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Safety of Tea Tree Oil

-second stage

A report for the Rural Industries Research and Development Corporation

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Foreword

Tea tree (*Melaleuca alternifolia*) oil is still popular throughout Australia and in many countries around the world as a topical antiseptic. Evidence regarding many of the antimicrobial properties of the oil has been scientifically established, and recent published reports of clinical trial success have stimulated intense interest overseas. Markets are likely to expand as a result of such information being available. However, as more people use the product, the possibility of finding a user who has an adverse reaction also increases.

Until now, little safety information relating to the use of tea tree oil was available. The prevalence of sensitivity to tea tree oil in the general population was determined in a previous study. Further knowledge on causes of irritant and allergic reactions to tea tree oil is essential for confirmation of consumer safety and the value of the product. The aim of this project was to produce such safety information.

This publication describes follow-up work that determines some of the causes of delayed sensitivity to tea tree oil, including both irritant and allergic skin reactions. It also provides an indication as to which components of the oil might be responsible for such reactions and the reasons these components might arise in oil.

Despite limited reports of poisonings related to tea tree oil ingestion, it is clear from this report that they do occur. No deaths have been recorded due to ingestion, however, the industry should not be complacent. Recommendations are made for ways to reduce such poisonings.

This project was funded from industry revenue which is matched by funds provided by the Federal Government.

This report, a new addition to RIRDC's diverse range of over 800 research publications, forms part of our Tea Tree Oil Program R&D program, and provides information that will allow continued development of a safe and efficacious product by the Australian tea tree oil industry.

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

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Contents

Executive Summary

Tea tree oil has a long history of safe use and the industry has relied heavily on this in many markets around the world. However, contemporary regulatory requirements are becoming more stringent, and comprehensive information about the safety of tea tree oil is required for the industry to maintain existing and pursue new markets.

Current safety information about tea tree oil in the biomedical literature is mainly in the form of short reports about adverse cutaneous reactions to the oil. This pattern of reporting does not provide an overall picture of the prevalence of adverse events to tea tree oil in the general population. The previous RIRDC-sponsored skin sensitivity project determined that approximately 2% of a non-dermatology self-selected population had positive patch tests to tea tree oil. Various tea tree oil components have been credited with inducing allergic reactions to tea tree oil and this project attempted to clarify this issue further and characterise which components of tea tree oil were responsible for the allergic reactions. Volunteers with a known allergy to tea tree oil were sought and tested with 12 components of tea tree oil at concentrations approximating those found in pure tea tree oil: terpinen-4-ol (40%), α-terpinene (25%), γ-terpinene (10%), aromadendrene (5%), 1,8-cineole (5%), ρ-cymene (5%), α-pinene (5%), α-terpineol (5%), terpinolene (5%), limonene (1%), α-phellandrene (1%) and viridiflorene (1%). Eight volunteers with confirmed allergy to tea tree oil were patch tested to the components. The results suggest that oxidation products of tea tree oil, rather than individual components of fresh tea tree oil, are at least partially responsible for allergic reactions.

The numerous reports in the literature of allergy to tea tree oil have led to the suggestion that tea tree oil should be incorporated into routine diagnostic dermatology patch tests. The exact nature of the tea tree oil to be included in routine testing has not been determined and it has been suggested that aged, oxidised tea tree oil should be included. If this happened, the occurrence of reports about contact dermatitis or positive patch tests to tea tree oil is likely to increase. This would obviously be detrimental to the tea tree oil industry and intensifies the need for more information on the stability and allergenicity of the oil. Some investigations of the stability of tea tree oil and the influence of storage conditions were conducted in this project. One batch of tea tree oil was exposed to a range of storage conditions using the

variables of light, air and temperature. In summary, exposure to light and/or air accelerated the production of oxidation products in tea tree oil. Preliminary in vivo tests to determine if this influenced the irritancy of the oil were inconclusive and further work is required.

Poisoning due to ingestion of tea tree oil has been reported infrequently and no deaths have been recorded in contrast to eucalyptus oil. However, based on a retrospective collection of data from Poisons Information Centres around Australia, poisoning events are relatively common. Most occur in the very young (2 years of age or less) and could probably be prevented by having child-proof caps on all bottles of pure oil.

Tea tree oil has been in use for almost eight decades. In this time, relatively few and minor adverse events have occurred. The present regulatory environment demands that more comprehensive safety data be available. This report contributes to our present understanding of the safety of tea tree oil and will influence future investigations into this complex issue.

1 Introduction

The reputation of tea tree oil as a natural medicine has largely relied on a "long history of use" which has been relatively incident free. As a result of increased production and marketing, tea tree oil products are now available in many countries and are particularly popular as "alternative" remedies. In recent years, the reputation of tea tree oil has been threatened by increasing numbers of both published (Apted 1991; de Groot and Weyland 1992; de Groot and Weyland 1993; Elliott 1993; Knight and Hausen 1994; Moss 1994; Selvaag *et al*. 1994; van der Valk *et al*. 1994; de Groot 1996; Anonymous, 1997; Bhushan and Beck 1997; Kranke 1997; Leach 1997; Southwell *et al*. 1997; Beckmann and Ippen 1998; Fritz and Elsner 1998; Hausen *et al*. 1999) and anecdotal reports of adverse reactions, resulting in distrust of the product amongst some groups. However, there has been little comprehensive safety data available, to health professionals in particular, to provide a complete picture and enable informed judgements about the appropriate use of tea tree oil.

A study funded by RIRDC investigating the prevalence of sensitivity to tea tree oil in the general population was recently completed at The University of Western Australia. Allergic and irritant reactions occurred in a limited number of individuals (approximately 2-4% and 6-8%, respectively). While irritant reactions should be avoidable by use of the oil at low concentrations, the nature of allergic reactions is more complex. Further work was necessary to investigate more thoroughly the characteristics of reactions to tea tree oil, and this report provides the results of these and other studies into safety aspects of tea tree oil use. Safety data are an essential part of the information required by regulatory authorities and are also important for consumer confidence and the security of the industry.

2 Objectives

Most of the information available to health professionals relating to safe usage of tea tree oil consists of reports of single adverse events (Apted 1991; de Groot and Weyland 1992; de Groot and Weyland 1993; Elliott 1993; Knight and Hausen 1994; Moss 1994; Selvaag *et al*. 1994; van der Valk *et al*. 1994; de Groot 1996; Anonymous, 1997; Bhushan and Beck 1997; Kranke 1997; Leach 1997; Southwell *et al*. 1997; Beckmann and Ippen 1998; Fritz and Elsner 1998; Hausen *et al*. 1999). This gives a biased picture of tea tree oil safety. Industry commissioned safety studies are often not released to a wider audience, and rarely in the accepted form of peer-reviewed publications. Judgements are made on the limited information that is available, but assessments would be more balanced if comprehensive safety data were accessible.

The aim of this project was to continue an investigation of safety issues related to the use of tea tree oil and make this information available by publication in peer-reviewed biomedical journals. The problems to be addressed followed on from the first year of this project, including further assessment of the nature of allergic reactions to tea tree oil, investigation of the effects of storage conditions on the oxidation of oil and the extent of poisonings involving tea tree oil.

3 Characterisation of allergic reactions to tea tree oil

3.1 Introduction

From anecdotal reports, our own studies and cases reported in the biomedical literature, it is clear that tea tree oil has the capacity to elicit delayed (type IV) hypersensitivity reactions in some individuals. The pathogenesis of such allergic reactions is, however, less clear. At various times individual components of tea tree oil have been implicated as the causative agents, and we wished to continue our work assessing the role of various components.

During our previous study (UWA-42A) one male subject who displayed a clearly allergic reaction had been using (and continued to use) a shaving cream containing tea tree oil (2%) without experiencing any adverse effects. Thus, while less concentration dependent than irritant responses, allergic reactions to tea tree oil may have a clear threshold concentration below which they will not occur. By testing a series of concentrations of tea tree oil we aimed to determine what this threshold was for each allergic individual.

Petrolatum (white soft paraffin) is often the diluent of choice for making many substances to the appropriate concentration for patch testing (Maibach *et al*. 1993). We have used petrolatum as a diluent for this reason, however, we are aware that other published reports have used different diluents such as ethanol. It was considered possible that a different diluent might produce a different result from a tea tree oil patch test. Consequently, we compared responses to the same concentration of tea tree oil in different diluents.

While a large proportion of tea tree oil sales are of undiluted oils, there are also numerous products containing tea tree oil available to the consumer. We have demonstrated that the antimicrobial properties of tea tree oil are compromised by some product components (Hammer *et al*. 1999). Because of this, it was considered possible that some product components might interact with tea tree oil in such a way as to alter its capacity to elicit reactions. Reactions to tea tree oil when mixed individually with a number of excipients commonly found in products were assessed.

3.2 Methodology

Patch testing was performed on healthy consenting adults with a known or suspected tea tree oil allergy. Factors precluding participation in the study included severe skin conditions, immunosuppressant treatment or the use of various medications within a specified time period (in particular corticosteroids, antihistamines and antidepressants). After a full explanation was provided regarding participation, signed consent was obtained as required by the Committee for Human Rights of The University of Western Australia. Five volunteers had participated in initial tests performed in 1998 and consented to further testing. New volunteers were recruited by various means including posters placed in the local area and articles in local print media. Five people who responded were eligible and willing to participate, but upon testing two could not be confirmed as being allergic to tea tree oil. Thus the results refer to information on 8 participants.

The tea tree oil used in these tests was kindly supplied by Australian Plantations (Wyrallah NSW). Only one oil was used as our previous work showed no difference in reactions to oils meeting the ISO 4730 standard. For the threshold concentration tests, the oil was made to the relevant concentration (0.5 – 50%) in petrolatum. For the diluent tests, four concentrations of tea tree oil (2, 5, 10, 20%) were made up in ethanol for comparison with the same concentrations of tea tree oil in petrolatum. For the excipient tests, tea tree oil was mixed in one of the excipients (propylene glycol, sorbitol, glycerol, glyceryl stearate) and then made up in petrolatum to give a final concentration of 10% tea tree oil and 10% excipient. The tea tree oil components (aromadendrene, 1,8-cineole, limonene, α-phellandrene, viridiflorene, ρ-cymene, α-pinene, terpinen-4-ol, α-terpinene, γ-terpinene, α-terpineol) that had been made to relevant concentrations toward the end of the previous study (UWA-42A) were used again. Terpinolene (Fluka, Switzerland), which was not available for the previous study, was included in the test battery. All test mixtures were prepared on-site by the Sir Charles Gairdner Hospital (SCGH) pharmacy, stored in brown glass bottles with plastic screw caps and added to the patch chambers with a metal spatula.

Patch testing procedures were based on the guidelines of the International Contact Dermatitis Research Group (ICDRG) and are outlined here briefly (for a more complete description of testing procedures see the previous report). IQ chamber patch test units

(Chemotechnique Diagnostics, Sweden), consisting of inert polyethylene plastic chambers attached in units of 10 to hypoallergenic non-woven adhesive tape, were used. The chambers were applied to the mid-section of the upper back. Subjects were instructed to keep the site dry and to leave the patches in place for 48 h unless excessive discomfort due to a reaction necessitated removal of a section. After removal of the patch and 2-5 days later, the appearance of the skin at each test site was graded according to ICDRG recommendations (Beltrani and Beltrani 1997; Wilkinson and Shaw 1997): 0 = no reaction; doubtful (?) = erythema; 1 (+) = erythema and oedema; 2 (++) = vesiculation; 3 (+++) = bulla formation. A positive reaction (+) was defined as at least homogeneous redness and palpable induration in the test area (al-Sheikh and Gad el-Rab 1996; Nielsen and Menne 1992). Irritant responses were differentiated by sharply demarcated dry and red skin without oedema (Maibach *et al*. 1993).

3.3 Results

Allergic individuals involved in the previous study were tested with 11 components of tea tree oil. At that time, two of the five subjects displayed allergic reactions to ρ-cymene. Since that study terpinolene had been acquired and one of these subjects was allergic to this component as well. New subjects were also tested with the components that had been diluted in late 1998, as well as the newly diluted terpinolene. All three of the tea tree oil allergic subjects exhibited responses to terpinolene and α-terpinene, and one reacted also to γ-terpinene.

By testing a series of tea tree oil concentrations in petrolatum from 0.5% up to the lowest concentration expected to cause a response, we were able to define the reaction threshold concentration for each volunteer. These levels varied between individuals, with a reaction occurring even at 0.5% in one woman but still being somewhat doubtful at 10% in one other subject. The lowest concentration able to induce a level 1-3 response in the other volunteers fell between these: 1% (one person), 2% (three people) and 5% (two people).

Tea tree oil made to 2%, 5% and 10% in ethanol was used in patch tests and the outcomes compared with the same concentrations in petrolatum. For 6 of the 8 subjects the results were quite comparable, with virtually the same response at the selected concentrations

regardless of the diluent, noting that there were a few aberrations thought to be due to insufficient patch adhesion. The remaining two individuals clearly reacted to 10% tea tree oil in ethanol, but not in petrolatum (hence the previously mentioned “doubtful” 10% response threshold). One of these subjects had been involved in primary testing and had not responded to 10% in that instance and the other volunteer was not tested with a concentration higher than 10% based on the history she initially provided.

Four common product excipients (propylene glycol, glyceryl stearate, glycerol and sorbitol) were patch tested at 10%, with or without 10% tea tree oil. Note that the individual with a reaction threshold of 0.5% was not tested with 10% tea tree oil, and hence with none of these excipients. No responses were seen in the absence of tea tree oil. Three individuals displayed the same level of response in the presence of excipient as they did to 10% tea tree oil alone (including the woman for whom all responses to 10% tea tree oil were doubtful). One individual responded to the tea tree oil in the presence of the excipients, although the response was slightly weaker than the oil alone. Two individuals responded to the same level to all excipients but one, where only erythema was observed (to TTO + sorbitol in one case, and TTO + propylene glycol in the other), which may have been due to insufficient adhesion of the patch. The subject who did not respond to 10% tea tree oil in petrolatum exhibited only inconsistent erythema at a number of sites.

Table 1: Studies characterising tea tree oil (TTO) allergies - 2 readings of 48 hours patch test

Allergen	T216		T017		T183		T101		T066		T222		T223		T224		T225	
TTO in petrolatum																		
100% TTO	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
50% TTO	-	-	2	?	2	?	2	1	?	2	-	-	-	-	-	-	-	-
20% TTO	-	-	2	?	1	?	?	0	0	0	-	-	-	-	-	-	-	-
10% TTO	2	2	2	?	1	?	2	?	?	0	0	0	1	1	?	0	-	-
5% TTO	2	2	2	?	1	?	?	0	0	0	0	0	1	1	?	0	2	1
2% TTO	2	2	2	?	?	0	1	0	0	0	0	0	1	0	?	0	2	1
1% TTO	0	0	2	?	?	0	0	0	0	0	0	0	?	0	?	0	2	1
0.5% TTO	0	0	?	?	0	0	0	0	0	0	0	0	?	0	?	0	2	1
0% TTO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	?	0	0	0
TTO in ethanol																		
20% TTO	-	-	2	?	1	?	1	1	2	1	-	-	-	-	-	-	-	-
10% TTO	2	2	2	?	?	?	1	?	2	1	0	0	2	1	3	1	-	-
5% TTO	2	2	2	?	1	?	1	?	?	?	0	0	1	1	0	0	2	1
2% TTO	2	2	2	?	?	?	1	?	?	?	0	0	1	1	0	0	2	1
0% TTO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TTO in excipient in petrolatum																		
propylene glycol	2	2	2	?	1	?	1	?	?	0	0	0	?	0	0	0	-	-
w/o TTO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	?	0	-	-
glyceryl stearate	2	2	2	?	1	?	1	?	?	0	0	0	1	1	?	0	-	-
w/o TTO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	?	0	-	-
glycerol	2	2	2	?	1	?	1	?	?	0	0	0	1	1	?	0	-	-
w/o TTO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-	-
sorbitol	2	2	2	?	?	?	1	0	?	0	0	0	1	1	0	0	-	-
w/o TTO	0	0	0	0	0	0	0	0	0	0	?	0	0	0	0	0	-	-
TTO components																		
terpinolene 5%	2	2	0	0	0	0	0	0	0	0	0	0	1	1	2	1	2	1
α-phellandrene 1%	-	-	-	-	-	-	-	-	-	-	0	0	0	0	0	0	0	0
α-pinene 5%	-	-	-	-	-	-	-	-	-	-	0	0	0	0	0	0	0	0
γ-terpinene 25%	-	-	-	-	-	-	-	-	-	-	0	0	?	0	?	0	1	1
α-terpinene 10%	-	-	-	-	-	-	-	-	-	-	0	0	2	1	2	1	3	3
α-terpineol 5%	-	-	-	-	-	-	-	-	-	-	0	0	0	0	0	0	0	0
1,8-cineole 5%	-	-	-	-	-	-	-	-	-	-	0	0	0	0	0	0	0	0
aromadendrene 5%	-	-	-	-	-	-	-	-	-	-	0	0	0	0	0	0	0	0
limonene 1%	-	-	-	-	-	-	-	-	-	-	0	0	0	0	?	0	0	0
ρ-cymene 5%	[2]	[2]	-	-	-	-	-	-	[2]	[2]	0	0	0	0	?	0	0	0
terpinen-4-ol 40%	-	-	-	-	-	-	-	-	-	-	0	0	0	0	0	0	0	0
viridiflorene 1%	-	-	-	-	-	-	-	-	-	-	0	0	0	0	0	0	0	0

3.4 Discussion

The tea tree oil components that caused reactions were ρ-cymene, terpinolene, α-terpinene and γ-terpinene. Most of these components, as well as many others, have been reported to elicit delayed hypersensitivity reactions (de Groot and Weyland 1992; Knight and Hausen 1994; Southwell *et al*. 1997; Rubel *et al*. 1998; Hausen *et al*. 1999). ρ-Cymene levels increase with oxidation and it has previously been reported as eliciting allergic reactions (Knight and Hausen 1994). Hausen and colleagues have reported reactions to terpinolene (Knight and Hausen 1994; Hausen *et al*. 1999), with all 11 patients reacting to it in the most recent study, as well as a large number responding to ascaridol and α-terpinene (Hausen *et al*. 1999). No reactions were seen to α- and γ-terpinene with volunteers tested in our previous study, yet all three new subjects reacted to α-terpinene and one also reacted to γ-terpinene. In light of this and the fact that α- and γ-terpinene (and terpinolene) levels decrease as oil oxidises forming ρ-cymene and peroxides such as ascaridole (Leach 1997; Hausen *et al*. 1999), the diluted components were sent for GC analysis. γ-Terpinene had partially oxidised to ρ-cymene, while α-terpinene contained not only significant amounts of ρ-cymene but also substantial amounts of oxygenated components, possibly epoxides. While the original α-terpinene from which the test solution was made was also found to contain ρ-cymene and a number of other impurities, it did not contain the suspected epoxides found in the test solution. Since the volunteers who reacted to α-terpinene did not react to ρ-cymene or any of the other contaminating components that were tested, it is unlikely that they were the cause of reactions to the solution. Thus, while reactions may have been to α-terpinene, they may also have been due to oxidation products such as the probable epoxides, trace amounts of ascaridole, or δ-3-carene (Ian Southwell, personal communication). It is clear that there is increasing evidence, both from these results and others (Hausen *et al*. 1999), that possibly both allergic and irritant reactions to tea tree oil are at least partially due to oxidation products. These findings dictate a need for strict storage conditions and a limited usage life to maintain oil at optimal quality and minimise the likelihood of adverse reactions. Such care is just as important if routine patch testing with tea tree oil is ever to be performed, as has been suggested by some European groups (Hausen *et al*. 1999).

Reaction threshold concentrations were found to be quite individual, ranging from <0.5% to possibly >10%. Some of these thresholds clearly related to information provided by the participant. For example the subject reacting at 0.5% was unable to use anything containing tea tree oil, with reactions apparently becoming worse with each exposure. The subject who had previously reported continued uneventful use of a shaving cream containing 2% tea tree oil during primary testing, had a threshold concentration of 5%. Where the threshold is relatively high, tea tree oil products may still be able to be used, or at the very least unintentional exposure to low concentration products such as soaps should be uneventful. However, when the threshold concentration is very low, complete avoidance of all tea tree oil products is necessary. In terms of diagnosing suspected allergies, though admittedly limited in numbers, this work indicates that most delayed hypersensitivity reactions would be detected if a 5% tea tree oil patch test was performed, but weaker reactions might still be missed even with 10% tea tree oil.

Some other studies reporting reactions to tea tree oil and its components have used a diluent other than petrolatum (white soft paraffin) which is often used in routine patch testing (Maibach *et al*. 1993). One study used anhydrous ethyl alcohol (Knight and Hausen 1994), while communication with the author indicated that in another study diethyl phthalate was used, but had not been reported (Hausen *et al*. 1999). We chose to compare reactions to tea tree oil in ethanol against the same concentrations in petrolatum in our hypersensitive subjects. For the six subjects with quite a strong allergic reaction (that is, threshold concentration ≤5%), the diluent did not appear to alter the response (to tea tree oil at 2, 5 and 10%). In the two subjects displaying weaker reactions, responses were evident at 10% in ethanol but not in petrolatum. This may indicate a capacity for some diluents to exaggerate or compromise the sensitivity of patch tests with tea tree oil. For example, ethanol may evaporate from the test material (which would be possible if a patch lifted), increasing the relative concentration of tea tree oil. Alternatively, petrolatum may isolate tea tree oil away from the skin's immune system, preventing reactions. This is possible as it has been argued that the petrolatum vehicle may incompletely release hydrophobic allergens (Fischer and Kihlman 1989). Thus it seems that weak reactions to tea tree oil may be affected by the diluent, shifting the thresholds at which reactions will be evident.

Various product components have been found to detrimentally alter the antimicrobial properties of tea tree oil (Hammer *et al*. 1999). It is possible that similar interactions may alter the allergenic nature of tea tree oil. To investigate this, we mixed tea tree oil with four common product excipients and compared the responses of allergic individuals to these solutions and control solutions of tea tree oil or excipient alone. Responses to tea tree oil were similar in the presence of the various excipients. This indicates that allergic responses are unlikely to be dampened by the presence of other product components, at least those that were tested.

These investigations provide useful information with regard to diagnosing and living with allergies to tea tree oil, as well as insight into the characteristics of oil and products that may be important in minimising the likelihood of reactions.

4 Storage of oil

4.1 Introduction

It became clear during previous sensitivity testing in 1998 that oxidation of tea tree oil can occur in particular storage conditions, and this may alter the ability of the oil to cause adverse events. Similar suggestions have recently appeared in the literature. Leach (1997) reported that storage of oil in dark glass bottles at room temperature for two years resulted in increases in ρ-cymene and/or terpinen-4-ol, and decreases in the monoterpene hydrocarbons α- and γ- terpinene and α-terpinolene. It was suggested that ρ-cymene levels provide a good indication of oil age and treatment during processing and storage, and the ISO upper limit of 12% may be too high. Hausen *et al*. (1999) reported that exposure to light and/or air over 2 months caused oil to oxidise, the main products being ρ-cymene and peroxides, including ascaridole. The oxidised oil had increased capacity to cause sensitisation and allergic or irritant reactions. Harkenthal *et al*. (1998) reported similar results while Beckmann and Ippen (1998) also suggested that hydroperoxides resulting from auto-oxidation may cause contact allergies.

4.2 Methodology

Pure 100% tea tree oil was provided by Australian Plantations (Wyrallah, NSW) and stored in a set of glass bottles (capacity ~25ml) in a range of conditions involving:

- temperature (4ºC, room temperature, 37ºC),
- bottle opacity (brown or clear glass),
- air exposure (bottles full or half-full, and opened weekly or left undisturbed).
- light exposure (either protected from, or exposed to fluorescent &/or daylight).

The oils were sent to Dr Ian Southwell (Principal Research Scientist, NSW Agriculture, Wollongbar) for GC analysis at three monthly intervals.

Oils used in the previous study (UWA-42A) for patch testing had oxidised markedly by the end of the test period. These oils were stored in the dark at 4ºC in brown glass dropper bottles that had a flexible teat to facilitate aspiration of the oil. While it did not appear that the rubber-like material had degraded (and it had not been in contact with the liquid oil), we wished to determine whether components of the rubber might have contaminated the tea tree oil after extended exposure. To this end, one of the rubber-like teats was submerged in a (clear) bottle of oil at 4ºC and left unopened and protected from light.

After 6 months of storage in various conditions, one of the oils displaying marked changes was chosen for testing. This oil had been stored at room temperature in a clear bottle exposed to light, was half full and had been opened weekly. As the bottle was already only partially full, removing an aliquot (2.5ml) of oil for testing would not greatly alter the relative air exposure (as opposed to removing a similar quantity from a "full" bottle). The sample of oil was made to a concentration of 50% in petrolatum for testing. We believed this concentration would minimise the risk of a marked reaction whilst hopefully allowing sufficient reaction to distinguish between this oxidised oil and a control sample. The control oil was taken from the original flask of oil that had been left undisturbed after initially removing oil for storage in the different conditions. This oil was made to 50% in petrolatum and a petrolatum control was also used.

Routine patch testing (as described earlier) was performed on 10 consenting adult volunteers using the oxidised sample and two controls described above. Volunteers who knew they were not allergic to tea tree oil were tested as we wished to determine whether there was a difference in the capacity of the oils to cause irritation. While the 48 h occluded patch test is not strictly diagnostic for irritant reactions, they may be discernible, as was clearly shown during the previous study.

4.3 Results

Table 4.1 provides the 3-monthly GC analyses of tea tree oil stored in the various conditions listed for each oil sample. The most marked changes in the tea tree oil were observed in four of the five clear bottles, while little change occurred in the brown bottles,

regardless of other conditions. The changes are consistent with oxidation of the oil, including decreases in α- and γ- terpinene and terpinolene and increases in ρ-cymene, 1,2,4-trihydroxymenthane and total sesquiterpenoids. Changes occurred in the clear bottles at all temperatures tested and all were exposed to light. The only clear bottle that did not change markedly was a full bottle exposed to light at 4°C, even though a half-full bottle opened weekly but otherwise kept in similar conditions did oxidise.

The bottle of oil in which the rubber-like teat was submerged displayed no evidence of oxidative changes. While the oil had become quite orange in colour and the peroxide level had increased, there were not marked quantities of unknown substances in the GC analysis to indicate rubber-related impurities in the oil.

Patch testing of 10 volunteers with the oxidised oil and two controls yielded no visible change at any test site on any subject.

4.4 Discussion

These results indicate that the greatest oxidation risk is storage of oil in clear rather than brown bottles. Whilst weekly opening of half-full brown bottles stored in the dark at 4°C did not cause oxidation in this study, oil which oxidised during the previous study was stored in similar conditions but the seal on the bottle incorporated a dropper with flexible teat. The more frequent opening of those bottles and aspiration of the oil into a dropper would have resulted in greater exposure to air, enhancing the probability of oxidation occurring, but the changes that occurred in those oils were not as great as seen in this second study. This does however indicate that extensive exposure to air may also cause oxidation, as has been reported by others (Hausen *et al*. 1999). The rubber teat on the bottles used in the previous study may have facilitated exposure to air, however, the rubber itself is unlikely to have contributed based on the result showing no obvious oxidation or impurities after complete submersion of the teat material in tea tree oil.

Table 4.1: GC analyses of tea tree oil stored in various conditions (marked changes shown in bold)

storage conditions																					
temperature		sample	4°C	4°C	4°C	room	room	37°C	37°C	4°C	4°C	room	room	room	room	4°C	room	37°C	4°C	room	4°C
opacity		prior to	metal	brown	brown	brown	brown	brown	brown	brown	brown	brown	brown	brown	brown	clear	clear	clear	clear	clear	clear
air exposure		storage	original	full	full	full	full	full	full	half (o)	half (o)	half (o)	half (o)	half	half	full	full	full	half (o)	half (o)	full
light exposure			flask	dark	light	dark	light	dark	light	dark	light	dark	light	dark	light	light	light	light	light	light	dark
component	**ISO range**		**3 month analysis**																		*rubber
a-pinene	1-6	2.6	2.5	2.5	2.5	2.5	2.4	2.4	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.6	2.4
sabinene	tr-3.5	0.8	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.8	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.8	0.7
a-terpinene *	5-13	9.6	9.1	9.2	9.2	9.1	9.1	9.1	9.0	8.6	8.9	8.8	8.9	8.7	8.9	9.2	**7.0**	8.2	**6.9**	**3.8**	8.8
limonene	0.5-4	1.2	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.2	1.1
p-cymene #	0.5-12	2.6	2.7	2.6	2.5	2.6	2.6	2.6	2.6	3.4	2.9	3.0	2.8	3.1	2.9	2.5	**5.8**	4.1	**6.2**	**10.9**	2.9
1,8-cineole	0-15	4.0	4.0	4.0	3.9	3.9	3.9	3.9	3.9	4.0	4.0	4.0	4.0	3.9	4.0	3.9	4.0	3.9	4.0	4.1	3.9
g-terpinene *	10-28	20.6	19.7	19.9	19.8	19.7	19.7	19.6	19.6	19.1	19.4	19.4	19.5	19.3	19.4	19.8	**17.3**	18.6	**16.8**	**13.4**	19.0
terpinolene	1.5-5	3.5	3.3	3.6	3.3	3.3	3.4	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.4	3.0	3.2	3.0	**2.4**	3.2
terpinen-4-ol	30->	37.2	38.1	38.0	37.8	38.2	38.5	38.3	38.3	38.3	38.2	38.2	38.4	38.3	38.2	38.0	38.2	38.2	38.3	37.9	38.9
a-terpineol	1.5-8	2.9	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.2	3.2
aromadendrene	tr-7	1.2	1.3	1.2	1.2	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.4	1.3	1.3	1.4	1.2
ledene	0.5-6.5	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
d-cadinene	tr-8	1.1	1.2	1.1	1.1	1.1	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.1
globulol	tr-3	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.5	0.4	0.5	0.5	0.5
viridiflorol	tr-1.5	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.4	0.3	0.4	0.4	0.4	0.4	0.3	0.5	0.4	0.5	0.6	0.3
1,2,4-trihydroxymenthane			<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	**<0.4**	<0.2
total sesquiterpenoids			8.3	8.6	9.3	8.9	8.2	9.2	8.1	8.4	8.3	8.4	8.3	8.4	9.1	8.3	**10.0**	**10.2**	8.9	**10.5**	8.5
component	**ISO range**		**6 month analysis**																		
a-pinene	1-6	2.6	2.5	2.5	2.5	2.5	2.5	2.5	2.4	2.5	2.5	2.5	2.4	2.3	2.5	2.5	2.6	2.5	2.4	2.6	2.4
sabinene	tr-3.5	0.8	0.8	0.8	0.9	1	0.8	0.8	0.8	0.9	0.9	0.8	0.8	0.8	0.8	0.9	0.9	0.8	0.8	0.9	0.8
a-terpinene *	5-13	9.6	9.1	9.2	9.2	9	9.2	9.1	8.8	8.3	8.7	8.5	8.8	8.3	8.7	9.2	**2.4**	**4.4**	**4.4**	**2.8**	8.3
limonene	0.5-4	1.2	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.2	1.2	1.2	1.2	1.1
p-cymene #	0.5-12	2.6	2.7	2.6	2.6	2.6	2.6	2.6	3.1	4	3.4	3.5	2.9	3.6	3.1	2.6	**14**	**10.3**	**10.4**	**12.2**	3.7
1,8-cineole	0-15	4.0	3.9	4	4	3.9	4	4	4	4	4	4	4	4	4	4	4.2	4.1	4.1	4.2	3.9
g-terpinene *	10-28	20.6	19.7	19.7	19.9	19.5	19.7	19.6	19.3	18.7	19.1	18.9	19.3	18.8	19.2	19.8	**11**	**14**	**13.4**	**12.4**	18.3
terpinolene	1.5-5	3.5	3.3	3.3	3.4	3.3	3.3	3.3	3.3	3.2	3.3	3.2	3.3	3.2	3.3	3.4	**2.1**	**2.5**	**2.5**	**2.2**	3.2
terpinen-4-ol	30->	37.2	38.1	38.4	38.1	38.6	38.2	38.3	38.6	38.3	38.4	38.5	38.7	38.9	38.5	38.2	37.6	38	38.9	38	39.4
a-terpineol	1.5-8	2.9	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.2	3.1	3.1	3.2	3.2	3.2	3.3	3.2
aromadendrene	tr-7	1.2	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.5	1.6	1.4	1.5	1.3
ledene	0.5-6.5	1.0	1	1.1	1	1	1	1	1	1	1	1	1	1	1	1	0.8	1	1	1	1
d-cadinene	tr-8	1.1	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.3	1.2	1.3	1.3	1.2
globulol	tr-3	0.4	0.4	0.4	0.4	0.4	0.5	0.4	0.5	0.4	0.4	0.4	0.5	0.5	0.5	0.4	0.5	0.5	0.5	0.5	0.5
viridiflorol	tr-1.5	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.3	0.6	0.7	0.7	0.6	0.4
1,2,4-trihydroxymenthane			0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	**0.4**	**0.2**	0.02	**0.5**	0.02
total sesquiterpenoids			10.2	10	9.8	10.1	10.1	9.9	10.2	10.5	10.4	10.1	10.2	10.4	10.4	9.9	**15.2**	**13.7**	**13.1**	**14.4**	10.5

Table 4.1 continued (marked changes shown in bold)

storage conditions																					
temperature		sample	4°C	4°C	4°C	room	room	37°C	37°C	4°C	4°C	room	room	room	room	4°C	room	37°C	4°C	room	4°C
opacity		prior to	metal	brown	brown	brown	brown	brown	brown	brown	brown	brown	brown	brown	brown	clear	clear	clear	clear	clear	clear
air exposure		storage	original	full	full	full	full	full	full	half (o)	half (o)	half (o)	half (o)	half	half	full	full	full	half (o)	half (o)	full
light exposure			flask	dark	light	dark	light	dark	light	dark	light	dark	light	dark	light	light	light	light	light	light	dark
component	**ISO range**		**9 month analysis**																		*rubber
a-pinene	1-6	2.6	2.5	2.5	2.5	2.5	2.5	2.4	2.4	2.5	2.5	2.5	2.4	2.4	2.4	2.5	2.6	2.5	2.4	2.5	2.4
sabinene	tr-3.5	0.8	0.8	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
a-terpinene *	5-13	9.6	9.2	9.2	9.3	9.2	9.1	8.9	6.4	8.1	8.5	8.2	8.6	8.0	8.5	7.2	0.4	4.2	1.6	1.2	8.3
limonene	0.5-4	1.2	1.2	1.2	1.2	1.1	1.1	1.1	1.1	1.2	1.2	1.1	1.1	1.1	1.1	1.2	1.2	1.2	1.2	1.2	1.1
p-cymene #	0.5-12	2.6	2.8	2.6	2.6	2.7	2.7	2.8	6.1	4.4	3.8	3.8	3.1	4.1	3.3	5.9	20.7	10.7	16.6	16.4	3.9
1,8-cineole	0-15	4.0	3.9	3.9	3.9	3.9	3.9	3.9	4.0	4.0	4.0	4.0	3.9	3.9	4.0	4.0	4.3	4.1	4.2	4.3	3.9
g-terpinene *	10-28	20.6	19.8	19.9	19.9	19.8	19.7	19.5	17.2	18.6	18.9	18.7	19.2	18.4	19.1	17.3	5.6	14.0	8.4	9.3	18.3
terpinolene	1.5-5	3.5	3.4	3.4	3.4	3.4	3.4	3.3	3.0	3.2	3.3	3.2	3.3	3.2	3.3	3.1	1.1	2.6	1.7	1.7	3.2
terpinen-4-ol	30->	37.2	37.8	37.9	37.8	37.9	38.0	38.4	38.5	38.2	38.1	38.5	38.6	38.8	38.5	38.2	35.3	37.8	38.0	37.2	39
a-terpineol	1.5-8	2.9	3.1	3.1	3.1	3.1	3.1	3.1	3.2	3.1	3.1	3.2	3.2	3.2	3.2	3.1	3.2	3.2	3.2	3.3	3.2
aromadendrene	tr-7	1.2	1.3	1.3	1.3	1.3	1.3	1.3	1.4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.8	1.6	1.5	1.7	1.3
ledene	0.5-6.5	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.6	1.0	0.8	0.8	1
d-cadinene	tr-8	1.1	1.1	1.1	1.1	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.0	1.2	1.1	1.2	1.1
globulol	tr-3	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.5	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.5
viridiflorol	tr-1.5	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.7	0.4	0.4	0.5	0.4	0.5	0.4	0.5	0.6	0.7	0.7	0.6	0.4
1,2,4-trihydroxymenthane			0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.9	0.2	0.2	0.6	0.02
total sesquiterpenoids			9.8	10.8	9.6	10.0	10.0	10.3	11.4	10.6	10.4	10.7	10.6	10.5	10.2	10.8	20.3	14.5	16.3	17.9	10.4

* decreases with oxidation
# increases with oxidation

In order to minimise the possibility of eliciting strongly irritant reactions on our volunteers, the oxidised oil was tested at a concentration of 50%. As no clear differences were seen between the test and control oils it is not possible to say whether the irritation causing capacity of the oil had increased as a result of oxidation. However, based on previous results this is likely. Irritant reactions are strongly concentration dependent (Beltrani and Beltrani 1997), so decreasing the concentration of the test oil to 50% may well have masked any capacity to elicit irritant reactions. This possibility provides further support for the proposition of using diluted tea tree oil (products) in order to minimise the risk of adverse reactions whilst still utilising the beneficial properties of the oil.

5 Tea tree oil related poisoning reports

5.1 Introduction

Tea tree oil is classified as an S6 poison, yet is a popular "natural medicine" and widely available. As a volatile essential oil, it has the potential to cause systemic effects, including central nervous system depression [Jacobs MR, 1994 #238]. There have been four reports of human tea tree oil poisoning in the literature covered by Medline and Current Contents databases (Seawright 1993; Jacobs and Hornfeldt 1994; Elliott 1993; Del Beccaro 1995), leading to suggestions that poisonings due to tea tree oil are neither frequent nor serious. Inquiries to Poisons Information Centres (PICs) around Australia indicated that poisoning incidents involving tea tree oil occur far more frequently than reports in the biomedical literature would imply. However, little is known about the frequency and circumstances of these poisonings. We therefore set out to retrospectively determine the frequency of reported tea tree oil poisonings from databases at the Poisons Information Centres (PIC) throughout Australia, and prospectively determine the frequency and circumstances of reported tea tree oil poisonings from calls to the PICs. Ethics approval for the prospective study took many months to obtain and, for some centres, was not obtained until after the project had finished. Because of this difficulty only the retrospectively collected data are presented in this report.

5.2 Methodology

The most time-consuming part of a multi-centre study such as this is obtaining the approval of the Ethics Committee at each site. This took many months at some centres. The retrospective study of reported tea tree oil poisonings involved searching database and paper records from each PIC. In some centres, database systems did not allow sufficiently detailed retrieval of records, particularly where tea tree oil was not coded separately from other essential oils and it was necessary to scrutinise hardcopy records which, in one state, involved sifting through ~30000 records/year. Although personal data was evident in some cases, it was not recorded for this study.

5.3 Results

Data were collected for the 2-year period 1998-99 from eight PICs in all States and Territories. During the 2 years there were 386 reports of tea tree oil poisoning (identified as such because a call was made to a PIC), 169 in 1998 and increasing to 217 in 1999. By State or Territory, the breakdown was as follows: WA (76), NSW (135), Qld (56), Vic (91), Tas (6), SA (9), ACT (6) and NT (6). The distribution by gender was 55% female and 45% male (16 not recorded). Over half the poisonings reported (202) came from children aged 2 years or less. The vast majority of cases of reported poisoning (80%) related to ingestion, however, there were 23 reports of tea tree oil being applied to the eye.

In Western Australia, data were also available on reports of poisoning with other oils, such as eucalyptus oil. For comparative purposes, total other oil poisonings (Figure 1.) were related to tea tree oil poisonings (Figure 2.). Over a period of nearly 18 months, an average of 19 other oil poisonings per month was reported compared to 3 per month for tea tree oil. The largest contributor to the other oils category was eucalyptus oil or eucalyptus oil containing products (Figure 3.).

Figure1. Total number of oil related "poisonings" reported to the WA PIC, 1998-99, by month

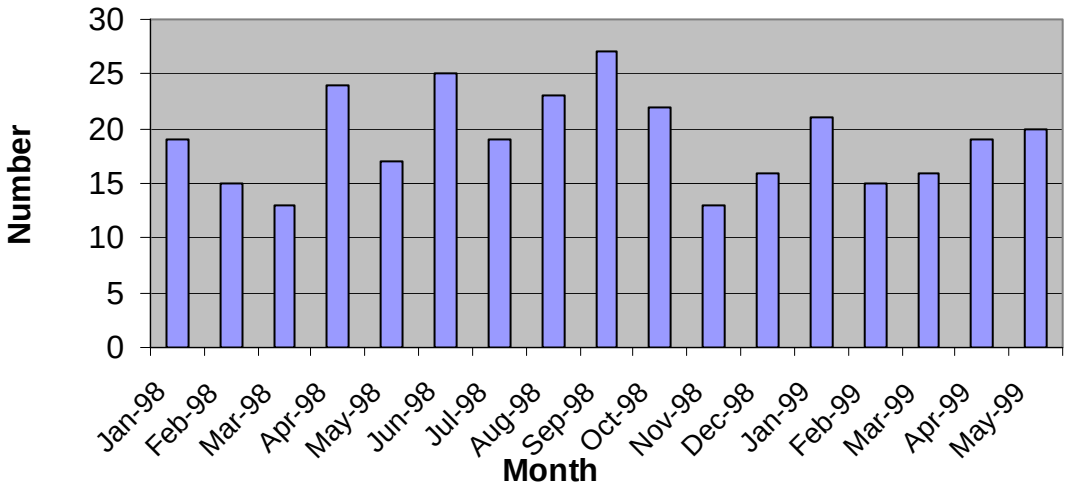
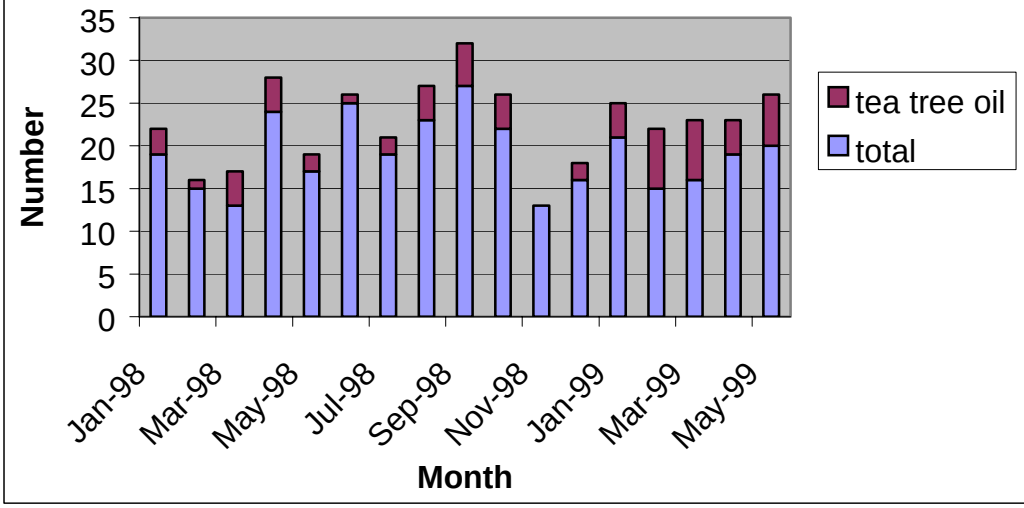
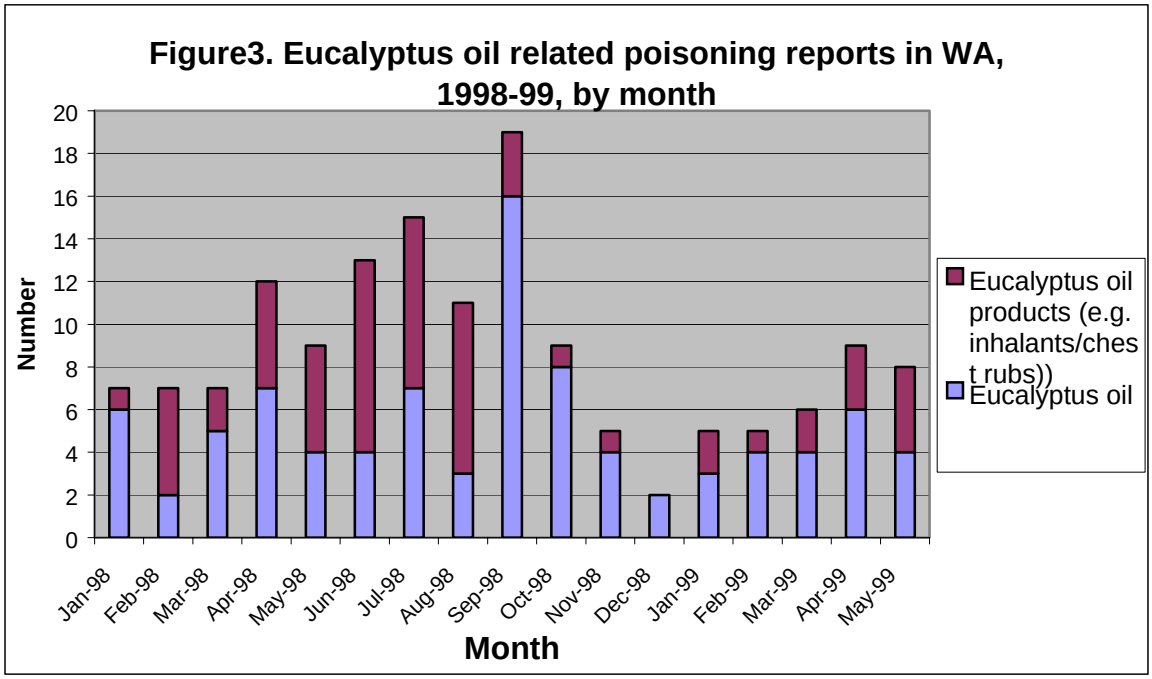


Figure2. Reported oil related poisonings in WA, 1998-99





5.4 Discussion

Poisoning is the second leading cause of hospitalisations for injury in Victoria for children under 5 years of age. Eucalyptus oil accounts for around 40 hospital admissions per year, about 25% of total admissions for poisoning (Day *et al*. 1997). While tea tree oil poisonings were significantly less than eucalyptus oil, they are probably much higher than generally thought by the industry. While deaths caused by tea tree oil have not been recorded, it is the industry's responsibility to ensure that tea tree oil is marketed in a safe manner. This should probably include child-proof caps on bottles of pure oil of all sizes. From the data we had access to, it was not possible to determine the severity of poisoning, nor to determine how complete reporting was. Thus, we do not know if the figures we have are an under representation of the problem or an over representation. Most tea tree oil poisonings occur in the very young, 2 years of age or less. This suggests that much of the problem relates to adults leaving tea tree oil in places where very young children had access and a child-proof cap would solve this problem readily. We had hoped to determine the circumstances surrounding poisoning prospectively but the delay in getting ethics approval prevented this part of the study from being completed. It may be worthwhile to try and complete the prospective study at some stage in the future. It is certainly worthwhile

advertising within the industry that poisoning is an issue that so far has not really impacted on Australian producers, however, it has the capacity to do so. Recent experience overseas indicates that other countries do consider this an issue and the industry here would do well to recognise this fact.

6 Implications

The results of this study have significant implications for the tea tree industry in three areas:

1) irritant and allergic responses to tea tree oil,
2) storage of tea tree oil,
3) poisonings due to tea tree oil.

Confirming our previous work that true allergic reactions do occur with tea tree oil, our findings were extended to offer putative causes for these reactions. From our work, and that of others, it is apparent that allergic reactions are due in part to oxidation products that appear in oil over time. Both irritant and, surprisingly, some allergic reactions appeared to be concentration dependent in some circumstances. The base in which tea tree oil products are formulated may influence adverse skin reactions.

Storage conditions for oil are perhaps more important than generally appreciated. Oil in clear bottles experienced much greater degradation than oil in brown bottles, independent of other variables. Some tea tree oil sellers use clear bottles exclusively and this may need revision. In addition, storage time is a significant factor and it may be necessary to shorten expiry dates on oil bottles.

True poisoning with tea tree oil following ingestion is a rare thing, according to the published literature. Our retrospective survey showed that ingestion occurred quite commonly. Although ingestion was never fatal, these figures should serve to alert the industry to a potentially serious problem.

7 Recommendations

Based on our findings several recommendations may be prudent:

1) To help maintain the good safety record of tea tree oil, it may be better to promote the use of appropriately formulated tea tree oil products rather than pure oil.
2) Storage conditions for tea tree oil need to be better defined and the use of a dark bottle is recommended.
3) All pure tea tree oil sold needs to have an expiry date of not more than 12 months after opening bottles.
4) Further investigation of formulation issues is required, particularly in relation to how certain excipients may enhance or reduce adverse reactions.
5) Child-proof caps should be fitted to all bottles of pure oil.

8 Communications Strategy

One of the aims of this project was to make the results available to a broad range of interested groups. This has been facilitated in part by the availability of progress updates in RIRDC publications, providing knowledge of our ongoing work to tea tree industry in particular. In addition, Tom Riley, Christine Carson and Jane Greig have been involved in a number of meetings with industry groups and the press in Australia and overseas.

Work from this and the previous study (UWA-42A) has been presented to the biomedical community on a number of occasions. Martin Stuckey attended the Australasian Society of Clinical Immunology and Allergy Annual Scientific Meeting at Uluru in September 1999 and gave a poster presentation. Jane Greig attended the European Association of Dermatology and Venereology Scientific Meeting in Amsterdam in October 1999 and gave an oral presentation. Two articles have been accepted for publication:

Greig, J.E., Thoo, S-L., Carson, C.F. and Riley, T.V. (1999) Contact sensitivity to a tea tree oil product not due to tea tree oil. *Contact Dermatitis* **41:**354-355.

Greig, J.E., Carson, C.F., Stuckey, M.S. and Riley, T.V. (2000) Prevalence of contact sensitivity to the European standard series in a self-selected population. *Australasian Journal of Dermatology* **41:**86-89.

Another manuscript is in preparation for submission to a peer-reviewed international biomedical journal.

As a result of this project the community will have an increased awareness about tea tree oil following the appearance of articles about the work in local print media, including the Community Newspapers News Chronicle, local editions of the POST Newspaper, and The University of Western Australia's Campus Review. In addition, Jane Greig was interviewed by ABC Rural Radio for the Country Hour program.

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