THE EFFECTIVENESS AND SAFETY OF AUSTRALIAN TEA TREE OIL

Australian Government
Rural Industries Research and Development Corporation

Australian Tea Tree Industry Association

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RIRDC Shaping the future

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Australian
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Foreword

The Rural Industries Research and Development Corporation (RIRDC) has been working closely with the Australian tea tree oil industry for more than a decade on the efficacy, safety and production of tea tree oil. Many research reports have now demonstrated tea tree oil's effectiveness as an antibacterial, antiviral and anti-inflammatory agent. More recently, the Australian Tea Tree Oil Industry Association and RIRDC have worked closely to develop a comprehensive safety dossier for tea tree oil. The results of RIRDC and related research on efficacy and safety of tea tree oil are summarised in this report in order to make them accessible to a wide range of interested producers of tea tree oil and tea tree oil products, companies, regulatory authorities and researchers.

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Executive summary

Tea tree oil is one of Australia's most studied essential oils – numerous studies have been done into its efficacy, stability, oxidation and toxicity.

Multiple studies have demonstrated the capacity for tea tree oil to serve as an antiseptic, antibacterial, antiviral, antifungal and anti-inflammatory agent. For almost a century it has been used for one or more of these purposes.

Many years of use in a wide range of products has clearly demonstrated the safety of tea tree oil to human health. Further, company adverse reporting data shows that adverse effects from tea tree oil use is very low – less than 0.0016%, with only minor complaints reported.

Exposure of tea tree oil to air and light results in oxidation of some of its components. These oxidation products increase the toxicity of tea tree oil. Although 100% tea tree oil is a weak skin sensitiser in susceptible individuals, oxidized tea tree oil has a greater propensity to cause skin sensitisation. The tea tree oil industry is unanimous in its recommendation that oxidized tea tree oil should not be used.

However, when used and stored properly – tightly sealed and kept away from light and heat – 100% tea tree oil does not pose a risk to human health. Correctly formulated products containing tea tree oil also pose no risk.

The Australian Tea Tree Oil Industry Association has developed a Code of Practice and guidelines to ensure the quality of tea tree oil supplied to the market.

An education program is also underway to advise manufacturers and consumers on the proper formulation, storage and use of tea tree oil and tea tree oil products as well as use-by dates after opening.

This document gives an overview of the key safety and efficacy studies relating to tea tree oil.

About tea tree oil

Tea tree oil is an essential oil distilled from the Australian plant *Melaleuca alternifolia*. It has been used medicinally by Australian Aborigines for centuries and was identified as an antiseptic by the New South Wales chief chemist in the 1920s. In the decades since, tea tree oil has also been found to have substantial anti-fungal, antibacterial, anti-viral and anti-inflammatory activity.

The oil is steam-distilled and has been produced and marketed in Australia for the past 80 years. It is only in the past 20 years, however, that *Melaleuca alternifolia* has been cultivated intensively as a commercial agricultural crop.

The species is unique to Australia and plants with the genetic makeup necessary to produce the oil are native to northern New South Wales. Consequently, it is here that most commercial production occurs. There is currently around 3000 hectares of cultivated tea tree growing in Australia and about 100 producers. More than 80 per cent of the world's tea tree oil is produced in Australia.

Almost 90 per cent of Australian tea tree oil is exported, principally to North America and Europe. The major end-use of the oil is in antimicrobials and cosmetics, with much of it being sold as pure oil to manufacturers of these products.

The cosmetics to which tea tree oil is added – and its typical concentration in the formulation – are moisturisers (1.25%), body lotions (1.25%), shampoos and conditioners, mouth washes (0.2%), face cleansing washes (0.7%), hand washes (0.7%), soaps (2%), foot sprays (2%), foot powders (1%), shaving products (2%), post-waxing treatments (1.25%) and deodorants (2%).

Because of its anti-fungal, antibacterial, anti-viral and anti-inflammatory activity, tea tree oil is also sold over-the-counter as neat oil or in 10-15% tea tree oil solutions.

The oil of *Melaleuca alternifolia* has more than 100 components. The most abundant of these is terpinen-4-ol which makes up at least 30 per cent and has an important role in the oil's antimicrobial activity.

Levels of 15 components are stipulated in the International Standard for Oil of Melaleuca, Terpinen-4-ol type (ISO 4730).

These levels are shown in the table.

Component	ISO 4730 (range %)
α-pinene	1 – 6
sabinene	trace – 3.5
α-terpinene	5 – 13
limonene	0.5 – 1.5
p-cymene	0.5 – 8
1,8, cineole	trace – 15
γ-terpinene	10 – 28
terpinolene	1.5 – 5
terpinen-4-ol	30 – 48
α-terpineol	1.5 – 8
aromadendrene	trace – 3
ledene	trace – 3
δ-cadinene	trace – 3
globulol	trace – 1
viridiflorol	trace – 1

An increasing number of other national and international standards apply to tea tree oil. The European Pharmacopoeia and the World Health Organsation have produced international monographs, and Australia, France and Germany have published national standards.

Regulating tea tree oil

North America and Europe are significant markets for Australian tea tree oil. About 40 per cent of the oil produced in Australia each year is imported into North America and about 50 per cent into Europe.

In the early 1970s the Member States of the European Union decided to harmonise their national cosmetic regulations in order to enable the free circulation of cosmetic products within the EU.

As a result, Council Directive 76/768/EEC was adopted on 27 July 1976. Under this directive a cosmetic manufacturer has a legal obligation to provide products that are safe. The legislation does not specify how safety should be established, merely that the product must be safe and that the safety information must be recorded in a safety dossier.

Tea Tree Oil and its components are not regulated in any of the annexes of the Cosmetic Directive 76/768/EEC.

However, in 2004, the European Union's Scientific Committee on Consumer Products (SCCP) was asked to answer a series of questions concerning formulated products containing tea tree oil, as well as the whole oil.

In December 2004, having reviewed the research then available, the SCCP concluded that the use of undiluted Tea Tree Oil as a commercial product for cosmetic use may be unsafe. It also questioned the stability of tea tree oil in cosmetic formulations but stated it had insufficient data available on which to assess the use of tea tree oil as a cosmetic ingredient. The SCCP then requested that the tea tree industry provide a complete dossier on tea tree oil safety.

In March 2007 the Australian Tea Tree Industry Association and the Australian Rural Industries Research and Development Corporation submitted a dossier on the toxicology and safety of tea tree oil to the Committee. The dossier included a review of studies done before 2004 as well as the results of several new studies on tea tree oil safety and stability.

This document provides an overview of the key safety areas reviewed in the dossier as well as the considerable research done on the effectiveness of tea tree oil in treating bacterial, viral and fungal infections as well as inflammation.

Effectiveness

Tea tree oil has a long history of use for medicinal purposes. It was identified as an antiseptic by the New South Wales chief chemist in the 1920s.

Many tea tree oil products are listed as antiseptics by Australia's Therapeutic Goods Administration but the oil has not yet been registered as a pharmaceutical.

However considerable research, much of it by the Tea Tree Oil Research Group at The University of Western Australia, has revealed tea tree oil to be effective as an antibacterial, antifungal, anti-viral and anti-inflammatory. The Rural Industries Research and Development Corporation has funded the bulk of this research.

Antibacterial

A most promising new function of tea tree oil is countering methicillin-resistant *Staphylococcus aureus* (MRSA), also called a hospital super bug or golden staph. The spread of MRSA is an important infection control problem in hospitals worldwide as MRSA infections are resistant to most conventional antibiotics, except vancomycin.

However, a clinical trial at Westmead Hospital in Sydney has shown that tea tree oil body wash can help eradicate golden staph from hospital patients.

The 18-month trial involved 180 patients with golden staph infections who were treated with either tea tree oil-based products or the products routinely used in hospitals.

Treatment took place for a minimum of three days and a series of swabs were taken to check for the presence of golden staph.

Of the 96 patients who completed the trial, the final clearance rate was similar for both treatments. Twenty-one per cent of those treated with tea tree oil products were no longer infected after the trial compared with 23 per cent who received the regular treatment.

Professor Tom Riley from The University of Western Australia's Tea Tree Oil Research Group was involved in the study and said its outcome was an important step in developing tea tree oil-based products for use in a clinical setting.

"Although clearance was low in both groups, and this is often the case, there was no statistical significant difference between the treatments, suggesting that tea tree oil products may be suitable for decolonising patients carrying golden staph," Professor Riley said.

These findings have been confirmed by an English study published in the *Journal of Hospital Infection*[1] in 2004 .

"If we can introduce some tea tree products such as hand washes, antiseptics and topical microbials into the hospital environment, what that will do, I believe, is reduce the pressure on antibiotic usage," Professor Riley said. "Once you reduce the pressure on antibiotic usage, even if it's only slightly, then you ultimately will have an impact on antibiotic resistance which is a worldwide problem."

Antiviral

Until 2005 there was scant data on the anti-viral activity of tea tree oil. However a study by Dr Christine Carson and her colleagues at The University of Western Australia was the first to show that tea tree oil has significant anti-viral activity against the herpes simplex virus, which causes cold sores.

The study clearly demonstrated that tea tree oil and several of its components can inactivate the herpes virus

[1] Dryden MS, Dailly S, Crouch M (2004). A randomized, controlled trial of tea tree topical preparations versus a standard topical regimen for the clearance of MRSA colonization. *Journal of Hospital Infection*, Volume 56, Issue 4, pages 283-286.

in vitro. Further, evidence gained from this study suggested that tea tree oil may be effective in the treatment of cold sores[2]. There is strong interest in cold sore treatments because 20 to 40 per cent of people are prone to developing them, yet there is no cure.

Antifungal

Fungi are significant human pathogens, causing common superficial infections such as tinea and vaginal thrush.

A study conducted in 2002 found that tea tree oil can inhibit and kill yeasts, dermatophytes (which cause superficial nail and skin infections) and other filamentous fungi. Of particular note was its effectiveness against *Candida albicans*, a common cause of vaginal thrush.

The study authors concluded that the sorts of infections or conditions that are associated with fungi and which may be suitable for treatment with topical tea tree oil included oral or vaginal candidiasis (caused predominantly by *C. albicans*), tinea and ringworm (caused by dermatophytes) and dandruff and seborrhoeic dermatitis (caused by *Malassezia* yeasts)[3].

Anti-inflammatory potential

The ability of tea tree oil to reduce two types of human skin inflammation has been shown in studies conducted by researchers at Flinders University in South Australia[4].

Team leader Professor John Finlay-Jones, now assistant director of the Telethon Institute for Child Health Research in Western Australia, said the first type of inflammation tested was related to 'immediate' hypersensitivity responses in skin, which includes responses such as hives and the skin reaction to bee stings.

"In this type of hypersensitivity, mast cells in the skin release histamine which is responsible for many of the symptoms in skin that can be seen within minutes of exposure," Professor Finlay-Jones said.

The Flinders University study showed that the application of 100% tea tree oil significantly reduced skin inflammation in a group of volunteers injected with the irritant histamine.

"These were the first studies in humans to show experimentally that tea tree oil can reduce histamine skin inflammation," said Professor Finlay-Jones.

The second type of inflammation reaction tested was 'contact' hypersensitivity such as the sensitivity to nickel displayed by up to one in 10 people, particularly women who are exposed to nickel, for example, in jewellery.

A clinical trial found that applying 100% tea tree oil to nickel-induced rashes also reduced skin inflammation in some, but not all, patients.

"The results suggest that tea tree oil can be used for the treatment of inflammatory reactions of the skin including those following insect bites and in those sensitive to nickel," Professor Finlay-Jones said. "It may be possible to extend that treatment to sensitivity reaction to other chemicals including plant components and other irritants."

Skin relief from wound dressings

A trial at the Sydney Adventist Hospital has shown tea tree oil hydrogel dressings provide relief of symptoms related to radiation skin reactions[5]. It is estimated that at least 60 per cent of cancer patients receive radiation treatment, with as many as 95 per cent of those experiencing a skin reaction to the treatment.

The trial's objective was to develop a wound dressing using tea tree oil in order to take advantage of the oil's anti-inflammatory and antimicrobial properties. In the trial, patients with acute radiation skin reactions were treated with either tea tree oil hydrogel dressing or paw paw ointment, which was used as a positive control.

[2] Carson, CF et al (2005). Antiviral activity of tea tree oil – in vitro and in vivo. RIRDC Report #05/130.
[3] Hammer KA, Carson CF, Riley, TV (2002). Antifungal activity of tea tree oil. Project UWA-58A. Rural Industries Research and Development Corporation.
[4] Finlay-Jones J, Hart P, Riley T, Carson C (2001). Anti-inflammatory activity of tea tree oil. RIRDC Report #01/10.
[5] Bain G et al (2005). Tea tree/hydrogel dressings for use in wound care. RIRDC Report #05/114.

"Both products had soothing effects on the skin, although tea tree oil tended to achieve a slightly better result than the paw paw ointment," said Project Manager Hilary Kuwahata. "The tea tree oil dressing also had a cooling effect on the skin which patients found beneficial."

Despite its limited size, the study consistently showed the tea tree oil dressing impacted positively on radiotherapy patients' skin integrity and comfort, and therefore their quality of life. The study also found evidence suggesting earlier use of this dressing may further reduce the signs and symptoms of radiation skin reactions.

Treating acne

The antibacterial and antifungal properties of tea tree oil prompted an investigation of its effectiveness in treating acne. A clinical trial involving 124 teenage patients evaluated the effectiveness of 5% tea tree oil gel in treating mild to moderate acne when compared with 5% benzoyl peroxide lotion (a commonly used topical anti-acne treatment).

The results showed that both 5% tea tree oil gel and 5% benzoyl peroxide lotion had a significant effect in ameliorating the patients' acne by reducing the number of inflamed and non-inflamed lesions.

Encouragingly, fewer side effects (such as skin dryness, itching, stinging, burning and redness) were experienced by patients treated with tea tree oil[6].

Tea tree oil and oral disease

A study by the Tea Tree Oil Research Group at UWA examined the susceptibility of a range of oral bacteria to tea tree oil.

The tests on 162 different bacterial types showed all were inhibited and killed by concentrations of 2% tea tree oil. Two bacterial species – *Streptococcus mutans* and *Lactobacillus rhamnosus* – that are associated with dental caries were quite rapidly killed by 0.5% tea tree oil[7].

Tea tree oil hand washes

Hospitals in Australia and overseas are evaluating tea tree oil-containing products for routine hand washing following a study that revealed them to be effective in eliminating bacteria.

Death and disease due to hospital-acquired bacterial infections is a significant problem in health care worldwide. Most infections are thought to be caused by bacteria that have been passed from the hands of hospital staff to patients or from patient to patient.

In the study, Professor Tom Riley from The University of Western Australia tested a 5% tea tree oil hygienic skin wash, a 5% tea tree oil alcohol hygienic skin wash, and a 3% tea tree oil alcohol hand rub. The effectiveness of these products against four bacterial species was compared to that of povidone iodine, a commonly used hospital hand wash.

The study, published in the *Journal of Hospital Infection*[8] in 2005, showed that some tea tree oil formulations could play a role in reducing hospital-acquired infections such as those caused by *Staphylococcus aureus*, or 'golden staph'[9]. Encouragingly, it has been demonstrated that hospital staff with access to tea tree oil hand washes show greater compliance with hand washing procedures.

[6] Bassett IB, Pannowitz DL, Barnetson R StC (1990). A comparative study of tea tree oil versus benzoyl peroxide in the treatment of acne. Medical Journal of Australia 153:455-458.
[7] Riley, TV (2003). Antimicrobial activity of tea tree oil against oral microorganisms. RIRDC Report #03/019.
[8] Messager S, Hammer KA, Carson CF, Riley TV (2005). Assessment of the antibacterial activity of tea tree oil using the European EN 1276 and EN 12054 standard suspension tests. *Journal of Hospital Infection*, Volume 59, Issue 2, pages 113-125.
[9] Carson CF, Riley TV (1995). Toxicity of the essential oil of *Melaleuca alternifolia* or tea tree oil. *Journal of Toxicology – Clinical Toxicology*, Volume 33, pages193-195.

Safety

Skin irritation

Undiluted tea tree oil has been reported to cause skin irritation in a small proportion of people.

In one study[10], where 311 people were exposed to undiluted tea tree oil daily for 21 consecutive days, 5.5 per cent experienced weak skin irritation reactions. However when exposed to a cream, ointment and gel containing concentrations of 25% or less of tea tree oil, no irritation occurred.

In another study[11], where 10 different samples of undiluted tea tree oil were applied to the skin of 219 healthy volunteers for 48 hours, marked irritancy to 100% tea tree oil ranged from 2.4 per cent to 4.3 per cent.

And a further study[12], conducted on 217 volunteers in 2004, showed that 10% tea tree oil (in petrolatum base) applied for 48 hours did not cause irritation. A newly formulated 5% lotion tested on 160 subjects caused five weak reactions (3.1%).

It is likely that the irritation potential of tea tree oil may be related to the age of the oil, with aged oils (presumably containing higher levels of peroxides and degradation products such as ascaridol) displaying a greater incidence of irritation.

Skin sensitisation

There have been some reported cases of sensitisation to tea tree oil after repeated exposure. This has typically manifested as skin inflammation or rash and occurs because the immune system has reacted to the presence of the tea tree oil.

Ten separate human patch test studies involving almost 9400 people have focused on the sensitisation potential of tea tree oil. Patch tests are frequently used to determine whether a person is allergic to a particular substance. They involve applying the substance to a small part of the skin and observing whether the skin 'breaks out'.

In the patch test studies, an average of 1.6 per cent of people showed some allergic reaction to tea tree oil. It is known, however, that in several of the patch test studies degraded tea tree oil was used to test for sensitisation. Tea tree oil degrades when it is repeatedly exposed to air, light and high temperatures.

When tea tree oil is degraded, peroxide levels increase – and degradation products can form, such as 1,2,4-trihydroxymenthane which has been shown to be a skin sensitiser. The incidence of sensitisation in the patch test studies may therefore be an overestimate due to peroxides and their degradation products in the oils tested.

A 2001 study for the Rural Industries Research and Development Corporation[13] investigated the threshold concentration for allergic reactions to tea tree oil in eight people who had been confirmed to be sensitised to tea tree oil.

The lowest concentration of tea tree oil able to elicit a skin reaction in these subjects was 0.5% (one person), 1% (one person), 2% (three people), 5% (two people) and 10% (one person).

[10] Aspres N and Freeman S (2003). Predictive testing for irritancy and allergenicity of tea tree oil in normal human subjects. *Exogenous Dermatology*, Volume 2, pages 258-261.
[11] Crieg JE, Carson CF, Stuckey MS, Riley TV (1999). Skin sensitivity testing for tea tree oil. Project UWV-42A. Rural Industries Research and Development Corporation.
[12] Veien NK, Rosner K, Skovgaard GL (2004). Is tea tree oil an important contact allergen? *Contact Dermatitis*, Volume 50, pages 378-379.
[13] Crieg JE, Carson CF, Stuckey MS, Riley TV (1999). Skin sensitivity testing for tea tree oil. Project UWV-42A. Rural Industries Research and Development Corporation.

This, and other studies generally have demonstrated that the tea tree concentration at which an allergic response may be elicited is greater than 2% in the majority of sensitised subjects. As the concentration of tea tree oil in the majority of formulated products is 2.5% or below, the incidence of allergic reactions being elicited by good quality tea tree oil in sensitised individuals is likely to be small.

Evidence of this is borne out by adverse event data collected by six companies that supply tea tree oil products. The company data shows that the incidence of adverse reports is dependent on the concentration of oil, with most of the reports occurring with undiluted tea tree oil. Overall, with records from more than 10 years covering 38 million products – many of which were full strength or high concentration tea tree oil, the incidence of adverse events reported for all tea tree oil-containing products is low (0.0016%).

Skin penetration

The absorption of substances from outside the skin to positions beneath the skin is referred to as percutaneous absorption.

Substances can penetrate the layers of the skin by moving across cells, in between cells, or via structures such as hair follicles or sweat glands.

A report on the percutaneous absorption of tea tree oil was completed for the Rural Industries Research and Development Corporation in 2006[14]. This study showed that when undiluted tea tree oil is applied to human skin, only three of the more than 100 components (terpinen-4-ol, alpha-terpineol and 1,8-cineole) in tea tree oil can penetrate the skin.

Only two of these components, terpinen-4-ol and alpha-terpineol, are able to penetrate the entire thickness of the epidermis (the outer layer of skin).

When a 20% tea tree oil formulation was used, only terpinen-4-ol was able to fully penetrate the epidermis.

The data showed that only a small quantity – 1.1-1.9% (of 20% tea tree oil solution) and 2-4% (of pure tea tree oil) – of the applied amount penetrated into or through human epidermis.

A further study demonstrated that evaporation removes more than 90 per cent of tea tree oil from the skin surface, thereby quickly removing any potential for it to be absorbed into the bloodstream[15].

Overall, it is apparent that the penetration of TTO components through human skin is limited but that enough is absorbed by the skin for it to be an effective antibacterial, anti-viral, anti-inflammatory and anti-fungal.

[14] Cross S and Roberts M (2006). In-vitro human epidermal membrane penetration of tea tree oil components from pure oil and a 20% formulation. Report to the Rural Industries Research and Development Corporation.

[15] Southwell IA (2007). Tea tree oil stability and evaporation rate. An addendum to p-Cymene and Peroxides, indicators of oxidation in tea tree oil. A report for the Rural Industries Research and Development Corporation, September 2006, RIRDC Publication No 06/112, RIRDC Project No ISO-2A.

Toxicity

All substances, water included, have a level at which they are considered toxic. Because individuals from one species can respond differently to the same dose of a toxin, a measure called LD50 is used to define a substance's toxicity.

LD50 is the amount of a chemical that is lethal to one-half (50 per cent) of the animals exposed to it. Lethal dosage often varies depending on the method of administration - it can be fed (oral LD50), applied to the skin (dermal LD50), or administered in the form of vapours (inhalation LD50). LD50s are usually expressed as the weight of the chemical per unit of body weight (mg/kg).

LD values obtained from animal studies may be used to estimate human toxicity. A large safety factor is usually used to allow for differences between species. This is because the biology of test animals, while similar to that of humans in many respects, sometimes differs in important aspects.

The lower the LD50 figure the more toxic the substance. Tea tree oil has a LD50 (oral) in rats of 1900 mg/kg. For comparison, the LD50 in rats of some other common substances are shown in the table.

Substance	LD50 amount
Vitamin C	11,900 mg/kg
Ethyl alcohol ('alcohol')	7060 mg/kg
Citric acid (found in citrus fruits)	5040 mg/kg
Sodium chloride (table salt)	3000 mg/kg
Ferrous sulphate(food additive)	320 mg/kg
Dieldrin (insecticide)	38 mg/kg

Undiluted tea tree oil should not be taken orally and is classified as harmful via the oral route according to European Union's Dangerous Preparations Directive. There have been five studies[16,17,18,19,20] published on accidental tea tree oil poisoning in humans. The amount of oil accidentally ingested varied from less than 10 mls to half a cup. At these relatively high doses, tea tree oil exposure led to diarrhoea, abdominal pain, rash, incoordination and muscle weakness. These symptoms had generally resolved within 36 hours.

Given tea tree oil is usually applied to the skin (either indirectly as a component of products such as moisturisers or soap, or directly as an antiseptic) dermal toxicity studies are of particular interest.

The dermal acute toxicity of tea tree oil has been investigated in rabbits[21]. There were no deaths and the LD50 (dermal) was determined to be greater than 2000 mg/kg body weight. Similar results have been obtained in another study where the acute dermal LD50 in rabbits was greater than 5000 mg/kg body weight.

When extrapolated to humans, and examined in conjunction with skin absorption studies, it can be concluded that the doses of tea tree oil delivered to the skin through cosmetic products or undiluted tea tree oil are not toxic. Further, not enough tea tree oil is absorbed by the skin to cause acute effects as most of it evaporates after application.

[16] Jacobs MR, Hornfeldt CS (1994). Melaleuca oil poisoning. *Clinical Toxicology*, Volume 32, pages 461-464.
[17] Del Beccaro MA (1995). Melaleuca oil poisoning in a 17-month-old. *Veterinary and Human Toxicology*, Volume 37, pages 557-558.
[18] Morris M, Donoghue A, Markovitz J, Osterhoudt K (2003). Ingestion of tea tree oil (Melaleuca oil) by 4-year-old boy. *Pediatric Emergency Care*, Volume 19, pages169-171.
[19] Seawright A. (1993). Tea tree oil poisoning - comment. *Medical Journal of Australia*. Volume 159, page 831.
[20] Elliott C (1993). Tea tree oil poisoning. *Medical Journal of Australia*, Volume 159, pages 830-831.
[21] PSC (1989b). Final report; Acute dermal toxicity limit of tea tree oil batch 88/375 in the rabbit. Project No.:T1239. Pharmaceutical Consulting Service, Box 42, Round Corner, NSW, Australia.

Health effects

Early in 2007 a study was published in the *New England Journal of Medicine (NEJM)*[22] that suggested a link between tea tree oil use and breast development in young boys (a condition called prepubertal gynecomastia). It was claimed that three boys had developed breasts after using products containing lavender oil and tea tree oil.

Upon investigation it was found that in two of the cases the boys had been using products that contained no tea tree oil. In the third case, shampoo and hair gel containing tea tree oil and other products was used. Analysis of the composition of these products showed negligible levels of tea tree oil.

A number of inaccuracies and inconsistencies in the *NEJM* report have been noted and published. The Australian tea tree industry has made a formal request to the *NEJM* for the article to be retracted pending further and more serious investigation of the article's allegations.

Over the past 21 years two of the world's largest manufacturers of tea tree oil products have together sold more than 150 million bottles of product containing tea tree oil. Both companies keep detailed records of any adverse reactions to their products. The product complaint rate over this period of time for this volume of products is 0.0016%, with only minor complaints reported.

There remains no objective scientific and credible evidence of a connection between prepubertal gynaecomastia and tea tree oil.

An important step in determining the safety of a product is testing whether it has the capacity to damage genetic material within an organism's cells, produce extreme sensitivity to sunlight or whether it is poisonous to cells.

Tea tree oil has been assessed for safety in each of these areas.

Genotoxicity

The potential for tea tree oil to damage a cell's genetic material, a phenomenon called genotoxicity, has been investigated in bacteria. Because bacteria reproduce rapidly, any mutations quickly become apparent. In one study, samples of commercially available tea tree oil were added to bacterial colonies to see whether any mutations developed. No mutagenic effect was observed in any of the brands of tea tree oil on any of the strains of bacteria tested.

The same study found that terpinen-4-ol, the active ingredient in tea tree oil, also did not damage bacterial DNA[23].

A subsequent study on mouse bone marrow cells showed that tea tree oil at a dose of up to 1750 mg/kg bodyweight did not break, nor alter the structure of, chromosomes. Because the genetic material remained intact this study indicates that tea tree oil is not genotoxic[24].

Phototoxicity

Some chemicals are phototoxic, so-called because they can cause humans or animals to have an extreme reaction to sunlight or other ultraviolet light. This reaction frequently manifests as severe sunburn. Several common medications – ranging from antibiotics to tranquilizers and cancer medicines – are phototoxic. A phototoxicity study, performed with undiluted tea tree oil in hairless mice, showed tea tree oil is not phototoxic[25].

Cytotoxicity

Substances that are toxic to cells are considered cytotoxic. A 1996 study demonstrated that tea tree oil at a concentration of 100 µg/ml did not cause any significant cytotoxicity[26]. However at concentrations of 300 µg/ml or higher, significant cytotoxicity was observed. In humans, blood levels of tea tree oil components are very unlikely to reach these levels.

[22] Henley DV, Lipson N, Korach KS, Bloch CA (2007). Prepubertal gynecomastia linked to lavender and tea tree oils. *New England Journal of Medicine*, Volume 365, pages 479-485.

[23] Fletcher JP, Cassella JP, Hughes D, Cassella S (2005). An evaluation of the mutagenic potential of commercially available tea tree oil in the United Kingdom; *International Journal of Aromatherapy*, Volume 15, Issue 2, pages 81-86.

[24] ICP Firefly Pty Ltd (2005). In vivo micronucleus test of Australian Tea Tree Oil (*Melaleuca alternifolia*) Batch ATTIA/0501. ICP Firefly Study No.: ICPQN436.A.A. ICP Firefly Pty Ltd, PO Box 6198, Alexandria, NSW, Australia.

[25] Forbes PD and Davies RE (1982). Phototoxicity of selected materials, Report No. QFM-8, Q-Test Inc., Pennsylvania USA.

[26] Söderberg TA, Johansson A, Gref R (1996). Toxic effects of some conifer resin acids and tea tree oil on human epithelial and fibroblast cells; *Toxicology*, Volume 107, pages 99-109.

Can bacteria resist tea tree oil?

The capacity of tea tree oil to kill bacteria has been well-established.

Investigations have now turned to whether bacteria, just as they can become resistant to antibiotics, can also become resistant tea tree oil.

Dr Christine Carson and colleagues from the Tea Tree Oil Research Group at The University of Western Australia have examined the susceptibility of bacterial strains to tea tree oil, while also looking at whether bacteria are likely to develop resistance to the oil.

Working with PhD researcher Ms Chelsea Papadopoulos, Dr Carson investigated the response to tea tree oil of *Pseudomonas aeruginosa*, a bacterium that typically infects the respiratory tract, urinary tract, burns and wounds and has been observed to be resistant to many commonly used antibiotics, antiseptics and disinfectants.

She also assessed the activity of tea tree oil components, such as terpinen-4-ol, and whether they could provoke bacterial resistance.

Many bacteria have previously been shown to be susceptible to tea tree oil at concentrations ranging from 0.06-0.5%, while *Pseudomonas aeruginosa* has consistently shown reduced susceptibility to tea tree oil, with concentrations of 2-8% required to inhibit it.

Dr Carson's study found that *P. aeruginosa* is less susceptible to tea tree oil because its outer membrane makes it more difficult for tea tree oil to permeate. However, Dr Carson said repeated attempts to make *P. aeruginosa* more resistant to tea tree oil had met with limited success.

Other work by colleague Dr Katherine Hammer on the bacterium *Staphylococcus aureus* showed similar results.

"Bacteria appear to be overwhelmed by tea tree oil and its many active components," Dr Carson said. "Overall, it is unlikely that resistance to tea tree oil would develop in *P. aeruginosa* following long-term continuous exposure. The development of resistance in other species of bacteria also seems unlikely to occur."

Tea tree oil stability

The composition of tea tree oil changes over time, particularly when it is exposed to the air but also when the oil is exposed to light and high temperatures.

In 2006, a comprehensive study was conducted[27] to see how the composition of tea tree oil changed over a 12 month period. The study design replicated the conditions under which tea tree oil might be used by consumers – bottles of oil were regularly opened, exposing the oil to air and light for short periods, and small amounts of the oil were removed.

The chemical composition of this oil was analysed. When the oil was not in use it was stored in 100ml amber glass bottles fitted with child-resistant polypropylene caps at 22°C away from heat sources and light.

When assessing the quality of tea tree oil and the extent of degradation by exposure to the air, peroxide value and p-cymene levels are useful indicators. Both peroxide values and p-cymene levels increase when tea tree oil is degraded.

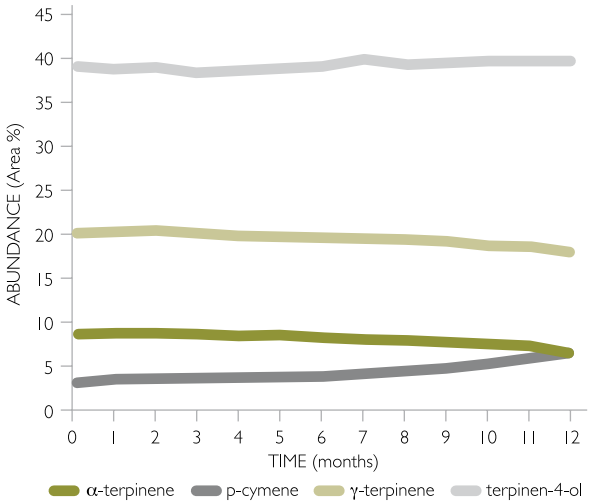
Over the first six months of the study the composition of the oil remained relatively unchanged.

After this time there was a slight increase in p-cymene levels. However, the p-cymene level was still less than 6.7% after 12 months, which is below the upper limit of 8% specified in the International Standard.

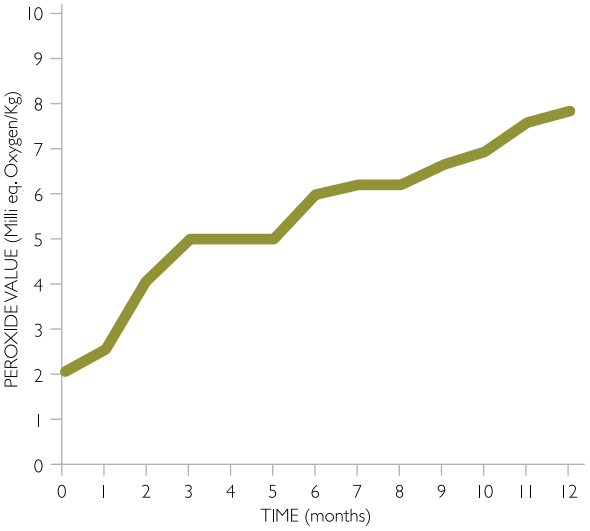
Similarly, the peroxide value remained under 10 milli-equiv O_2 throughout the study. This indicated that there was no appreciable oxidation or degradation of the oil for at least 12 months under typical in-use conditions.

To reduce oxidation, the tea tree industry Code of Practice recommends tea tree oil products be kept tightly sealed and stored away from light and heat.

Abundance of major tea tree oil components over time (in-use conditions)



Peroxide level over time (in-use conditions)



Stability in formulated products

The stability of tea tree oil in formulated products is dependent on several factors. Good formulation design and manufacturing practices play an important role. More importantly, formulated products should be stored appropriately by consumers. They should be kept away from direct sunlight and excessive heat and exposure to air should be minimised.

Storage stability data on several formulated products has been collated and the stability of the products monitored using the p-cymene content of the tea tree oil. Generally, the p-cymene content increased with storage time, but remained below the upper limits specified in the ISO Standard. The rates of degradation of the oil varied according to the medium containing the oil.

In Europe a shelf-life of 12 months after opening is recommended for formulated tea tree oil products.

[27] RIRDC Project USC-9A: Stability of Tea Tree Oil. Report to the Rural Industries Research and Development Corporation from the Centre for Phytochemistry & Pharmacology, Southern Cross University.

Code of Practice and standards

Tea tree oil oxidizes when it is exposed to air and also when exposed to sunlight and high temperatures.

As part of its responsibility to consumers, the Australian tea tree industry adheres to stringent legal requirements that ensure the quality and safety of its products. Pure tea tree oil of more than 15ml in volume is bottled in ribbed dark glass bottles and fixed with a child-proof safety cap. Tea tree oil is a Schedule 6 Poison in Australia.

Tea tree oil sold in clear glass bottles of greater than 15ml volume is not 100% tea tree oil. Pure tea tree oil should only be stored in clear glass containers for limited periods of time, as over-exposure to light will alter its quality.

Chemical composition

Tea tree oil contains more than 100 naturally-occurring compounds. The required levels of 15 components are stipulated in the International Standard for Oil of Melaleuca, Terpinen-4-ol type (ISO 4730) and the Australian Standard for Oil of Melaleuca, terpinen-4-ol type (AS 2782-1997). These standards require the oil to have more than 30% terpinen-4-ol and less than 15% cineole.

It is generally accepted that terpinen-4-ol plays an important role in tea tree oil's antimicrobial activity and that a high concentration is therefore desirable.

The purity, composition and physico-chemical properties of tea tree oil are further defined in French Standard T75-358 as well as in the Deutscher Arzneimittel Codex (DAC 1986) 8th supplement, 1996; European Pharmacopoeia; British Pharmacopoeia; and Martindale Extra Pharmacopoeia. The pharmacopoeia contain monographs that give quality standards for tea tree oil.

Quality control

The Australian tea tree industry is committed to ensuring that tea tree oil produced in Australia complies with the International Standard.

Through the Australian Tea Tree Industry Association, the industry follows and regularly updates a Code of Practice to guide the safe storage, handling and manufacture of tea tree oil and tea tree oil products.

In addition, the Australian tea tree industry undertakes an education program for downstream users and consumers to address the proper use of tea tree oil. This includes a recommendation to consumers that they discard opened bottles of oil that are more than 12 months old.

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