nitrofluorene. Antimutagenicity was concentration-dependent: the maximal concentration (0.80 mg/plate) reduced the number of histidine-independent revertant colonies by 66.4%. Lavender oil (0.80 mg/plate) also showed moderate antimutagenicity against the TA98 strain exposed to the direct mutagen 1-nitropyrene. Its antimutagenic property makes **lavender** oil a promising candidate for new applications in human healthcare.

Carcinogenicity

Free radicals/reactive oxygen species are related to many biological phenomena such as inflammation, aging, and carcinogenesis. The body possesses various antioxidative systems (free radical scavenging activity, FRSA) for preventing oxidative stress, and saliva contains such activity. In a recent study by Atsumi and Tonosaki, [32] they measured the total salivary FRSA induced after the smelling of **lavender** and rosemary essential oils that are widely used in aromatherapy. Various physiologically active substances in saliva such as cortisol, secretory IgA, and alpha-amylase activity were found to be correlated with aroma-induced FRSA. The subjects (22 healthy volunteers) sniffed aroma for 5 min, and each subject's saliva was collected immediately. FRSA was measured using 1,1-diphenyl-2-picrylhydrazyl. The FRSA values were increased by stimulation with low concentrations (1000 times dilution) of lavender or by high-concentrations (10 times dilution) of rosemary. In contrast, both **lavender** and rosemary stimulations decreased cortisol levels. A significant inverse correlation was observed between the FRSA values and the cortisol levels with each concentration of rosemary stimulation. No significant changes were noted in sIgA or alpha-amylase. The authors concluded that these findings clarify that lavender and rosemary enhance FRSA and decrease the stress hormone, cortisol, which protects the body from oxidative stress.

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[31] Evandri MG, Battinelli L, Daniele C, Mastrangelo S, Bolle P, Mazzanti G (2005) The antimutagenic activity of Lavandula angustifolia (lavender) essential oil in the bacterial reverse mutation assay. Food Chem Toxicol. 43(9): 1381-7.

[32] Atsumi T, Tonosaki K (2007) Smelling lavender and rosemary increases free radical scavenging activity and decreases cortisol level in saliva. Psychiatry Res. 150(1): 89-96.

Lavandula latifolia is not listed in any carcinogen database.

Conclusion

Evidential data are supportive that **Spike Lavender Oil** would not cause a chronic health effect with acute or prolonged dermal or inhalation exposure. The potential for idiosyncratic allergenicity may exist and should be forewarned, but this effect would be readily identified and reversible. It is not proposed as a label caution. Adverse effects during pregnancy are unknown but assumed minimal given the history of product use. It is not proposed as a label caution.

Appendix 1 – Author's Biosketch

Daniel E. McLain, PhD, CNS, DABFE (Toxicology)**,** is a cofounder and president of Walker Downey & Associates, Inc., an evidence-based product safety and development consultancy located near the heart of the Third Coast Scientific/Biotechnology Community (Madison, WI). He received his MS/Ph.D. in nutritional toxicology and preventive medicine from Cornell University (Ithaca, NY) and has more than 25 years of broad-based experience in toxicology, drug and device development, vaccine development, statistics, and risk assessment. He has specific expertise in medical device material biocompatibility, immunotoxicology, and Developmental and Reproductive Toxicity (DART), and is the current AAMI US Chair and Convener of ISO 10993 Biological Evaluation of Medical Devices – Part 11: Systemic Toxicity Evaluation (revised 2006). He has contributed to and has meaningful personal experience with IND, BLA, 510(k), IDE, GTAC and CTD preparation. He is fully experienced with the design, conduct, analysis, and reporting of preclinical safety and pharmacokinetic studies for drugs, devices, biologics, and combination products, and with the international regulatory submissions associated with them. Dr. McLain is board-certified and a Diplomate and Fellow of the American College of Forensic Examiners (Toxicology) and the American College of Nutrition (Nutritional Toxicology). Additionally, he is an active and contributing member of the Society of Toxicology (25-years), the Regulatory Affairs Professional Society (16-years), the International Standards Organization/Association for the Advancement of Medical Instrumentation (13-years), and the American Society for Quality (13-years).