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Compilation and Review of Published and Unpublished Tea Tree Oil Literature

A report for the Rural Industries Research and Development Corporation

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Foreword

The aim of this project was to assess, compile and review the available published and unpublished data on tea tree oil. This information is presented in the form of a Database of Tea Tree Oil Literature, a review of the literature for publication in a scientific journal and a Material Safety Data Sheet appropriate for use by all suppliers of tea tree oil.

There are now many scientific publications describing many aspects of tea tree oil, ranging from tree breeding, harvesting and oil distillation to its effectiveness in reducing inflammation, treating dandruff and cold sores. However, much of this scientific literature is not readily accessible for industry stakeholders. Similarly, no significant compilation and review of the data has occurred recently, meaning that areas of research that have been overlooked are not obvious. Finally, the compilation of available data into a standard tea tree oil Material Safety Data Sheet is useful to all industry stakeholders in the tea tree oil industry.

This report includes a review of the available tea tree oil literature (including eco-toxicity), a tea tree oil literature database, and a Material Safety Data Sheet created for tea tree oil.

This project was funded from industry revenue which is matched by funds provided by the Australian Government. This report, a new addition to RIRDC's diverse range of over 1500 research publications, forms part of our Tea tree oil R&D Program, which aims to support the continued development of a profitable tea tree oil industry.

Most of our publications are available for viewing, downloading or purchasing online through our website:

- downloads at www.rirdc.gov.au/reports/Index.htm
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Peter O'Brien

Managing Director
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Abbreviations

h	hour
l	litre
LC_{50}	Concentration per litre of aqueous solution lethal to 50% of test organisms
LC_{50}	Dose per kilogram of body weight that is lethal to 50% of test organisms
LC_0	Concentration per litre of aqueous solution lethal to 0% of test organisms
LC_{100}	Concentration per litre of aqueous solution lethal to 100% of test organisms
µ l	microlitre
min	minute
mg	milligrams
MSDS	Material safety data sheet
PDF	portable document file
ppm	parts per million

Contents

Executive Summary

The body of literature about tea tree (*Melaleuca alternifolia*) oil has grown dramatically over the last 10 years as a number of Australian and international researchers investigate tea tree oil. Collectively, their results represent a significant advance in our knowledge of tea tree oil and its properties. The inclusion of a literature review in this report is therefore a timely contribution to our understanding of tea tree oil.

The tea tree oil literature was reviewed focusing on the more recent literature but incorporating older publications for historical perspective. This review article will be published in a peer-review scientific journal and will be a significant benefit to the tea tree oil industry as it strives to establish tea tree oil as a bona fide alternative therapeutic agent.

The ecotoxicity of tea tree oil was reviewed. However, since very little data are available describing the ecotoxicity of tea tree oil, information from secondary related sources was sought. Data pertaining to the ecotoxicity of other essential oils and essential oil components against various aquatic and terrestrial vertebrates and invertebrates were compiled and reviewed. While these data may not substitute for tea tree oil data, they can guide and inform future ecotoxicity studies. This area of tea tree oil research has not received adequate attention.

The tea tree oil literature was compiled into a database designed to be accessible via the internet, potentially through the ATTIA web site. More than 500 tea tree oil publications were found, including research articles, reviews, conference abstracts or presentations, books and theses. Over 100 requests were made to publishers for copyright permissions to reproduce articles in full. In many cases this was granted or permission was granted to reproduce abstracts only. The availability of such a collection to industry stakeholders is unique and should facilitate greater appreciation of the work that has been done to date and the areas that require more attention.

A Material Safety Data Sheet (MSDS) was compiled from scientific publications, industry documents and various regulatory codes. This represents the most up to date and comprehensive MSDS available for tea tree oil. It is designed for universal application throughout the tea tree oil industry and will be of significant benefit to tea tree oil exporters. It may also enhance the standing of ATTIA to stakeholders, purchasers and regulatory agencies.

The collection and evaluation of all of this literature, and the construction of the MSDS made it possible to identify areas of research that have been overlooked or neglected, and to make recommendations regarding future tea tree oil studies. The two areas that require significant further work fall into two broad categories; (1) Safety and toxicity and (2) Clinical efficacy. Expansion of research in these two areas is an absolute requirement for further regulatory approvals for tea tree oil.

In conclusion, the contents of this report represent a unique collection and digest of the existing tea tree oil literature. This report should help industry stakeholders have a better understanding of the state of tea tree oil research and development.

Chapter 1. Introduction

Compared to the early 1990's, there is now an extraordinary amount of literature available describing the properties of tea tree oil. In particular, ATTIA and industry participants have compiled an extensive collection of tea tree oil literature. However, the usefulness of these data collections could be significantly enhanced, as described below.

The existing scientific literature are somewhat incomplete and are not readily accessible to most industry stakeholders. A comprehensive collection of tea tree oil literature in the form of an electronic database would therefore be extremely valuable. Furthermore, the availability of the database to industry stakeholders would be a valuable resource for the industry.

As a natural extension of this, a collation and review of the safety, toxicity and eco-toxicology data is required. This could reduce or eliminate future duplication of effort, and highlight areas of research that have been overlooked. Since these areas of oversight are likely to be numerous, a review is unlikely to reduce research expenditures for the industry but will at least allow the industry to focus their limited resources on areas of priority.

Preparation of generic Material Safety Data Sheet (MSDS) for TTO suitable for multiple importing destinations will be of significant benefit to tea tree oil exporters. It could also enhance the standing of ATTIA to stakeholders, purchasers and regulatory agencies. The preparation of the MSDS may also highlight areas of research or inquiry that require further work.

In conclusion, despite the amount of literature available on tea tree oil, data have not been compiled into a readily accessible format for industry participants. The benefits of a review and compilation of tea tree oil literature to industry are numerous, and the preparation of an up-to-date, generic MSDS may simplify matters for both Australian exporters and overseas importers.

Chapter 2. Objectives

The objectives of this work, in order of priority, are:

1. **1.** A review published in a peer-reviewed journal and for RIRDC of the following for TTO: safety and toxicity, clinical efficacy
2. **2.** An assessment and/or review of the eco-toxicology of TTO based on direct and indirect data. If sufficient data are available a review will be published in a peer-reviewed journal and RIRDC report.
3. **3.** Conversion of tea tree oil literature into an electronic resource for researchers, industry participants and stakeholders
4. **4.** Production of a Material Safety Data Sheet (MSDS) suitable for multiple importing destinations
5. **5.** Written recommendation for future TTO studies

Chapter 3. Review of literature

Tea tree oil

Many complementary and alternative medicines have enjoyed increased popularity in recent decades. Efforts to justify their use have seen their putative biological properties come under increasing scrutiny *in vitro* and, in some cases, *in vivo*. One such product is tea tree oil (TTO), the volatile essential oil derived mainly from the Australian native plant *Melaleuca alternifolia*. Employed largely for its antimicrobial properties, TTO is incorporated as the active ingredient in many topical formulations used to treat cutaneous infections. It is widely available over-the-counter in Australia, Europe and North America and is marketed as a remedy for various ailments.

Composition and chemistry

TTO is composed of terpene hydrocarbons, mainly monoterpenes, sesquiterpenes and their associated alcohols. Terpenes are volatile, aromatic hydrocarbons and may be considered as polymers of isoprene which has the formula C_5H_8 (Sharp, 1983). Early reports on the composition of TTO described 12 (Guenther, 1968), 21 (Laakso, 1965 cited in Altman, 1988) and 48 (Swords & Hunter, 1978) components. The seminal paper by Brophy and colleagues (1989) examined over 800 TTO samples by gas chromatography and gas chromatography mass spectrometry and reported approximately 100 components and their range of concentrations. Given the scope for variation, it is fortunate that the composition of oil sold as TTO is regulated by an international standard for "Oil of *Melaleuca* –terpinen-4-ol type" which sets maxima and/or minima for 14 components of the oil (International Organisation for Standardisation, 1996) (see Table 3.1). Notably the standard does not dictate the species of *Melaleuca* from which the TTO must be sourced. Instead, it sets out physical and chemical criteria for the desired chemotype. There are several varieties, or chemotypes, of *M. alternifolia* and each produces oil with a distinct chemical composition. Six chemotypes have been described as follows: terpinen-4-ol chemotype (1), terpinolene chemotype (2), and four 1,8-cineole chemotypes (3-6) (Homer *et al*., 2000). The terpinen-4-ol chemotype typically contains levels of terpinen-4-ol of between 30-40% (Homer *et al.,* 2000) and is the chemotype used in commercial TTO production. This is the chemotype that will be discussed below. The components specified by the standard were selected for a variety of reasons including biological activity and provenance verification. For example, terpinen-4-ol is a major component of TTO and has long been considered the main antimicrobial component of the oil. Consequently, to optimise antimicrobial activity, a lower limit of 30% and no upper limit were set for terpinen-4-ol content. An upper limit of 15% and no lower limit were set for 1,8-cineole, although the rationale for this may not have been entirely sound; for many years cineole was erroneously considered to be a skin and mucous membrane irritant fuelling efforts to minimise its level in TTO. Recent work soundly refutes this notion but since cineole levels are usually inversely proportional to terpinen-4-ol levels, minimising cineole content in order to maximise terpinen-4-ol content remains an important consideration.

Despite the scope for batch to batch variation in TTO, no obvious differences in its bioactivity have been noted so far. The suggestion that oil from a particular *M. alternifolia* clone possesses enhanced cidal activity has been made (May *et al*., 2000) but the evidence is not compelling.

TTO has a relative density of 0.885-0.906 (International Organisation for Standardisation, 1996), is only sparingly soluble in water and is miscible with non-polar solvents. Some of the chemical and physical properties of TTO components are shown in Table 3.2.

The composition of TTO may change considerably during storage with ρ-cymene levels increasing and α- and γ-terpinene levels declining (Brophy *et al*., 1989). Light, heat, exposure to air and

moisture all affect oil stability and TTO should be stored in dark, cool, dry conditions preferably in a vessel that contains little air.

Provenance and nomenclature

The provenance of TTO is not always clear from its common name or those of its sources. It is known by a number of synonyms including "melaleuca oil" and "ti tree oil", "ti tree" being a Maori and Samoan common name for plants in the genus *Cordyline* (Weiss, 1997). Even the term "melaleuca oil" is potentially ambiguous since several chemically distinct oils are distilled from other *Melaleuca* species such as cajuput oil (also cajeput or cajaput) from *M. cajuputi* and niaouli oil from *M. quinquenervia* (often misidentified as *M. viridiflora*) (Lassak and McCarthy, 1983; Southwell & Lowe, 1999). However, the term has been adopted by the Australian Therapeutic Goods Administration as the official name for TTO. The use of common plant names further confounds the issue. In Australia, "tea trees" are also known as "paperbark trees" and collectively these terms may refer to species in the *Melaleuca* or *Leptospermum* genera of which there are several hundred. For instance, common names for *M. cajuputi* include "swamp tea tree" and "paperbark tea tree" while those for *M. quinquenervia* include "broad-leaved tea tree" and "broad-leaved paperbark" (Lassak & McCarthy, 1983). Many *Leptospermum* species are cultivated as ornamental plants and are often mistakenly identified as the source of TTO. In addition, the essential oil kanuka and manuka derived from the New Zealand plants *Kunzea ericoides* and *Leptospermum scoparium*, respectively, are referred to as New Zealand TTOs (Christoph *et al*., 2000) although they are very different in composition from Australian TTO (Perry *et al*., 1997). In this review article, the term TTO will refer only to the oil of *M. alternifolia*.

As explained above, the international standard for TTO does not specify which *Melaleuca* species must be used to produce oil. Rather it sets out the requirements for an oil chemotype. Oils that meet the requirements of the standard have been distilled from *Melaleuca* species other than *M. alternifolia* including *M. dissitiflora*, *M. linariifolia* and *M. uncinata* (Murtagh, 1999). However, in practice commercial TTO is produced from *M. alternifolia* (Maiden and Betche) Cheel. The *Melaleuca* genus belongs to the Myrtaceae family and contains approximately 230 species almost all of which are native to Australia (Craven, 1999). When left to grow naturally, *M. alternifolia* grows to a tree reaching heights of approximately 5-8 metres (Colton & Murtagh, 1999). Trees older than three years flower typically in October and November (Lassak & McCarthy, 1983, Baker, 1999) and flowers are produced in loose, white to creamy coloured terminal spikes, which can give trees a "fluffy" appearance (Weiss, 1997).

Commercial production

The commercial TTO industry was born after its medicinal properties were first reported by Penfold in the 1920s as part of a larger survey into Australian essential oils with economic potential. During that nascent stage, TTO was produced from natural bush stands of plants, ostensibly *M. alternifolia*, that produced oil with the appropriate chemotype. The native habitat of *M. alternifolia* is low-lying, swampy, sub-tropical, coastal ground around the Clarence and Richmond Rivers in north-eastern New South Wales and southern Queenland (Swords & Hunter, 1978) and, unlike several other *Melaleuca* species, it does not occur naturally outside Australia. The plant material was hand-cut and often distilled on the spot in make-shift, mobile, wood-fired bush stills. The industry continued in this fashion for several decades. Legend has it that the oil was considered so important for its medicinal uses that Australian soldiers were supplied oil as part of their military kits during World War II and that bush-cutters were exempt from national service (Carson & Riley, 1993). However, no evidence to corroborate these accounts could be found (A.-M Conde & M. Pollard, Australian War Memorial, Canberra, Australia, personal communication). Production ebbed after World War II as demand for the oil declined presumably due to the development of effective antibiotics and the waning image of natural products. Interest in the oil was rekindled in the 1970s as part of the general renaissance in natural products. Commercial plantations were established in the 1970s and 1980s allowing the industry to mechanise and produce large quantities of a consistent product (Brophy *et*

al., 1989; Johns *et al*., 1992). Today there are plantations in Western Australia, Queensland and New South Wales although the majority is in New South Wales around the Lismore region. Typically, plantations are established from seedlings sowed and raised in greenhouses prior to planting out in the field at high density. The time to first harvest varies from 1-3 years depending on the climate and rate of plant growth. Harvesting is by a coppicing process in which the whole plant is cut off close to ground level and chipped into smaller fragments prior to oil extraction.

Oil extraction

TTO is produced by steam distillation of the leaves and terminal branches of *M. alternifolia*. Once condensed, the clear to pale yellow oil is separated from the aqueous distillate. The yield of oil is typically 1-2% of the wet weight of the plant material. Alternative extraction methods have been considered including those using microwave technology but none has been utilised on a commercial scale.

Antimicrobial activity

Of all the properties claimed for TTO, it is those regarding antimicrobial activity that have received the most attention. The earliest reported use of the *M. alternifolia* plant that presumably exploited this property is the traditional use by the Bundjalung Aborigines of northern New South Wales. Crushed leaves of "tea trees" were inhaled to treat coughs and colds, or were sprinkled on wounds after which a poultice was applied (Shemesh & Mayo, 1991). In addition, tea tree leaves were soaked to make an infusion to treat sore throats or skin ailments (Low, 1990; Shemesh & Mayo, 1991). The oral history of Australian Aborigines also tells of healing lakes which were lagoons into which *M. alternifolia* leaves had fallen and decayed over time (Altman, 1988). Use of the oil itself, as opposed to the unextracted plant material, did not become common practice until Penfold published the first reports of its antimicrobial activity in a series of papers in the 1920s and 1930s. In evaluating the antimicrobial activity of *M. alternifolia* oil and other oils, he made comparisons with the disinfectant carbolic acid or phenol, the gold standard of the day, in a test known as the Rideal-Walker (RW) coefficient. TTO's activity was compared directly with that of phenol and rated at 11 times as active (Penfold & Grant, 1925). The RW coefficient of several of the components of TTO were also reported including cineole (3.5) and cymene (8) (Penfold & Grant, 1923), linalool (13) (Penfold & Grant, 1924), terpinen-4-ol (13.5) and terpineol (16) (Penfold & Grant, 1925). As a result, TTO was promoted as a therapeutic agent (Anon., 1930; Anon., 1933a; Anon., 1933b). It must be mentioned that in terms of the evidence they provide for the medicinal properties of TTO, these and many other early publications (Humphery, 1930; MacDonald, 1930; Halford, 1936; Penfold & Morrison, 1946; Feinblatt, 1960; Peña, 1962) are of limited value since by today's standards the data they provide are mostly anecdotal.

In contrast, contemporary data clearly show that the broad-spectrum antimicrobial activity of TTO includes antibacterial, antifungal, antiviral and anti-protozoal activity. Not all the activity has been characterised well in vitro and in the few cases where in vivo work has been done, data are promising but thus far inadequate. In vitro, methodological issues have plagued evaluation of the oil's antimicrobial activity since the lipophilic oil does not lend itself to standard aqueous test systems. Despite this, considerable work has been done, particularly on the antibacterial activity of the oil.

Antibacterial activity

Evaluation of the antimicrobial activity of TTO has been impeded by its physical properties; TTO is only sparingly soluble in water and this limits its miscibility in test media. The solubility of several components of TTO is shown in Table 3.2. Different strategies have been used to counteract this problem, the addition of surfactants to broth and agar test media being used most widely (Atkinson & Brice, 1955; Beylier, 1979; Carson *et al*., 1995a,b; Griffin, Markham & Leach, 2000; Banes-Marshall *et al*., 2001). Dispersion of TTO in liquid media usually results in a turbid suspension that makes determination of endpoints in susceptibility tests difficult. Occasionally dyes have been used as

visual indicators of the MIC with mixed success (Chand *et al*., 1994; Carson *et al*., 1995a,b Mann & Markham, 1998).

TTO has been tested in vitro against a wide variety of bacteria. Only a few reports of the antibacterial activity of TTO appear in the literature from 1940 to the 1980s. The earliest of these was published by Atkinson and Brice (1955), who assessed plants of the Myrtaceae family for antibacterial activity by both agar and broth dilution assays. Antibacterial titres (% v/v) as determined by agar and broth dilution assays were 0.63 and 0.31, respectively, for *Staphylococcus aureus,* 1.25 and 0.24 for *Salmonella typhi* and 0.31 and 0.10 for *Mycobacterium phlei* (Atkinson & Brice, 1955). Similarly, Low *et al*. (1974) described the antibacterial activity of a number of essential oils from the Myrtaceae family. They used the agar dilution method of Atkinson and Brice and found MICs (% v/v) of 0.062 for *S. aureus* and 0.031 for *Salm. typhi*. They also used an assay where test organisms were exposed to each neat essential oil for 10 minutes only, after which viable organisms were recovered. With *M. alternifolia* oil, *S. aureus* could not be recovered whereas viable *Pseudomonas aeruginosa* were recovered (Low *et al.*, 1974).

In the study by Beylier (1979), more than 100 oils were initially examined for antimicrobial activity, and 10 of these (including *M. alternifolia* oil) were selected for further investigation. The MIC (% v/v) ranges were 0.25 - 0.5 for *S. aureus*, 0.125 - 0.25 for *Escherichia coli* and 4 for *P. aeruginosa* (Beylier, 1979). MICs for *Candida albicans* and *Aspergillus niger* were also determined in this study and these will be discussed below.

Walsh and Longstaff (1987) used both broth and agar dilution methods to assess 'Melasol', a product containing 40% TTO, 13% isopropyl alcohol and 47% water, for activity against oral pathogens. MICs (% v/v) of Melasol were 0.08 for *S. aureus*, 0.16 for *Streptococcus faecalis*, 0.16 for *P. aeruginosa* and 0.08 for *E. coli*, by the agar method (Walsh & Longstaff, 1987). These MICs are low compared to those obtained in the previous studies, especially considering that Melasol contains only 40% TTO, however, the alcohol in the solution may have accounted for this activity. A range of oral microorganisms, such as *Actinomyces viscosus*, *Bacteroides gingivalis*, *Eikenella corrodens* and *Strep. mutans*, was tested also and MICs ranged from 0.02 - 0.08% (Walsh & Longstaff, 1987).

From the early 1990s onwards, many reports detailing the antimicrobial activity of TTO have appeared in the scientific literature. Although there was still a degree of discrepancy between the methods used in the different publications, often the MIC values reported were relatively similar. A summary of some of the published in vitro susceptibility data for bacteria is shown in Table 3.3. The majority of MICs and MBCs are in the range of 0.06% - 1.0%, however, MICs of more than 2% have been reported for some commensal skin staphylococci and micrococci, *Enterococcus faecalis* and *P. aeruginosa* (Hammer *et al.*, 1996; Banes-Marshall *et al.*, 2001).

The activity of TTO against antibiotic-resistant bacteria has attracted considerable attention with methicillin-resistant *S. aureus* (MRSA) receiving the most attention thus far. Since the potential to use TTO against MRSA was first hypothesised (Walsh & Longstaff, 1987), several groups have evaluated the activity of TTO against MRSA beginning with Carson *et al*. (1995a) who examined 64 MRSA from Australia and the United Kingdom, including 33 mupirocin-resistant isolates. The MIC and MBC of the Australian isolates were 0.25% and 0.5%, respectively, while those for the UK isolates were 0.312% and 0.625%, respectively. Subsequent reports on the susceptibility of MRSA to TTO have given similar results (Nelson, 1997; Chan & Loudon,1998; Elsom & Hide, 1999; May *et al*., 2000; Hada *et al*., 2001).

Resistance to TTO

Decreased susceptibility to TTO has been reported for a number of bacteria including *P. aeruginosa* (Hammer *et* al., 1996; Griffin *et al*., 2000, Banes-Marshall *et al*., 2001). The mechanism by which *P. aeruginosa* tolerates higher concentrations of TTO has begun to be explored and appears to be

associated with the outer membrane (Mann, Cox & Markham, 2000; Griffin, Wyllie & Markham, 2001).

Resistance to TTO *per se* has not been reported despite medicinal use of the oil in Australia since the 1920s. However, the question of whether or not true resistance to TTO can be induced *in vitro* or may occur spontaneously *in vivo* remains unanswered. It is possible that the multi-component nature of TTO may reduce the potential for resistance to occur spontaneously since multiple simultaneous mutations may be required to overcome all the antimicrobial components of TTO. These are important issues if TTO is to be used more widely, particularly against antibiotic-resistant organisms. There has been one report of induced resistance to TTO in *S. aureus* (Nelson, 2000) where stepwise exposure of five MRSA isolates to increasing TTO concentrations yielded three isolates whose MIC had risen to 1% and one isolate each whose MIC had increased to 2% and 16% TTO. All isolates had initial MICs of 0.25%. There has also been one report suggesting that *E. coli* which harbour mutations in the multiple antibiotic resistance (*mar*) operon, so-called Mar mutants, may exhibit decreased susceptibility to TTO. However, the decrease in susceptibility seen in this work by time-kill and broth dilution methods was marginal and cannot be considered strong evidence of this phenomenon (Gustafson *et al*., 2001), although it remains feasible and more data should be sought.

Mechanism of antibacterial action

The mechanism of action of TTO has now been partly elucidated. Prior to the availability of data, assumptions about its mechanism of action were made on the basis of its hydrocarbon structure and attendant lipophilicity. Hydrocarbons partition preferentially into biological membranes and disrupt their vital functions (Sikkema, deBont & Poolman, 1995) and TTO and its components were presumed to behave in this manner. This premise is further supported by data showing that TTO permeabilises model liposomal systems (Cox *et al*., 2000). In previous work with hydrocarbons not found in TTO (Jackson & deMoss, 1965; Uribe *et al*., 1990) and with terpenes found at low concentrations in TTO (Andrews, Parks & Spence, 1980; Uribe, Ramirez & Peña, 1985), lysis and the loss of membrane integrity and function manifested by the leakage of ions and the inhibition of respiration were demonstrated. Treatment of *S. aureus* with TTO precipitates the leakage of potassium ions (Cox *et al*., 2000; Hada *et al*., 2003) and 260 nm-absorbing materials (Carson, Mee & Riley, 2002) and inhibits respiration (Cox *et al*., 2000). TTO also sensitizes previously tolerant cells to sodium chloride (Carson, Mee & Riley, 2002) and produces morphological changes apparent under electron microscopy (Reichling *et al*., 2002). However, no significant lysis of whole cells was observed by electron microscopy (Reichling *et al*., 2002) or spectrophotometrically (Carson, Mee & Riley, 2002), no cytoplasmic membrane damage as evidenced by lactate dehydrogenase release could be detected (Reichling *et al*., 2002) and only modest uptake of propidium iodide was observed (Cox *et al*., 2001b) after treatment with TTO.

In *E. coli*, detrimental effects on potassium homeostasis (Cox *et al*., 1998), glucose-dependent respiration (Cox *et al*., 1998), morphology (Gustafson *et al*., 1998) and ability to exclude propidium iodide have been observed. A modest loss of 280 nm-absorbing material has also been reported (Cox *et al*., 2001b). In contrast to the absence of whole cell lysis seen in *S. aureus* treated with TTO, lysis occurs in *E. coli* treated with TTO (Gustafson *et al*., 1998) and this effect is exacerbated by co-treatment with EDTA (C Carson, unpublished data). All of these effects confirm that TTO compromises the structural and functional integrity of bacterial membranes.

When the effects on *S. aureus* of terpinen-4-ol and α-terpineol, two of the main antibacterial components of TTO, and 1,8-cineole were examined, none was found to induce autolysis and all were found to cause the leakage of 260 nm-absorbing material and render cells susceptible to sodium chloride (Carson, Mee & Riley, 2002). Interestingly, the greatest effects were seen with 1,8-cineole, a component often considered to be marginally antimicrobial. This raises the possibility that while cineole may not be one of the primary antimicrobial components of TTO, it may permeabilise bacterial membranes and facilitate the entry of other more active components. Little work on the effects of TTO components on cell morphology has been reported. Electron microscopy of terpinen-

4-ol treated *S. aureus* cells (Carson, Mee & Riley, 2002) revealed lesions similar to those seen after TTO treatment (Reichling *et al*., 2002), including mesosomes.

The loss of viability, inhibition of glucose-dependent respiration and induction of lysis seen after TTO treatment all occur to a greater degree with organisms in the exponential rather than stationary phase of growth (Cox *et al*., 1997; Gustafson *et al*., 1998). The increased vulnerability of actively growing cells was also apparent in the greater degree of morphological changes seen in these cells by electron microscopy (Cox *et al*., 1997). The differences in susceptibility seen with bacteria in different phases of growth suggest that additional targets may be involved.

In vivo antibacterial activity

Despite the increasing amount of in vitro data for bacteria, few in vivo (or clinical) investigations have been performed. Clinical studies investigating the effects of TTO treatment on acne, dental plaque formation and the elimination of MRSA colonisation have been published.

In an investigation of acne treatment, Bassett *et al.* (1990) compared the efficacy of 5% TTO and 5% benzoyl peroxide for therapy, with 58 and 61 evaluable patients in each treatment group, respectively (Bassett *et al.*, 1990). Patients were assessed at commencement, and at 1, 2, and 3 months. Parameters assessed were the numbers of inflamed and non-inflamed lesions, and a grade was given for oiliness, erythema, scaling, pruritis and dryness. The major findings of the study were that both treatments reduced the numbers of inflamed lesions, although benzoyl peroxide performed significantly better than TTO. The benzoyl peroxide group also showed significantly less oiliness than the tea tree group, however the tea tree group showed significantly less scaling, pruritis and dryness. Erythema did not differ between groups. Interestingly, significantly fewer overall side effects were reported by the TTO group (27 of 61 patients) than the benzoyl peroxide group (50 of 63 patients).

A study comparing the effects of mouthwashes containing either approximately 0.34% TTO, 0.1% chlorhexidine or placebo on plaque formation and vitality was performed using eight volunteers (Arweiler *et al.*, 2000). On day zero, volunteers had their teeth professionally cleaned, and for the next four days they rinsed twice daily with one of the treatments and did not clean their teeth in any other manner. Teeth were clinically evaluated on days 1, 2, 3 and 4. Each mouthwash was evaluated in this manner, with a wash-out period of 10 days between the end of one treatment and the beginning of the next. The plaque index and plaque vitality from the TTO mouthwash treatment did not differ from placebo mouthwash on any day, whereas the chlorhexidine mouthwash differed significantly on all days. Thus the TTO treatment was considered ineffective at reducing plaque regrowth or the vitality of plaque organisms (Arweiler *et al.*, 2000). In contrast, a small study evaluating the effect of a 0.2% TTO mouthwash on oral flora suggested that TTO could reduce the number of mutans streptococci, and the total number of oral bacteria and that residual activity maintained these reduced levels for two subsequent weeks (Groppo *et al*., 2002).

A pilot study conducted by Caelli *et al.* (2000) examined the effectiveness of a 4% TTO nasal ointment and a 5% TTO body wash for the eradication of MRSA carriage, as compared to conventional treatment of mupirocin nasal ointment and Triclosan body wash. Of the 15 patients receiving conventional treatment, two were cleared and eight were chronic carriers at the end of therapy, compared to the tea tree group where five were cleared and three were chronic carriers. In addition, five patients from the conventional treatment group and seven from the TTO group did not complete therapy. Due to the low patient numbers, these differences were not statistically significant, although they indicate that TTO therapy may be effective in decolonising MRSA carriers.

In addition to these clinical studies, there is a single case report of a woman who treated herself successfully with a 5 day course of TTO pessaries after having been clinically diagnosed with bacterial vaginosis (Blackwell, 1991b). Of the three studies described above, two are limited by low

numbers of patients and all have some ambiguous or equivocal outcomes, indicating that much remains unknown about optimising TTO efficacy *in vivo*.

Antifungal activity

Published studies investigating the antifungal activity of TTO have focussed on assessing either the in vitro activity of the oil against medically relevant fungi, or the use of TTO to treat human fungal infections. These studies will be discussed here.

The development of protocols for evaluating the susceptibility of fungi to antifungal agents has lagged behind similar methods that have been developed for bacteria and only recently have standard methods been published for evaluating the in vitro activity of antifungal agents (Rex *et al.*, 2001). Prior to the publication of these standard methods, researchers used a variety of different assays to assess in vitro activity, which means that data from these studies is often difficult to compare. Another limitation of some of these published studies is that very often only one isolate of a given species is tested in any particular investigation, meaning that generalisations about susceptibility are limited.

A range of yeasts from the genera *Candida*, *Malassezia* and *Trichosporon* are susceptible *in vitro* to concentrations of TTO of less than 1.0%. Since *Candida* yeasts (in particular *C. albicans*) are commonly chosen as test organisms, a moderate amount of susceptibility data are available for these organisms. Individual MICs and MIC_{90s} that have been reported for *C. albicans*, by either the broth or agar dilution assay include (%) 0.04 (Beylier, 1979), 0.2 (Griffin, Markham & Leach, 2000), 0.25 (Vazquez *et al.*, 2000), 0.3 (Christoph *et al.*, 2000) and 0.44 (Nenoff *et al.*, 1996). Several other *Candida* species, such as *C. parapsilosis*, *C. glabrata*, *C. tropicalis*, *C. kefyr* and *C. krusei*, have been tested against TTO *in vitro* and MICs ranged from 0.25 to 0.5% and minimum fungicidal concentrations (MFCs) ranged from 0.5 to 1.0% (Vazquez *et al.*, 2000; Banes-Marshall *et al.*, 2001; D'Auria *et al.*, 2001). *Malassezia* yeasts also appear to be susceptible to TTO with MICs in the range of 0.06 – 0.44% (Nenoff *et al.*, 1996; Griffin & Markham, 2000). TTO has activity against single isolates of *T. cutaneatum, Schizosaccharomyces pombe* and *Debaromyces hansenii* with MICs of 0.22% (Nenoff *et al.*, 1996), 0.5% and 0.5%, respectively (D'Auria *et al.*, 2001).

Two studies have used the disc diffusion method to investigate the activity of TTO against dermatophytes. In both studies, zones of inhibition were seen adjacent to discs containing either 10 or 20 µl of neat TTO, using isolates of *Epidermophyton floccosum*, *M. audouinii*, *M. canis*, *T. mentagrophytes, T. rubrum* and *T. tonsurans* (Ånséhn, 1990; Concha *et al.*, 1998). The exception was one strain of *E. floccosum* which showed no zone of inhibition (Concha *et al.*, 1998). Several studies have investigated the activity of TTO against dermatophytes in more depth and have shown MICs of 0.7% for *E. floccosum* (Christoph *et al.*, 2000), 0.11 – 0.5% for *M. canis* (Nenoff *et al.*, 1996; D'Auria *et al.*, 2001), 0.25% for *M. gypseum* (D'Auria *et al.*, 2001) 0.12 – 0.75% for *T. mentagrophytes* (Bassett *et al.*, 1990; Nenoff *et al.*, 1996; Griffin & Markham, 2000; D'Auria *et al.*, 2001) and 0.12 – 1.0% for *T. rubrum* (Bassett *et al.*, 1990; Nenoff *et al.*, 1996; Griffin & Markham, 2000; D'Auria *et al.*, 2001). MFCs of TTO have been determined as follows; 0.25 – 0.5% for *M. canis* and *T. mentagrophytes*, 0.5% for *M. gypseum* and 0.25 – 1.0% for *T. rubrum* (D'Auria *et al.*, 2001).

Similar to studies performed with the dermatophytes, several methods have been used to investigate the activity of TTO against other filamentous fungi. With a few exceptions, these fungi are susceptible. All isolates of *Aspergillus niger, Rhizopus oligosporus* and *Penicillium* spp. showed zones of inhibition to either 20 µl or 35 µl oil on a paper disc (Concha *et al.*, 1998; Chao *et al.*, 2000). MICs for the filamentous fungi, mostly obtained by the agar dilution method, were in the range of 0.2 – 1.0% for isolates of *A. flavus, A. niger*, *Penicillium* spp., *Rhizopus* spp. and *Scopulariopsis* spp. (Beylier, 1979; Bassett *et al.*, 1990; Southwell, 1993; Rushton *et al.*, 1997; Christoph *et al.*, 2000; Griffin & Markham, 2000). However, isolates of *A. fumigatus* and *A. nidulans*

were not inhibited at 2% TTO in another study (Vazquez *et al.*, 2000). Fungicidal data for these organisms have not been published.

In vivo antifungal activity

A small number of trials has been published investigating the efficacy of TTO for fungal infections. The earliest of these was by Walker (1972), who published a series of his observations of patients treated with a TTO solution for a range of foot problems, including tinea pedis and onychomycosis. More recently, two comparative trials investigating onychomycosis (Buck *et al.*, 1994; Syed *et al.*, 1999), two investigating tinea pedis (Tong *et al.*, 1992; Satchell *et al*., 2002b) and one investigating dandruff (Satchell *et al*., 2002a) have been published. In the first of the onychomycosis trials (Buck *et al.*, 1994), patients were treated twice daily with either neat TTO or 1% clotrimazole solution for a total of 6 months of treatment. After this time, of 64 patients treated with TTO, 18% were culture negative with a total of 60% of participants having full or partial resolution. This compared to the clotrimazole treatment group (n = 53) of whom 11% were culture negative and 61% had full or partial resolution. Overall, there were no statistically significant differences between the two treatment groups. The second onychomycosis trial (Syed *et al.*, 1999) compared two creams, one containing 5% TTO alone and the other containing 5% TTO and 2% butenafine, both applied 3 times daily for 8 weeks. At completion of treatment the overall cure rate in patients treated with 5% TTO was 0%, compared to 80% for patients treated with both butenafine and TTO. The observation that TTO may be useful adjunct therapy for onychomycosis has also been made by Klimmek *et al*. (2002).

In the first trial investigating tinea pedis, patients were treated with 10% TTO in sorbolene, 1% tolnaftate or placebo, applied twice daily for 4 weeks (Tong *et al.*, 1992). At completion of treatment, patients treated with TTO had mycological cure and clinical improvement rates of 30% and 65%, respectively. This compares to mycological cure rates of 21% in patients receiving placebo and 85% in patients receiving tolnaftate. Similarly, clinical improvement was seen in 41% of patients receiving placebo and 68% of patients receiving tolnaftate. In the second trial, the efficacy of 25% and 50% TTO solutions in ethanol and polyethylene glycol solutions was evaluated by comparison to treatment with placebo (vehicle) (Satchell *et al*., 2002b). Patients applied their randomly assigned treatment twice daily for four weeks and were assessed after 2 and 4 weeks of treatment. Marked clinical responses were seen in 72% and 68% of the 25% and 50% TTO treatment groups, respectively, compared to 39% in the placebo group. Similarly, there were mycological cures in 55% and 64% of the 25% and 50% TTO treatment groups, respectively, compared to 31% in the placebo group. Dermatitis occurred in one patient in the 25% TTO group and three patients in the 50% TTO group resulting in the recommendation that 25% TTO be considered an alternative treatment for tinea since it was associated with fewer adverse reactions and was as effective as 50% TTO. These studies highlight the importance of considering the formulation of the TTO product when conducting in vivo work, since it is likely that the sorbolene vehicle used in the first trial significantly compromised the antifungal activity of the oil.

The efficacy of TTO in the treatment of mild to moderate dandruff was evaluated in a large, randomised, single-blind, placebo-controlled trial in which patients used their allocated treatment daily for 4 weeks (Satchell *et al*., 2002a). In this study, the 5% TTO group (n = 63) showed statistically significant improvements in the investigator-assessed whole scalp lesion score, total area of involvement score and total severity score, as well as in the patient-assessed itchiness and greasiness scores compared to the placebo group (n = 62). There were no serious adverse events in either treatment group and only three patients in the TTO group reported events compared to eight in the placebo group. The data from this trial show that 5% TTO is well-tolerated and appears effective in the treatment of mild to moderate dandruff.

Lastly, a case series of patients using TTO mouthwash for oropharyngeal candidiasis has been published (Jandourek *et al.*, 1998). The 13 patients included in the series were HIV positive patients who had already failed treatment with a 14 day course of oral fluconazole. Patients were treated with

15ml of tea tree solution four times a day for up to 28 days. After treatment of the 12 evaluable patients, two were cured, six were improved, four were unchanged and one patient had deteriorated. Overall, eight patients had a clinical response, and seven had a mycological response. In summarising the outcomes of these trials it seems apparent that treatment with TTO does not elicit a high rate of infection cure. This is most likely due to many factors such as length and frequency of treatment and the formulation of the trial product. In addition, it is believed that onychomycosis is unresponsive to topical treatment therefore a high rate of cure should not be expected (Weitzman & Summerbell, 1995).

Antiviral activity

The few studies that have investigated the antiviral properties of TTO support the anecdotal notion that TTO has antiviral properties. The antiviral activity of TTO was first shown using tobacco mosaic virus and tobacco plants with agricultural applications in mind (Bishop, 1995). A field trial was conducted in which *Nicotiniana glutinosa* plants were sprayed with 100, 250 or 500 ppm TTO or control solutions, and all plants were then experimentally infected with tobacco mosaic virus. After 10 days, there were significantly fewer lesions per square centimetre of leaf of plants treated with TTO as compared to controls (Bishop, 1995).

Schnitzler *et al*. (2001) investigated the activity of tea tree and eucalyptus oils against herpes simplex virus (HSV). Briefly, the activity of TTO was determined by incubating virus with varying concentrations of TTO, and then using these treated viruses to infect cell monolayers. After 4 days, the numbers of plaques formed by virus treated with TTO, or untreated control virus, were determined and compared. The concentration of TTO inhibiting 50% of plaque formation, as compared to controls, was 0.0009% for HSV1 and 0.0008% for HSV2. These studies also showed that at the higher concentration of 0.003%, TTO reduced HSV1 titres by 98.2% and HSV2 titres by 93.0%. Also, by applying TTO at different stages in the virus replicative cycle, TTO was shown to have the greatest effect on free virus (prior to infecting cells) although when TTO was applied during the adsorption period a reduction in plaque formation was seen also.

Some activity against bacteriophages, or viruses that infect bacteria, has also been reported with exposure to 50% TTO at 4°C for 24 h reducing the number of plaques formed on a bacterial lawn (Chao *et al*., 2000).

Further evidence for antiviral activity comes from a pilot study investigating the treatment of recurrent herpes labialis (cold sores) with a 6% TTO gel or a placebo gel without TTO (Carson *et al.*, 2001). Comparison of each patient group (both containing nine evaluable patients) at the end of the study showed that re-epithelialisation after treatment occurred after 9 days for the tea tree group and after 12.5 days for the placebo group. Other measures such as duration of virus positivity by culture or polymerase chain reaction, viral titres and time to crust formation were not significantly different, possibly due to small patient numbers. Interestingly, when TTO was evaluated for its protective efficacy in an in vivo mouse model of genital HSV type 2 infection it did not perform well (Bourne *et al*., 1999). In contrast, 1,8-cineole, a component of TTO, performed well protecting 7 of 16 animals from disease.

The results of these studies indicate that TTO may act against viruses in several ways. In addition to lethal effects directly on virus particles, TTO can also affect the way virus adsorbs to tissue culture cells and can cause a reduced rate of infection in tobacco plants.

Anti-protozoal activity

TTO also has anti-protozoal activity although the data on this are limited to two publications. TTO caused a 50% reduction in growth (as compared to controls) of the protozoa *Leishmania major* and *Trypanosoma brucei* at concentrations of 403 μg/ml and 0.5 μg/ml, respectively (Mikus *et al*., 2000). Further investigation showed that terpinen-4-ol contributed significantly to this activity. In a different

study, TTO at 300 μg/ml killed all cells of *Trichomonas vaginalis* (Viollon *et al*., 1996). This combined with anecdotal in vivo evidence that *Trichomonas vaginalis* infections may be successfully treated with TTO (Peña, 1962) suggest that further work is warranted.

Antimicrobial components of TTO

Considerable attention has been paid to which components of TTO are responsible for the antimicrobial activity, mainly the antibacterial and antifungal activities. Early indications from RW coefficients were that much of the activity could be attributed to terpinen-4-ol and α-terpineol (Penfold & Grant, 1925). Data available today confirm that these two components contribute substantially to the oil's activity (Carson & Riley, 1995; Raman, Weir & Bloomfield, 1995; Hammer *et al*., 2003). However, of the components tested it seems that most possess at least some degree of antimicrobial activity (Carson & Riley, 1995; Raman, Weir & Bloomfield, 1995; Hammer *et al*., 2003) and while some may be considered less active, none can be considered inactive.

The possibility that components in TTO may exert synergistic or antagonistic effects on the overall antimicrobial activity has been explored *in vitro* (Cox *et al*., 2001a) as has the potential for interactions with other essential oils, such as lavender (Cassella *et al*., 2002), and other essential oil components such as β-triketones from manuka oil (Christoph, Kaulfers & Stahl-Biskup, 2001; Christoph, Stahl-Biskup & Kaulfers, 2001). Given the numerous components of TTO, the scope for such effects is enormous and much more work is required to examine this question.

Anti-inflammatory activity

Anti-inflammatory activity has also been attributed to TTO but for many years only anecdotal evidence was available. In vitro work over the last decade has demonstrated that terpinen-4-ol can inhibit the production of several inflammatory mediators (such as interleukins) by human peripheral blood monocytes (Hart *et al*., 2000). This suggests a mechanism by which TTO may reduce the normal inflammatory response. Terpinen-4-ol also suppresses superoxide production by agonist-stimulated monocytes, but not neutrophils (Brand *et al*., 2001). In vivo, topically applied TTO has been shown to modulate the oedema associated with the efferent phase of a contact hypersensitivity response (Brand *et al*., 2002a). This activity was attributed primarily to terpinen-4-ol and α-terpineol. Similarly, topical TTO reduced histamine-induced skin oedema of the type that is often associated with immediate type allergic hypersensitivities (Brand *et al*., 2002b). This activity also appeared to be due mainly to terpinen-4-ol.

Agricultural applications

The broad-spectrum antimicrobial activity of TTO lends itself to uses other than human and animal medicine. There has also been interest in exploiting its properties for disease protection in crops and produce. The greatest interest seems to have been in the antifungal properties of the oil and there are data from in vitro antifungal assays, greenhouse studies and field trials against many important agricultural pathogens. The plethora of methods used in this work preclude direct comparisons. However, of the in vitro data, Bishop & Thornton (1997) showed that the following organisms could be inhibited by exposure to TTO in a disc diffusion method or to TTO vapour: *Alternaria brassicicola*, *Alternaria solani*, *Botrytis cinerea*, *Fusarium solani*, *Myocentrospora acerina*, *Pythium ultimum*, *Rhizoctonia solani*, *Rhizopus sexualis*, *Rhizopus stolonifer*, *Sclerotinia sclerotiorum*, *Sclerotium cepivorum* and *Serpula lacrymans*. Further work on *B. cinerea* using a bioassay with *Brassica oleracea* var. *capitata* (Dutch White cabbage) demonstrated that a concentration of 3.2% TTO compared favourably with three commercial fungicides (Bishop & Reagan, 1998). Vapourised TTO also inhibited the germination of *B. cinerea* spores at 12.5% but not 6.25% TTO (Wilson *et al*., 1997). Caolo-Tanski *et al*. (2002a,b) showed that TTO can inhibit a similar range of fungal pathogens *in vitro*, and in some cases in greenhouse studies and field trials. The fungi tested were *Alternaria alternata*, *A. solani*, *Cercospora beticola*, *Cochliobolus sativum*, *Fusarium graminearum*, *Phytophthora infestans*, *Pythium paroecandrum*, *Rhizoctonia solani* and *S. sclerotiorum*. Greenhouse

studies also confirmed the potential for 1% TTO to be used for the control of powdery mildew of cucurbits caused by *Sphaerotheca fuliginea* (Olsen *et al*., 1988). The same concentration of oil proved effective in greenhouse trials in controlling false smut of palms caused by *Graphiola phoenicis* (Polizzi & Agosteo, 1995). Although the microbial pathogens were not identified, TTO vaporised at a concentration of 100 $\mu l\ l^{-1}$ reduced post-harvest decay in raspberries (*Rubus idaeus* L.) (Wang, 2003). Washington and colleagues (1999) showed in field trials on strawberries that TTO could control leather rot caused by *Phytophthora cactorum* and anthracnose (or blackspot) caused by *Colletotrichum acutatum*. Earlier work by this group had shown that a commercially available TTO crop treatment could reduce numbers of the predatory two spotted mites, *Typhlodromus occidentalis* (Washington *et al*., 1991).

In one of the few investigations to examine bacterial disease in plants, TTO applied to soil infested with *Ralstonia solanacearum* failed to reduce the subsequent incidence of wilt in tomatoes (Pradhanang *et al*., 2002). Similarly, TTO did not successfully control *Xanthomonas campestris* pv. *campestris* when applied to *Brassica oleracea* var. *capitata* (Dillard *et al*., 2000). Antiviral activity has also attracted some attention and spray solutions containing TTO significantly decreased lesion numbers in tobacco plants when applied prior to inoculation with tobacco mosaic virus (Bishop 1995).

Insecticidal activity

Anecdotally many essential oils have been mooted as insecticidal agents. Few have been investigated scientifically. TTO has been evaluated *in vitro* against *Pediculus humanus capitis* (head lice) (Veal, 1996; Downs *et al*., 2000) and a shampoo containing several plant extracts including TTO performed well in a pilot study of lice treatment (McCage *et al*., 2002). *Scabies sarcopti* (scabies) has also been tested in vitro and found to be susceptible to the oil (Walton, Myerscough & Currie, 2000). In contrast, in one in vitro test, a natural mosquito repellent product containing TTO provided almost no protection against *Aedes aegypti* (Chou *et al*., 1997).

The activity of TTO against house dust mites has also been shown in two studies. In the first, the activity of several essential oils (including TTO) against house dust mites was compared to that of benzyl benzoate, a standard treatment. Oils of citronella and tea tree were as effective as 0.5% benzyl benzoate and TTO at a concentration of 0.8% killed 79% of mites after a 10 min exposure time (McDonald & Tovey, 1993). In the second study, TTO was the most effective at killing the house dust mite *Dermatophagoides pteronyssinus*, when compared to lavender and lemon essential oils (Priestley *et al*., 1998). TTO at a concentration of 10% caused 100% immobility after 30 min and 100% mortality after 2 h.

Other properties

It is likely that TTO possesses other properties common to the terpene family of chemicals. Many of the components in TTO have been shown to improve the percutaneous penetration of topically applied drugs. Most notable of these are cineole (Obata *et al*., 1991; Yamane *et* al., 1995; Gao & Singh, 1997;1998), and terpinen-4-ol and α-terpineol (Magnusson *et* al., 1997; Godwin & Michniak, 1999). By inference, it seems likely that TTO can also enhance the transdermal penetration of other compounds although it has not been reported to date. If TTO can penetrate the outer layers of the dermis this may help implementation of its antimicrobial properties; rather than inhibiting or killing microorganisms in the uppermost skin layers only, it may penetrate deeper eliminating underlying organisms and preventing relapses.

Anecdotally, TTO is also credited with anti-pruritic activity. No scientific data exist for this property although it may be linked to its anti-inflammatory activity since the pathophysiology of itch is thought to be related to the inflammatory response (Hägermark & Wahlgren, 1992).

Claims of analgesic properties have been made for TTO (Markham, 1999) but there are almost no data to support them and it is impossible to confirm or refute these claims. The exception is one paper describing reductions in the degree of pain and the total use of analgesics post-operatively after twice daily inhalation of tea tree and peppermint oils (Takahashi *et al*., 2002).

Other applications

Numerous other applications have been suggested for TTO. One for which several products have been developed but for which little research has been done is aerosolised TTO. There are anecdotal reports of aerosolised TTO reducing hospital acquired infections (Bowden, 2001) but no scientific data. Some preliminary in vitro work has been done with several researchers showing that vaporised TTO can inhibit bacteria including *Mycobacterium avium* ATCC 4676 (Maruzzella & Sicurella, 1960) and the respiratory pathogens *E. coli*, *Haemophilus influenzae*, *Streptococcus pyogenes* and *Strep. pneumoniae* (Inouye, Takizawa & Yamaguchi, 2001), and fungi (Inouye, Uchida & Yamaguchi, 2001). Related work on agricultural applications of TTO has made similar observations (Bishop & Thornton, 1997; Wilson *et al*., 1997).

TTO products designed for application to burns have also been developed but scientific data on their suitability for use are lacking and their use has been questioned (Faoagali, George & Leditschke, 1997; Price, 1998). Some preliminary work has been done (Smith, 1995; Faoagali, George & Leditschke, 1997; Jandera *et al*., 2000; Osti & Osti, 2002) but substantial additional research is required before informed conclusions about their role can possibly be made.

There has been some interest in using TTO in veterinary medicine and it has been suggested for the treatment of chronic dermatitis in dogs (Fitzi *et al*., 2002).

Consideration has been given to using *M. alternifolia* in constructed wetlands for sewage treatment (Bolton & Greenway, 1997; 1999a,b). In addition to water treatment, this type of scheme offers the benefits of native habitat rehabilitation and TTO production.

TTO has been assessed as an alternative solvent for the gutta-percha solvents used in dentistry (Kaplowitz, 1990; Kaplowitz, 1991; Görduysus *et al*., 1997).

Product formulation issues

TTO's physical characteristics present certain difficulties for the formulation of products. Its lipophilicity leads to miscibility problems in aqueous based products while its volatility means that packaging must provide a suitable barrier to losses through volatilisation. Consideration must also be given to the properties of the finished product. Early suggestions that TTO's antimicrobial activity may be compromised by organic matter came from disc diffusion studies in which the addition of blood to agar medium decreased zone sizes (Ånséhn, 1990). This observation contrasts sharply with the old claim that the activity of TTO may be enhanced in the presence of organic matter such as blood and pus. Data from Hammer and colleagues comprehensively refuted this idea (Hammer, Carson & Riley, 1999) and also showed that product excipients may compromise activity.

Some work on the characteristics and behaviour of TTO within formulations has been conducted. Caboi *et al*. (2002) examined the potential of a monoolein/water system as a carrier for TTO and terpinen-4-ol. However, if stable, biologically-active formulations of TTO are going to be developed, much remains to be done.

Safety and toxicity

Most TTO is used topically. Anecdotal evidence from almost 80 years of use suggests that topical use is safe, and that adverse events are minor and occasional. The toxicity of TTO can be considered in three major areas; toxicity from ingestion, from topical application and eco-toxicity. Topical or dermal toxicity can be further divided into allergic and irritant types of reaction.

Oral toxicity

Tea tree is categorised as a Schedule 6 poison in Australia. According to the Drugs, Poisons and Controlled Substances Act 1981, substances classed within this category have "a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label". To this end, neat TTO is labelled that it must be kept out of the reach of children, is packaged with a childproof cap and is labelled 'not to be taken internally'.

TTO can be toxic if ingested, as evidenced by studies with animals and from cases of human poisoning. An established laboratory method for measuring the toxicity of a substance is to determine the LD_{50}, which is the ingested dose that is lethal to 50% of a test population. This is expressed as units of toxic substance per kilogram of body weight. The LD_{50} for TTO in a rat model is 1.9 – 2.6 ml/kg (Russell, 1999). Although values determined in animal models are not necessarily directly related to human toxicity, the animal model data indicate that TTO is orally toxic and therefore not suitable for internal use.

Several incidences of oral poisoning in humans have been reported in the literature. Such occurrences tend to be more dramatic in children because of their low body weight compared to an adult. One such case report involved a 23 month old child who drank approximately 10 ml of TTO. After a nap of approximately 30 min, the child was unsteady on his feet and appeared as if 'drunk'. The child was taken to a hospital and treated with activated charcoal and sorbitol via a naso-gastric tube, and approximately 5 h later he appeared to be asymptomatic. All other signs (such as respiratory rate, oxygen saturation, pupil reactivity, electrolytes and blood glucose) were normal throughout (Jacobs & Hornfeldt, 1994). The authors attribute the clinical symptoms to a central nervous system depression caused by the ingested TTO.

A case of poisoning in an adult occurred when a patient drank approximately half a tea cup of TTO corresponding to a dose of approximately 0.5-1.0 ml/kg body weight (Seawright, 1993). The patient was comatose for 12 h, and semi-conscious and hallucinatory for the following 36 h. Symptoms of abdominal pain and diarrhoea continued for approximately 6 weeks after this. In another incident, a 60 year old man who swallowed one and a half teaspoonfuls of TTO as a preventative for a cold presented with a red rash which covered his feet, knees, upper body and arms including his palms and elbows (Elliott, 1993). His hands, feet and face were also swollen. The rash and other symptoms gradually disappeared and approximately one week later he had more or less recovered.

Apart from these reports, there are no data on the systemic toxicity of TTO in humans. However, the ingestion of TTO should not be recommended. Despite this, deliberate ingestion is occasionally suggested (Belaiche 1985; Blackwell, 1991a) or reported.

Dermal toxicity

Systemic effects from topical TTO application in humans or other animals appear to be very rare, judging by published reports. The topical application of significant quantities of eucalyptus oil (containing approximately 80% 1,8-cineole) to a 6 year old girl caused systemic effects, including slurred speech, drowsiness, vomiting, ataxia and unconsciousness, although the girl recovered fully within approximately 6 h (Darben *et al.*, 1998). Severe systemic effects following dermal application of TTO to cats have been reported (Bischoff & Guale, 1998). Three cats with shaved but intact skin had approximately 120 ml of neat TTO applied to them topically as a flea repellant. Within 5 h all three cats were experiencing symptoms such as hypothermia, uncoordination, dehydration and trembling, and one was comatose (Bischoff & Guale, 1998). All cats were treated by a veterinarian and two recovered after 24 and 48 h, respectively, but the third cat was found dead 3 days after admission.

Irritant reactions

Irritant reactions are an inflammatory type of response caused when an irritating substance comes into contact with a body surface, usually the skin. Importantly, these reactions are often concentration dependent, but are not dependent on previous exposure to the irritating agent. Irritant reactions may usually be avoided through the use of lower concentrations of the irritant and this bolsters the case for discouraging the use of neat oil and promoting the use of well-formulated products. The irritant capacity of TTO has been evaluated in both animal models and human trials, however, only the human data will be discussed below.

The irritant capacity of TTO has been investigated using an occlusive patch test method with Finn chambers (Southwell *et al.*, 1997). TTO was prepared in white soft paraffin at a concentration of 25% and this mixture was applied in patch tests on the backs or upper arms of volunteers. After 24 h, patches were removed and the skin was checked for any reactions. A new chamber was then applied to the same area, and checked again 24 h later. This was repeated at subsequent 24 h intervals for a total of 21 days. None of the 25 participants produced an irritant reaction from these tests. However, three of the original 28 participants showed distinct allergic reactions and were withdrawn from the trial. The TTO component 1,8-cineole, which has a reputation as a skin irritant, was also tested at concentrations up to and including 28% and did not produce any irritant reactions in the 25 (non-allergic) participants (Southwell *et al.*, 1997). Another study similarly found that of 20 patients patch-tested with 1% TTO, none had irritant reactions (Knight & Hausen, 1994). This study also showed that TTO was a 'weak sensitiser' after attempts were made to experimentally sensitise guinea pigs to TTO. Subsequent experiments have confirmed that newly distilled TTO has a relatively low sensitising capacity whereas TTO that had been exposed to light, oxygen, warmth and moisture, and was considered 'degraded', was a moderate to strong sensitiser (Hausen *et al.*, 1999).

Contact allergy

Contact allergy is defined as a cutaneous reaction caused by direct contact with an allergen to which the patient has become sensitised (Hensyl, 1990). Once an allergic reaction to TTO has occurred it is likely that all subsequent exposures to TTO, no matter what concentration, will elicit further allergic reactions. A series of seven such patients were described in a report by Knight & Hausen (1994). All patients reacted to 1% TTO when tested by patch testing using Finn chambers. In addition, these patients also reacted to one or more of the components *d*-limonene, α-terpinene, aromadendrene, terpinen-4-ol and α-phellandrene at 1, 5 or 10%. In the study by Southwell discussed above, the three participants having allergic type reactions to 25% TTO were tested against TTO components and reacted mostly to the sesquiterpenoid fractions but not the pure monoterpenes (Southwell *et al.*, 1997). These studies indicate that contact allergy to TTO can occur, although the rate of occurrence is still not known.

Toxicity against cell lines in vitro

The testing of human or animal cells *in vitro* is seen as a modern alternative to animal testing to determine toxicity. Several studies have investigated the toxic effects of TTO and/or components on (human) cell lines *in vitro*. The amounts of TTO that reduced the growth of cells by 50% as compared to controls (IC_{50}) after 24 h, ranged from 20 to 2700 μg/ml for HeLa, K562, CTVR-1, Molt-4 and Hep G2 cells (Hayes *et al.*, 1997). IC_{50} values determined in other studies were 43.0 μg/ml for human HL-60 cells (Mikus *et al.*, 2000), 0.006% for RC-37 cells (Schnitzler *et al.*, 2001), 575 μg/ml for human fibroblasts and about 450 μg/ml for human epithelial cells (Söderberg *et al.*, 1996). In addition, TTO produced toxic effects against human monocytes at concentrations of ≥0.004% (Hart *et al.*, 2000) or ≥0.016% (Brand *et al.*, 2001) and at ≥0.016% against human neutrophils (Brand *et al.*, 2001).

Eco-toxicity

Literature on the ecotoxicity of TTO has been summarised and reviewed in Chapter 4.

Table 3.1. Composition of *M. alternifolia* (tea tree) oil

Component	Composition (%)	
	ISO 4730 Range[1]	Typical composition[2]
terpinen-4-ol	≥ 30[3]	40.1
γ-terpinene	10 - 28	23.0
α-terpinene	5 – 13	10.4
1,8-cineole	≤ 15[3]	5.1
terpinolene	1.5 - 5	3.1
ρ-cymene	0.5 - 12	2.9
α-pinene	1 – 6	2.6
α-terpineol	1.5 - 8	2.4
aromadendrene	traces - 7	1.5
δ-cadinene	traces - 8	1.3
limonene	0.5 - 4	1.0
sabinene	traces – 3.5	0.2
globulol	traces - 3	0.2
viridiflorol	traces – 1.5	0.1

[1] International Organisation for Standardisation

[2] Brophy et al., 1989

[3] no upper or lower limit set

Table 3.2. Properties of TTO components

Component	Type of compound	Chemical formula	Solubility (ppm)[1]	log K_{OW}[2]
terpinen-4-ol	monocyclic terpene alcohol	$C_{10}H_{18}0$	1491	3.26
γ-terpinene	monocyclic terpene	$C_{10}H_{16}$	1.0	4.36
α-terpinene	monocyclic terpene	$C_{10}H_{16}$	8.2	4.25
1,8-cineole	monocyclic terpene alcohol	$C_{10}H_{18}0$	907	2.84
α-terpinolene	monocyclic terpene	$C_{10}H_{16}$	4.3	4.24
ρ-cymene	monocyclic terpene	$C_{10}H_{14}$	6.2	
(+)-α-pinene	dicyclic terpene	$C_{10}H_{16}$	0.57	4.44
α-terpineol	monocyclic terpene alcohol	$C_{10}H_{18}0$	1827	3.28
aromadendrene	sesquiterpene	$C_{15}H_{24}$		
δ-cadinene	sesquiterpene	$C_{15}H_{24}$		
(+)-limonene	monocyclic terpene	$C_{10}H_{16}$	1.0	4.38
sabinene	dicyclic monoterpene	$C_{10}H_{16}$		
globulol	sesquiterpene alcohol	$C_{15}H_{26}0$		

[1] Griffin *et al*., 1999b

[2] Griffin *et al*., 1999a

Table 3.3 Susceptibility data for bacteria tested against *M. alternifolia* oil (% v/v)

Bacterial species	MIC, MIC_{range} or MIC_{90}	MBC, MBC_{range} or MBC_{90}
Acinetobacter baumannii	1.0[8]	1.0[8]
Actinomyces viscosus	0.6[6]	
Actinomyces spp.	1.0[14]	1.0[14]
Bacillus cereus	0.3[2]	
Bacteroides spp.	0.06[1], 0.5[1]	0.06-0.12[1]
Corynebacterium sp.	0.2-0.3[2], 2.0[8]	2.0[8]
Enterococcus faecalis	0.5-0.75[2]	
Enterococcus faecalis (vancomycin R)	0.5-1[4], >8[10]	0.5-1[4], >8[10]
Escherichia coli	0.25[3, 7], 0.08[11]	0.25[3, 7]
Fusobacterium nucleatum	>0.6[6]	
Klebsiella pneumoniae	0.25[8], 0.3[2]	0.25[8]
Lactobacillus spp.	1.0[14], 2.0[1]	2.0[1, 14]
Micrococcus luteus	0.06-0.5[8]	0.25-6.0[8]
Peptostreptococcus anaerobius	0.2[6], 0.25[1]	0.03-0.12[1]
Porphyromonas endodentalis	0.025-0.1[14]	0.025-0.1[14]
Porphyromonas gingivalis	0.11[6]	
Prevotella spp.	0.03[1], 0.25[1]	0.03[1]
Prevotella intermedia	0.003-0.1[14]	0.003-0.1[14]
Propionibacterium acnes	0.05[2], 0.31-0.63[5]	0.5[13]
Proteus vulgaris	0.08[11], 0.3[2], 2.0[10]	4.0[10]
Pseudomonas aeruginosa	1->2.0[2] ,1-8[10], 3.0[8]	2->8[10], 3.0[8]
Staphylococcus aureus	0.63-1.25[5], 0.5[7, 10]	1.0[10], 2.0[7]
Staphylococcus aureus (methicillin R)	0.04[11], 0.25[4, 9]	0.5[4], 0.5[9]
Staphylococcus epidermidis	0.63-1.25[5], 1.0[8]	4.0[8]
Staphylococcus hominis	0.5[8]	4.0[8]
Streptococcus pyogenes	0.12[12]	0.25[12]
Veillonella spp.	0.016-1.0[14]	0.03-1.0[14]

[1] Hammer *et al*., 1999a; [2] Griffin *et al*., 2000; [3] Gustafson *et al*., 1998; [4] Nelson, 1997;

[5] Raman *et al*., 1995; [6] Shapiro *et al*., 1994; [7] Carson *et al*., 1995b; [8] Hammer *et al*., 1996;

[9] Carson *et al*., 1995a; [10] Banes-Marshall *et al*., 2001; [11] Mann & Markham, 1998;

[12] Carson *et al*., 1996; [13] Carson & Riley, 1994; [14] Hammer *et al*., 2003

Chapter 4. Review of tea tree oil ecotoxicity data

Ecotoxicology can be loosely defined as the effects of pollutants on natural ecosystems. Although data from acute toxicity testing of single animal or insect species may be regarded as overly simplistic, they are often the starting point for assessing ecotoxicity.

Data describing the ecotoxicity of tea tree oil are very limited. The toxicity of tea tree oil against fish, amphibians, insects, worms or other aquatic and terrestrial species, or ecosystems, has not been assessed to any great extent.

4.1 Acute toxicity of tea tree oil to aquatic organisms

Two publications have assessed the potential for tea tree oil to be used as an antifungal agent in fish aquaculture (Campbell *et al*., 2001; Marking *et al*., 1994). Whilst both studies tested the efficacy of tea tree oil against aquatic fungi, Marking *et al*. (1994) also assessed the toxicity of tea tree oil to rainbow trout eggs. They found that tea tree oil was non-toxic to rainbow trout eggs at a concentration of 1500 ppm.

Ecotoxicity data for two essential oils and some essential oil components are shown in Table 4.1. In addition, clove oil (containing ~ 90% eugenol) has been evaluated as an anaesthetic for fish. It has been shown to anaesthetise fish at concentrations of 6 - 200 mg/l (Afifi *et al*., 2001; Sladky *et al.*, 2001) but data are not available describing lethal concentrations. The values shown in Table 4.1 show that thyme oil and eugenol are for the most part categorised as slightly toxic, having LC_{50} values of between 10 and 100 mg/l (Kamrin, 1997). Lovage oil and it's component ocimene are categorised as practically non-toxic (with LC_{50} values of > 100 mg/l) whereas cumene is categorised as moderately toxic (with LC_{50} values of 1 – 10 mg/l).

Ecotoxicity data for several components of tea tree oil are shown in Table 4.2.
Using the toxicity categories described above, and the limited data for tea tree oil components, limonene and cymene are classified as slightly toxic, a-terpineol is moderately toxic, α- pinene appears to be practically non-toxic and data for β-pinene are equivocal. Notably absent are any data for the tea tree oil components terpinen-4-ol or γ-terpinene, the two components present in the highest proportions in tea tree oil. Whilst ecotoxicity data for essential oils other than tea tree oil, or essential oil components, can only be used as a guide, they suggest that tea tree oil may fall into the 'slightly toxic' category, with LC_{50} values of between 10 – 100 μg/l.

Table 4.1 Acute toxicity data for thyme oil, eugenol, lovage oil, ocimene and cumene

Volatile oil	Aquatic species	Data	Reference
Thyme oil	Rainbow trout[1]	LC_{50} = 16.1 mg/l[a]	Bull Env Contam Toxicol 1998; 60: 923-930
	Coho salmon[2]	LC_{50} = 21.1 mg/l[a]	Bull Env Contam Toxicol 1998; 60: 923-930
Eugenol	Coho salmon[2]	LC_{50} = 67.6 mg/l[a]	Bull Env Contam Toxicol 1998; 60: 923-930
	Rainbow trout[1]	LC_{50} = 61.5 mg/l[a]	Bull Env Contam Toxicol 1998; 60: 923-930
	Rainbow trout[1]	LC_{50} = 9 mg/l [c]	Aqua Res 1998; 29: 89-101
	Rainbow trout[1]	LC_{50} = 125 mg/l [b]	J Aquatic Animal Health 2000; 12: 224-229
	Cherry salmon[5]	LC_{50} = 63 mg/l [b]	J Aquatic Animal Health 2000; 12: 224-229
	Goldfish[6]	LC_{50} = 250 mg/l [b]	J Aquatic Animal Health 2000; 12: 224-229
Lovage oil	Brine shrimp[3]	LD_{50} = 228 ppm	Int J Aromather 2001; 11: 145-151
Ocimene	Brine shrimp[3]	LD_{50} = 697 ppm	Int J Aromather 2001; 11: 145-151
Cumene	Sheepshead minnow	LC_{50} = 8.1 mg/l [a]	Ecotoxicol Env Saf 1995; 31: 287-289
	Rainbow trout[1]	LC_{50} = 6.4 mg/l [a]	Ecotoxicol Env Saf 1995; 31: 287-289
	Water flea[4]	LC_{50} = 4.8 mg/l [a]	Ecotoxicol Env Saf 1995; 31: 287-289

[1] *Onchorhynchus mykiss*

[2] *Onchorhynchus kisutch*

[3] *Artemia salina*

[4] *Daphnia magna*

[5] *Onchorhynchus masou*

[6] *Carassius aurantus*

[a] 24 h exposure time

[b] 60 min exposure time

[c] estimated over 8 – 96 h

Table 4.2 Acute toxicity of components of tea tree oil to aquatic species

Component	Aquatic species (life stage)	Data	Reference
α-Pinene	Water flea [4]	LC_{50} = 68 mg/l [a]	Bull Env Contam Toxicol 1980; 24: 684-691
	Brine shrimp [3]	LD_{50} = 494 ppm	Int J Aromather 2001; 11: 145-151
β-Pinene	Brine shrimp [3]	LD_{50} = 491 ppm	Int J Aromather 2001; 11: 145-151
	Rainbow trout (fry) [1]	LC_{50} = 1.2 mg/l [d]	J Great Lakes Res 1995; 21: 373-383
Limonene	Carp [7]	LC_0 = 26 mg/l LC_{50} = 34 mg/l LC_{100} = 43 mg/l	Z. Wasser-Abwasser Forsch 1978; 11(5): 161-164
	Brine shrimp	LD_{50} = 706 ppm	Int J Aromather 2001; 11: 145-151
α-Terpineol	Rainbow trout (fingerlings)	Toxic dose range: 10 – 100 mg/l [e]	Water Res. 1976; 10: 303-306
	Coho salmon	LC_{50} = 6.8 mg/l [a]	Bull Env Contam Toxicol 1998; 60: 923-930
	Rainbow trout	LC_{50} = 6.7 mg/l [a]	Bull Env Contam Toxicol 1998; 60: 923-930
p-Cymene	Water flea	LC_{50} = 9.4 mg/l [a]	Bull Env Contam Toxicol 1980; 24: 684-691
	Sheepshead minnow	LC_{50} = 56 ppm [a]	Bull Env Contam Toxicol 1981; 27: 596-604

[1] *Onchorhynchus mykiss;* [2] *Onchorhynchus kisutch*; [3] *Artemia salina;* [4] *Daphnia magna;* [5] *Onchorhynchus masou;*
[6] *Carassius aurantus;* [7] *Leuciscus idius melanotus*
[a] 24 h exposure time; [b] 60 min exposure time; [c] estimated over 8 – 96 h; [d] 60 day exposure time;
[e] 96 exposure time

4.2 Acute toxicity of tea tree oil to terrestrial insects

The acute toxicity of essential oils and components has most commonly been evaluated in the context of using essential oils as crop fumigants and protectants. Data describing the toxic effects of tea tree oil on insects are limited. However, the LD_{50} of tea tree oil against the rice weevil *Sitophilus oryzae* (L.) has been determined as >150 μl/l of air (Lee *et al*., 2001). In addition, varroa mites, which are parasitic to honey bees, have been shown to be susceptible to tea tree oil. After 6 h treatment, 59.4% of mites exposed to tea tree oil in air had died, compared to only 20% of control mites (Sammataro *et al*., 1998). The toxicity of several essential oils to insects is shown in Table 4.3. Whilst these data are a useful indication of which concentrations of essential oil are toxic, it remains to be determined whether tea tree oil has similar toxicity.

Table 4.3 Selected acute toxicity data for essential oils and terrestrial insects

Oil or Component	Insect species (life stage)	Data	Reference
Citronella oil	Rice weevil [3]	LD_{50} = > 150 μl/l of air	Crop Prot 2001; 20: 317-320
Lavender oil	Rice weevil [3]	LD_{50} = 54 μl/l of air	Crop Prot 2001; 20: 317-320
Oregano (*Oreganum vulgare* subsp. *hirtum*)	Fruit fly [2]	LD_{50} = 5.6 μl/fly	J Agric Food Chem 1998; 46: 1111-1115
Pennyroyal *(Mentha pulegium)*	Fruit fly [2]	LD_{50} = 2.09	J Agric Food Chem 1997; 45: 2690-2694
Rosemary oil	Rice weevil [3]	LD_{50} = 30.5 μl/l of air	Crop Prot 2001; 20: 317-320
Savory (*Satureja thymbra*)	Fruit fly [2]	LD_{50} = 3.3 μl/fly	J Agric Food Chem 1998; 46: 1111-1115
Spearmint *(Mentha spicata)*	Fruit fly [2]	LD_{50} = 1.12	J Agric Food Chem 1997; 45: 2690-2694
Tea tree oil	Rice weevil [3]	LD_{50} = > 150 μl/l of air	Crop Prot 2001; 20: 317-320
Thyme oil	Rice weevil [3]	LD_{50} = 63.9 μl/l of air	Crop Prot 2001; 20: 317-320
	Spodoptera litura	LD_{50} = 43.7 μg/larva	J Agric Food Chem 2001; 49: 715-720
	Fruit fly [2]	LD_{50} = 6.78 μl/fly	J Agric Food Chem 1998; 46: 1111-1115

[a]24 h exposure time; [1]*Musca domestica*; [2]*Drosophila melanogaster;* [3]*Sitophilus oryzae*

In addition to toxicity tests with whole oils, several studies have determined the toxicity of essential oil components. These data may give a general indication of the likely toxicity of tea tree oil to insects. Data are shown in Table 4.4.

Table 4.4 Selected acute toxicity data for essential oil components and terrestrial insects

Component	Insect species	Data	Reference
Carvacrol†	*Spodoptera litura*	LD_{50} = 1.6 μg/larva	J Agric Food Chem 2001; 49: 715-720
	Fruit fly [2]	LD_{50} = 42.7 μg/larva	J Agric Food Chem 1998; 46: 1111-1115
1,8-Cineole	Rice weevil [3]	LD_{50} = 23.5 μl/l of air	Crop Prot 2001; 20: 317-320
ρ-Cymene	Rice weevil [3]	LD_{50} = 25.0 μl/l of air	Crop Prot 2001; 20: 317-320
Limonene	*Spodoptera litura*	LD_{50} = 273.7 μg/larva	J Agric Food Chem 2001; 49: 715-720
	Rice weevil [3]	LD_{50} = 61.5 μl/l of air	Crop Prot 2001; 20: 317-320
	Cockroach [4]	LD_{50} = 700 μg/insect[a]	J Pest Sci 1988; 13: 287-290
	House fly [1]	LD_{50} = 90 μg/insect[a]	J Pest Sci 1988; 13: 287-290
	House fly [1]	LD_{50} = 50.4 μg/fly[a]	J Agric Food Chem 2002; 50: 4576-4580
Linalool	Rice weevil [3]	LD_{50} = 39.2 μl/l of air	Crop Prot 2001; 20: 317-320
α-Pinene	House fly [1]	LD_{50} = 111.5 μg/fly[a]	J Agric Food Chem 2002; 50: 4576-4580
α-Terpinene	House fly [1]	LD_{50} = 117.2 μg/fly[a]	J Agric Food Chem 2002; 50: 4576-4580
	Rice weevil [3]	LD_{50} = 71.2 μl/l of air	Crop Prot 2001; 20: 317-320
Terpinen-4-ol	Rice weevil [3]	LD_{50} = 25.6 μl/l of air	Crop Prot 2001; 20: 317-320
	Spodoptera litura	LD_{50} = 130.4 μg/larva	J Agric Food Chem 2001; 49: 715-720
α-Terpineol	Rice weevil [3]	LD_{50} = 69.1 μl/l of air	Crop Prot 2001; 20: 317-320
	House fly [1]	LD_{50} = 175.7 μg/fly[a]	J Agric Food Chem 2002; 50: 4576-4580
	Spodoptera litura	LD_{50} = 141.3 μg/larva	J Agric Food Chem 2001; 49: 715-720
Thymol†	*Spodoptera litura*	LD_{50} = 25.4 μg/larva	J Agric Food Chem 2001; 49: 715-720
	Fruit fly [2]	LD_{50} = 2.6 μg/larva	J Agric Food Chem 1998; 46: 1111-1115

[a]24 h exposure time; †component not found in tea tree oil
[1]*Musca domestica*; [2]*Drosophila melanogaster;* [3]*Sitophilus oryzae;* [4]*Blatella germanica*

In addition, another study showed that the treatment of insects for 14 h with several compounds at a concentration 0.05 μg/l of air resulted in varying mortalities. Treatment with linalool resulted in 100% mortality in house flies, German cockroaches and saw-toothed grain beetles, 10% mortality in red flour beetles and 0% in rice weevils. Terpineol resulted in 100% mortality in saw-toothed grain beetles, no mortality in German cockroaches, red flour beetles or rice weevils and 20% in house flies. Treatment with cineole resulted in 100% mortality in all insects. Similarly, treatment with limonene resulted in 100% mortality for all insects except red flour beetles, which had a mortality rate of 60% (Lee *et al*., 2003).

In addition to acute toxicity data, several studies have indicated that essential oils can have other effects, such as inhibition of larval growth (Hummerbrunner & Isman, 2001), inhibition of

reproduction (Regnault-Roger & Hamraoui, 1995) and deterrence of feeding (Hummerbrunner & Isman, 2001).

The above studies with both whole oils and components indicate that tea tree oil is likely to be toxic to insects. However, it has been stated that the acute toxicity of monoterpenes to insects is relatively low, compared to conventional insecticides (Lee *et al*., 1997). Whether this is also true for tea tree oil remains unknown.

4.3 Other acute toxicity data

One study has shown that d-limonene is toxic to the earthworm *Eisenia fetida* (Savigny) (Karr *et al*., 1990). The LD_{50} by topical application was 60 ppm, and when earthworms were exposed to 12.6 ppm it took 4.9 h for 50% of the organisms to die. Chronic exposure to limonene also resulted in weight loss.

4.4 Conclusions

Although very limited data are available regarding the ecotoxicity of tea tree oil, it can be extrapolated from data for other essential oils and components that tea tree oil should be considered slightly to moderately toxic, as a conservative estimate of overall ecotoxicity.

Chapter 5. Literature Database

The existing scientific literature on TTO are not readily accessible to most industry stakeholders. A comprehensive collection of TTO literature in the form of an electronic database available through the ATTIA web site would be a valuable resource for the industry.

5.1 Methods

The following electronic databases were searched for publications that include data on TTO, TTO components, *Melaleuca alternifolia* and other *Melaleuca* species of relevance to the TTO industry: Agricola (1979 to current), Biological Abstracts (1995 to current), CAB Abstracts (1973 to current), Current Contents (1993 week 27 to current), EMBASE (1988 to current) and Medline (1966 to current). Articles up to and including those indexed on these databases by June 2003 were included. Information on popular press books was primarily found from general internet searches, including searches of websites specifically dealing with books. Additional articles were sourced from the extensive literature collections of C. Carson and K. Hammer. Publications containing any of the above keywords were manually scrutinised to identify additional papers. Publications containing substantial reference to tea tree oil, in the form of one or more paragraphs, were included in the database.

The journal articles cited in the database came from approximately 200 different publications, from approximately 100 different publishers. Wherever possible, the contact details for each publisher were obtained. A request was sent to each publisher requesting permission to reproduce the relevant article(s) in full in the tea tree oil database. The majority of publishers were contacted by May 31, 2003. Articles that were written entirely in a language other than english were not contacted. In addition, journals for which no contact details could be found, despite extensive searching, were not contacted.

Where permission was granted to include the full text of articles, they were either obtained in the form of PDF files from journal websites or authors, or each page of the article was scanned to create an image and a PDF file was constructed.

5.2 Results

Citations

More than 500 tea tree oil publications were found, including research articles, reviews, conference abstracts or presentations, books and theses. Several citations were omitted from the database, usually because they had been made redundant by subsequent publication, were never officially published, or because of insufficient quality.

Obtaining permission for reproduction of material

Results of permission requests to publishers are shown in Appendix 2. Due to the modest budget for the project the decision was made to not pay fees if payment was required in order to reproduce articles. Permission to reproduce the full text of articles was requested on the basis that the articles would be available through the ATTIA web site, to ATTIA members only and that the database would be password protected.

Database construction and delivery

The database was structured as an introductory page, a list of citations (Appendix 1), with links to either the abstract or full text or both, and a list of abstracts. The list of abstracts is not included in an appendix because copyright permission to reproduce them in this report was not granted. It is intended that the database will be available through the ATTIA web site (http://www.teatree.org.au/). ATTIA bears responsibility for making the database available through its web site, for ensuring that it is available only to members and that it is password protected. It should be noted that permission has been granted for the use of the articles and abstracts within this database for ATTIA members for personal educational purposes only. Permission has not been granted for ATTIA members to reproduce or distribute this information. To do so would be an infringement of copyright.

Chapter 6. Material safety data sheet

A material safety data sheet (MSDS) was created for tea tree oil (Appendix 3), following the guidelines set out in the National Code of Practice for the Preparation of Material Safety Data Sheets (National Occupational Safety and Health Commission, 2003).

Industry personnel, scientific literature and the following data sources were consulted to obtain correct, up to date information for tea tree oil:

1. International Standards Organisation (1996) Oil of Melaleuca, terpinen-4-ol type (tea tree oil). International Standard ISO 4730:1996(E), International Standards Organisation, Geneva
2. Sweet DV. (Editor) (1997) Registry of toxic effects of chemical substances (RTECS), comprehensive guide. U.S. Department of Health and Human Services, Cincinnati, Ohio.
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7. National Occupational Health and Safety Commission (2003) National Code of Practice for the Preparation of Material Safety Data Sheets [NOHSC:2011 (2003)]. Australian Government Publishing Service, Canberra, April 2003.

Chapter 7. Recommendations for further studies

The recommendations for further studies listed below represent the opinions of the authors of this report. It is quite plausible that other experts, such as toxicologists, dermatologists or medical doctors may arrive at a different set of conclusions regarding what further tea tree oil research needs to be conducted. As such, this list must not be regarded as exhaustive, definitive or in order of priority.

The recommendations as to further research that should be conducted into tea tree oil can be subdivided into two broad categories, shown below.

1) Safety and toxicity

a. Toxicity studies, using an animal model
- Safety of inhaled tea tree oil
- Absorption through broken skin and/or wounds
- Reproductive toxicity, including mutagenicity and teratology studies
- Chronic toxicity

b. Toxicity studies, using human volunteers
- Absorption through skin, looking for oil or metabolites in blood and urine
- Repeat application studies
- Mucous membrane irritation studies

c. Ecotoxicity studies
- Aquatic and terrestrial insects
- Fish species
- Plant species

2) Clinical efficacy (pilot studies and full clinical trials)

- Wounds (diabetic ulcers, chronic wounds)
- Head lice
- Impetigo
- Vaginal candidiasis
- Mouthrinse for gingivitis
- Pre and post-operative wound infections

In addition, the work investigating the anti-inflammatory properties of tea tree oil must be continued and expanded. Corroboration of existing clinical data for infections or conditions such as tinea, dandruff, acne, MRSA carriage, onychomycosis and oral candidiasis is imperative.

There are several other potential clinical applications for tea tree oil that first require significant preliminary in vitro work.
- Tea tree oil has great potential as an intra-vaginal microbicide
- The activity of tea tree oil against microbial biofilms needs to be determined, with a view to using it to impregnate indwelling medical devices such as catheters.
- The efficacy of aerosolised tea tree oil against bacteria and microbial biofilms requires attention, as inhaled tea tree oil may be a potential therapy for lung infections such as cystic fibrosis

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Appendix 1 – Literature database

The following is a list of published documents that relate to tea tree oil. This is the most exhaustive and comprehensive bibliography of tea tree oil literature published to date. The abstracts and full text of many of the documents are available on the database. The remainder may be available through document delivery services such as Infotrieve, Ingenta, Loansome Doc on Public Medline or Science Direct. Visit these web sites for further information.

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Appendix 2 – Responses of publishers to permission requests

Full Journal Title	Publisher	Response of publisher to permission request
Yakugaku Zasshi	Pharmaceutical Society of Japan	Abstract and figures granted
New forests	Kluwer Academic Publishers	Abstract only granted
Annales de Dermatologie et Venereologie	SPPIF – Masson Service	Abstract only granted
Journal of the American Podiatric Medical Association	American Podiatric Medical Association	Abstract only granted
Journal of Chemical Ecology	Kluwer Academic Publishers	Abstract only granted
Journal of Dental Research	International Association of Dental Research	Abstract only granted
Acta Horticulturae	International Society for Horticultural Sciences	Abstract only granted
Australian Journal of Experimental Agriculture & Animal Husbandry	CSIRO Publishing	Abstract only granted
Australian Journal of Agricultural Research	CSIRO Publishing	Abstract only granted
Australian journal of botany	CSIRO Publishing	Abstract only granted
Australian journal of Experimental Agriculture	CSIRO Publishing	Abstract only granted
Archiv fur Hydrobiologie	E. Schweizerbart'sche Verlagsbuchhandlung	Abstract only granted
Fungicide and Nematicide tests	American Phytopathological Society Press	Abstract only granted
Phytopathology	American Phytopathological Society Press	Abstract only granted
Plant Disease	American Phytopathological Society Press	Abstract only granted
Antimicrobial Agents and Chemotherapy	American Society for Microbiology	Abstract only granted
Perfusion	Arnold Publishers	Abstract only granted
American Journal of Contact Dermatitis	BC Decker	Abstracts only granted
Journal of Family Practice	Dowden Health Media	Abstracts only granted
Perfumer and Flavourist	Allured Publishing Corp.	Abstracts only granted
Journal of Essential Oil Research	Allured Publishing Corp.	Abstracts only granted
Journal of Medical & Veterinary Mycology	Taylor and Francis	Abstracts only granted
Journal of Agricultural and Food Chemistry	American Chemical Society	Abstracts, figures, tables, bibliographic information granted
Langmuir	American Chemical Society	Abstracts, figures, tables, bibliography granted
EFamily Practice News	**Contact:** J. Sheffer	Denied
Business Review Weekly	Fairfax	Denied
Plant Systematics and Evolution	Springer	Denied
Journal of Nihon School of Dentistry	Contact: M. Nomura	Denied
Journal of Antimicrobial Chemotherapy	Oxford University Press	Fee payable
New Zealand Pharmacy	Methode Media	Fee payable ($200 NZ/ article)
Acta Dermato Venereologica	Taylor & Francis Health Sciences	Fee payable ($250 USD/article)
Hautarzt	Springer	Fee payable (~$1561 AUD/ article)
Support Care Cancer	Springer	Fee payable (~$1561 AUD/article)
Theoretical and Applied Genetics	Springer	Fee payable (~$1561 AUD/article)
Oecologia	Springer Verlag AG	Fee payable (~$1561 AUD/article)
British Medical Journal	BMJ Group	Fee payable (~$180 AUD/ article)
Skin Pharmacology	Karger	Fee payable (~$266 AUD/ article)
Audiology & Neuro Otology	Karger	Fee payable (~$266 AUD/article)
Journal of Chemotherapy	http://www.jchemother.it/	Fee payable ($200 US/ article)

Full Journal Title	Publisher	Response of publisher to permission request
American Journal of Clinical Dermatology AND Adverse Drug Reactions & Toxicological Reviews	ADIS	Fee payable (US$1000/ article or $500/ abstract (1 year only))
Am J Alzheimers Dis Other Demen	Prime National Publishing Corporation	Fee payable for full text, abstract granted
Phytomedicine	Urban and Fischer	Full text (Saller); abstract only (McCage) granted
Archives of Dermatology	Contact: R. Bailey	Full text denied, abstracts $150 USD each
The Bulletin	Contact: M. Cameron	Full text granted
Search	Control Publications	Full text granted
Chemistry In Australia	Contact: H Hugel	Full text granted
Aroma Research	Contact: R. Kimura	Full text granted
Veterinary and Human Toxicology	Contact: Prof Fred Oehme	Full text granted
Molecules	Contact: Dr Shu-Kun Lin	Full text granted
Medical Journal of Australia	Australasian Medical Publishing Company	Full text granted
Journal of Tropical Agriculture & Food Science	Malaysian Agriculture R&D Institute	Full text granted
Alternative and Complementary Therapies	Mary Ann Liebert Inc Publications	Full text granted
Int. Journal of Alternative & Complementary Medicine.	Mary Ann Liebert Inc Publications	Full text granted
American Bee Journal	Dadant & Sons Inc.	Full text granted
International Dental Journal	FDI World Dental Press, Ltd	Full text granted
The Progressive Fish-Culturist	Allen Press	Full text granted
Australian Journal of Pharmacy	Australian Pharmaceutical Publishing Co. Ltd	Full text granted
Journal of Veterinary Diagnostic Investigation	Contact: J Kreeger	Full text granted
The Australian Journal of Hospital Pharmacy		Full text granted
Revista Iberoamericana de Micologia	Revista Iberoamericana de Micologia	Full text granted
Periodontology	Contact: B. Taylor	Full text granted
Australian Forestry	Institue of Foresters of Australia	Full text granted
Australian Pharmacist	Pharmaceutical Soc. of Australia	Full text granted
Chemical Weekly	Sevak Publications	Full text granted
Manufacturing Chemist	Wilmington Publications	Full text granted
Agro-Food-Industry Hi – Tech	Tekno Scienze sr, Italy	Full text granted
Australian Farm Journal	Contact: P. Francis	Full text granted
Australian Journal of Medical Herbalism	National Herbalists Association of Australia	Full text granted
Aromatherapy today		Full text granted
Acta Phytotherapeutica		Full text granted
Annali italiani di Dermatologia allergologica	Luciano de Fiore	Full text granted
Austrobaileya		Full text granted
California Agriculture	California Agriculture	Full text granted
Pz Prisma	Govi Verlag	Full text granted
Pharmazie (die Pharmazie)	Govi Verlag	Full text granted
Australasian Journal of Experimental Biology and Medicine	Blackwell	Full text granted
Journal of the National Medical Association		Full text granted
Jounral of Pharmacy and Pharmacology	Pharmaceutical Press, London,	Full text granted

Full Journal Title	Publisher	Response of publisher to permission request
Journal of the Science of Food and Agriculture	Blackwell	Full text granted
Veterinary Dermatology	Blackwell	Full text granted
Clinical and Experimental Dematology	Blackwell	Full text granted
Australasian Journal of Dermatology	Blackwell	Full text granted
Contact Dermatitis	Blackwell	Full text granted
Dermatologic Therapy	Blackwell	Full text granted
Immunology	Blackwell	Full text granted
Journal of Applied Microbiology	Blackwell	Full text granted
Journal of the European Academy of Dermatology and Venereology	Blackwell	Full text granted
Letters in Applied Microbiology	Blackwell	Full text granted
Mycoses	Blackwell	Full text granted
Oral Microbiology & Immunology	Blackwell	Full text granted
Tropical Medicine & International Health	Blackwell	Full text granted
Molecular Ecology	Blackwell	Full text granted
British Journal of Dermatology	Blackwell	Full text granted
Aquaculture Research	Blackwell	Full text granted
Australian Journal of Biotechnology	Australian Biotechnology Association	Full text granted (from author)
The Foot	Harcourt	No response
Allergo Journal	Urban and Vogel	No response
Medycyna sportowa	http://www.medsport.pl/ (publishers website)	No response
Nursing times		No response
Ganzheitliche Tiermedizin		No response
Inflammation research	Birkhäuser Publishing Ltd.	No response
Mikologia lekarska		No response
Perfumery and Essential oil records		No response
Acta Botanica Sinica	Science publications	No response
Grand Rounds		No response
HRC Journal of High Resolution Chromatography	Wiley	No response
Canadian Pharmaceutical Journal	Canadian Pharmacists Association	No response
British Journal of Phytotherapy	School of Phytotherapyin, East Sussex	No response
Soap Perfumery and cosmetics	Wilmington Publications	No response
Schweizer Archiv fur Tierheilkunde	VERLAG HANS HUBER AG	No response
Microbiology and Immunology	Centre for Academic Publishing, Japan	No response
Journal of British Podiatric Medicine	Soc. of Chiropodists & Podiatrists, UK	No response
Advances in Food Science	AFS	No response
Journal of the American Holistic Veterinary Association	American Holistic Veterinary Medical Assoc.	No response
Cosmetics and Toiletries Manufacture Worldwide	Aston Publishing	No response
Phytochemistry	Elsevier	No response
Antiviral Research	Elsevier	No response
BioMed Central Surgery	Elsevier	No response

Full Journal Title	Publisher	Response of publisher to permission request
ESkin and Allergy News	Elsevier	No response
European Journal of Pharmacology	Elsevier	No response
Lancet	Elsevier	No response
Obstetrics and Gynecology	Elsevier	No response
Thermochimia Acta	Elsevier	No response
Industrial Crops & Products	Elsevier	No response
Biochemical Systematics and Ecology	Elsevier	No response
Plant Science	Elsevier	No response
Fitoterapia	Elsevier	No response
Journal of Microbiological Methods	Elsevier	No response
Journal of Chromatography A	Elsevier	No response
Journal of Hospital Infection	Elsevier	No response
Burns	Elsevier	No response
Clinics in Dermatology	Elsevier	No response
American Journal of Infection Control	Elsevier	No response
Toxicology	Elsevier	No response
Clinics in Podiatric Medicine and Surgery	Elsevier	No response
Complementary Therapies in Nursing & Midwifery	Elsevier	No response
The Foot	Elsevier	No response
Journal of Allergy and Clinical Immunology	Elsevier	No response
Journal of the American Academy of Dermatology	Elsevier	No response
Food and Chemical Toxicology	Elsevier	No response
Seminars in Cutaneous Medicine and Surgery	Elsevier	No response
Journal of Manipulative and Physiological Therapies	Elsevier	No response
Complementary Therapies in Medicine	Elsevier	No response
International Journal of Aromatherapy	Elsevier	No response
FASEB Journal	Fed. American Soc. of Experimental Biology	No response
Aktuelle Dermatologie	Georg Thieme Verlag	No response
Planta Medica	Georg Thieme Verlag	No response
Water Science and Technology	IWA publishing	No response
Forschende Komplementarmedizin und Klassische Naturheilkunde	Karger	No response
AIDS	Lippincott Williams & Wilkins	No response
Journal of Endodontics	Lippincott Williams & Wilkins	No response
Cosmetics Aerosols and Toiletries in Australia	Manor Enterprises P/L	No response
Journal of Toxicology – Clinical Toxicology	Marcel Dekker, Inc.	No response
Asthma and Allergy Proceedings	OceanSide Publications, Inc	No response
Revista Iberoamericana de Micologia	Revista Iberoamericana de Micologia	No response
Transactions of the Royal Society of Tropical Medicine & Hygiene	Royal Society of Tropical Medicine & Hygiene	No response
Podiatry Now	Soc. Chiropodists & Podiatrists, UK	No response
British Journal of Biomedical Science	Step Publishing Ltd, UK	No response

Full Journal Title	Publisher	Response of publisher to permission request
Occupational Health and Safety	Stevens Publishing Corp., USA	No response
Pathology	Taylor & Francis Health Sciences	No response
Phytotherapy Research	Wiley	No response
Flavour and Fragrance Journal	Wiley	No response
Journal of Separation Science	Wiley	No response
Acta Botanica Yunnanica	(Not found)	Not contacted
Bulletin from SADRAC	Swedish Medical Products Agency, Sweden	Not contacted
Current Podiatry	(Not found)	Not contacted
Dermatosen	(Not found)	Not contacted
Deutsche Lebensmittelrundschau	Wissenschaftliche Verlagsgellschaft MBH	Not contacted
Eurocosmetics	Inter-Euro Medien GmbH	Not contacted
Forest Research	(Not found)	Not contacted
Journal of Southwest Agricultural University	(Not found)	Not contacted
La Difesa delle Piante	(Not found)	Not contacted
Microbios	Faculty Press	Not contacted
Nederlands Tijdschrift voor Geneeskunde	Kluwer Academic Publishers	Not contacted
Oto-Rhino-Laryngology Tokyo	(Not found)	Not contacted
Phytotherapy	(Not found)	Not contacted
Plantes médicinales et phytothérapie	(Not found)	Not contacted
Postepy Fitoterapii	(Not found)	Not contacted
Progress in Essential oil research	(Not found)	Not contacted
Schweizer Monatsschrift fur Zahnmedizin	Offizielles organ der Schweizerischen	Not contacted
SOFW journal	Jahresbezugspreis Inland DM	Not contacted
Swedish Journal of Biological Medicine	(Not found)	Not contacted
The Lower Extremity	(Not found)	Not contacted
Deutsche Apotheker Zeitung,	(Not found)	Not contacted
Forschritte der Medizin,	(Not found)	Not contacted
Guangdong Chemical Industry,	(Not found)	Not contacted
Lakartidningen,	(Not found)	Not contacted
Parfümerie und Kosmetik,	(Not found)	Not contacted
Tw Dermatologie,	(Not found)	Not contacted
Ugeskrift for Laeger	(Not found)	Not contacted
Zeitschrift fur Hautkrankheiten,	(Not found)	Not contacted
Zeitschrift fur Phytotherapie,	(Not found)	Not contacted
Österreichischen Apotheker-Zeitung	(Not found)	Not contacted
Hospital and Healthcare	Yaffa publishing	Not contacted (Copyright belongs to each author)
Nature and Health	Yaffa Publishing	Not contacted (Copyright belongs to each author)
Journal of Food Protection	International Association for Food Protection	Undecided
Journal and Proceedings of the Royal Soc. of New South Wales	Royal Society of New South Wales	Undecided

Appendix 3 – Material Safety Data Sheet

NOTE:

1) Do not photocopy this MSDS.
2) The document in its original format can be obtained from ATTIA.

MATERIAL SAFETY DATA SHEET

Classified as hazardous according to the criteria of NOHSC Australia

1. IDENTIFICATION

Name:	Tea tree oil
Other names:	melaleuca oil, *Melaleuca alternifolia* oil, T36-C7, teebaumol
Recommended use:	Topical antibacterial agent, antiseptic, anti-inflammatory agent
SUSDP name:	Melaleuca oil (tea-tree oil)
Supplier name:	(Manufacturer to complete)
Street address:	(Manufacturer to complete)
	(Manufacturer to complete)
Telephone:	(Manufacturer to complete)
Emergency contact:	(Manufacturer to complete)

2. HAZARDS IDENTIFICATION

Hazard classification:	Classified as Hazardous according to the criteria of NOHSC Australia. Classified as Dangerous Goods for the purpose of transport by road or rail.
Risk phrases:	R10 Flammable R22 Harmful if swallowed R36/37/38 Irritating to eyes, respiratory system and skin
Safety phrases:	S26 In case of contact with eyes, rinse immediately with plenty of water and contact a doctor or Poisons Information Centre (13 11 26, Australia wide). S36 Wear suitable protective clothing
HAG phrases:	(9) Form: liquid (15) Flammable (18) Combustible (51) Does not mix with water (62) Avoid personal/skin contact (83) Fire fighting: foam (85) Fire fighting: dry agent
RTECS number	RJ3697600

3. COMPOSITION

Chemical identity:	Melaleuca oil (tea-tree oil)
Common names:	melaleuca oil, *Melaleuca alternifolia* oil, T36-C7, teebaumol ,Tea tree (melaleuca alternifolia) oil
CAS#:	68647-73-4, 85085-48-9, 8022-72-8

4. FIRST AID MEASURES

Poison Information Centres can provide additional assistance on 13 11 26 (Australia wide).

Eye: Irrigate with copious amounts of water. Seek immediate medical attention.

Inhalation: If over-exposure occurs leave exposure area immediately. If other than minor symptoms are displayed seek immediate medical attention.

Skin: Gently flush affected areas with water. Remove contaminated clothing and wash thoroughly before re-use. Seek medical attention if irritation develops.

Ingestion: If swallowed do NOT induce vomiting. Give a glass of water. Seek immediate medical attention.

Facilities: Eye wash facilities and safety shower are recommended.

5. FIRE FIGHTING MEASURES

Suitable extinguishing media: Dry agent, carbon dioxide, foam or water fog. Do not use full water jet.

Hazards from combustion products: May evolve toxic gases (hydrocarbons, carbon oxides) if burning.

Precautions and special protective equipment: Evacuate area and contact emergency services. Remain upwind and notify those downwind of hazard. Wear full protective equipment including Self Contained Breathing Apparatus when combating fire. Use waterfog to cool intact containers and nearby storage areas.

Hazchem code: 3[Y]

6. ACCIDENTAL RELEASE MEASURES

Spillage: In case of spillage (bulk), wear splash-proof goggles, PVC/rubber gloves, coveralls and rubber boots (see section 8). Keep people away, evacuate area.

Containment and clean up: Absorb spill with sand or similar, collect and place in sealable containers using non-sparking tools and transport outdoors for disposal. Ventilate area and wash spill site after material pick-up is complete. Prevent spill from entering drains or waterways. Caution: slippery when spilt.

7. HANDLING AND STORAGE

Handling: Measures should be taken to prevent materials from being splashed into the eyes or on the skin. Wear eye-shields and protective clothing. Smoking should not be permitted in work areas. Provide adequate ventilation.

Storage: Store in a cool, dry, well-ventilated area, away from oxidising agents (eg hypochlorites), acids (eg sulfuric acid), heat and light sources, and foodstuffs. Ensure containers are adequately labelled, protected from physical damage and sealed when not in use. Keep only in original container. Check regularly for leaks or spills. Large storage areas should have appropriate ventilation systems. This material is a Scheduled Poison (S6) and must be stored, maintained and used in accordance with the relevant regulations.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

National exposure standards: No exposure standard allocated

Biological limits: No biological limit allocated

Engineering controls: Ensure adequate ventilation. In poorly ventilated areas, mechanical explosion-proof extraction ventilation is recommended. Keep containers closed when not in use.

PPE: Wear coveralls, splash-proof goggles and PVC or rubber gloves. Where an inhalation risk exists, wear a Type A (organic vapour) Respirator. In a laboratory situation, wear a laboratory coat.

9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance: Colourless to pale yellow liquid
Odour: Characteristic, myristic
Solubility: Insoluble in water, 1 part miscible with 2 parts ethanol (85% v/v) at 20°C.

pH:	Not applicable
Vapour pressure:	Not available
Vapour density:	Not available
Boiling point/range:	116° – 265°C
Freezing point:	Not available
Specific density:	0.885 - 0.906 at 20°C.
Flash point:	57° - 60°C (closed cup)
Fire point:	72°C (Cleveland open cup (IP 36))
Upper flammable limit in air:	Not available
Lower flammable limit in air:	Not available
Ignition temperature:	Not available
Specific heat value:	Not available
Percent volatile:	100%
Refractive index:	1,475 0 – 1,482 0 at 20°C.
Optical rotation:	Between +5° and +15° at 20°C.

10. STABILITY AND REACTIVITY

Chemical stability: Stable

Conditions to avoid: Heat, light, open flames and other sources of ignition

Incompatible materials: Strong oxidising or reducing agents. Protect from air.

Hazardous decomposition products: Carbon monoxide and carbon dioxide (from combustion).

Hazardous reactions: Hazardous polymerisation will not occur.

11. TOXICOLOGICAL INFORMATION

ACUTE EFFECTS

Eye contact: Severe irritant

Skin contact: Irritant. May cause erythema, irritation or oedema. Repeated or prolonged skin contact may lead to allergic contact dermatitis.

Inhalation: Potential irritant. Over-exposure at high levels may result in mucous membrane irritation of the nose and throat with coughing.

Ingestion: May be harmful if swallowed. Swallowing can result in allergic dermatitis, hallucinations, ataxia, diarrhoea, central nervous system depression, sleep or coma.

Acute toxicity*:

Ear TD (guinea pig): 100% (instilled for 30 min)
Toxic effects: D40 (change in acuity)[11]

Dermal LD_{50} (rabbit): >5 g/kg[1]

Dermal LDLo (rabbit): 5 g/kg[1]

Dermal TD (cat): 5-7 mL/kg[2]
Toxic effects: F19 (ataxia); P72 (changes in leucocyte count)

Dermal TD (dog): 0.143 – 0.164 g/kg[3]
Toxic effects: F07 (somnolence), F19 (ataxia), partial paralysis

Dermal TD (human adult): > 25% (in white soft paraffin, applied for 21 d)[4]

Oral LD_{50} (rat): 1.9 g/kg (1.4 – 2.7 g/kg)[1]

Oral LD_{50} (rat): 1.9 – 2.6 g/kg[13]

Oral TD (rat): 1.5 g/kg[5]
Toxic effects: F07 (somnolence) F18 (muscle weakness), F19 (ataxia), partial paralysis

Oral TD (human adult): 21 µL/kg (after repeated low dose exposure)[6]
Toxic effects: P20 (changes in cell count (unspecified)); R01 (dermatitis, allergic); R03 (dermatitis, other))[4]

Oral TD (human adult): 0.5-1.0 mL/kg[7]
Toxic effects: F08 (hallucinations, distorted perceptions); F24 (coma); K12 (hypermotility, diarrhoea)

Oral TD (human child): 0.5 mL/kg[8]
Toxic effects: F04 (sleep); F19 (ataxia)

Oral TD (human child): 0.5 mL/kg[9]
Toxic effects: F08 (hallucinations, distorted perceptions); F19 (ataxia)[5]

Oral TD (human child): 0.6 mL/kg (approx.)[10]
Toxic effects: F07 (somnolence), F19 (ataxia), F24 (coma)

Chronic toxicity:	No information available
Sensitisation potential:	Low (modified FCA method, guinea pig model)[12]
Other:	Not mutagenic as determined by the AMES test

* see Toxic Effects Code from the Registry of Toxic Effects of Chemical Substances (RTECS)

12. ECOLOGICAL INFORMATION

Ecotoxicity:	Not acutely toxic to fish (LC_{50} > 100 mg/l OECD 206)
Persistence/Degradability:	Readily biodegradeable (OECD301F)
Mobility:	No information available

13. DISPOSAL CONSIDERATIONS

Disposal methods: Dispose of small amounts at an approved landfill site. For larger amounts contact a licensed professional waste disposal service.

Precautions: Prevent contamination of drains or waterways.

14. TRANSPORT INFORMATION

UN number: 2319
UN proper shipping name: TERPENE HYDROCARBONS, N.O.S.
Un Packing group: III
ADG proper shipping name: Not listed in ADG code
Class and subsidiary risk(s): Class 3. No subsidiary risks listed.
Hazchem: 3 [Y]
EPG: 3A1

Special precautions for user: Classified as dangerous goods for the purpose of transport by road or rail. Class 3 Flammable Liquid. Do not transport with chemicals of class ; 1 (Explosives), 2.1/2.3 (Flammable/Toxic gases), 4.2 (Spontaneously combustibles), 5.1 (Oxidising agents), 5.2 (Organic peroxides), 6 (Toxics), 7 (Radioactives) and foodstuffs.

15. REGULATORY INFORMATION

Poison Schedule: 6
AICS: This material is listed on the Australian Inventory of Chemical substances
EINECS: This material is listed on the European Inventory of Existing Commercial Substances

16. OTHER INFORMATION

This document was last modified on: 18th July 2003

ABBREVIATIONS

ADG (Australian Dangerous Goods); **AICS** (Australian Inventory of Chemical Substances); **CAS** (Chemical Abstract Service); **EINECS** (European Inventory of Existing Commercial Substances); **EPG** (Emergency Procedure Guide); **FCA** (Freund's Complete Adjuvant); **HAG** (Hazmat Action Guide); **LD_{50}** (Dose lethal for 50% of the test population); **LDLo** (Lowest Published Lethal Dose); **N.O.S.** (Not Otherwise Specified); **NOHSC** (National Occupational Health and Safety Commission); **PPE** (Personal Protective Equipment); **RTECS** (Registry of Toxic Effects of Chemical Substances); **SUSDP** (Standard for the Uniform Scheduling of Drugs and Poisons); **TD** (Toxic Dose); **TDLo** (Lowest Published Toxic Dose); **UN** (United Nations)

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DATA SOURCES

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Sweet DV. (Editor) (1997) Registry of toxic effects of chemical substances (RTECS), comprehensive guide. U.S. Department of Health and Human Services, Cincinnati, Ohio.

Disclaimer: This Material Safety Data Sheet was prepared according to the National Code of Practice for the Preparation of Material Safety Data Sheets [NOHSC:2011(2003)]. The above information is believed to be correct but does not claim to be all inclusive and shall be used only as a guide.

- END OF REPORT -