Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

CMEC 48
Complementary Medicines Evaluation Committee

Extracted Ratified Minutes
Forty-eighth Meeting
15 October 2004

Abbreviations:

ADEC	Australian Drug Evaluation Committee
ADRAC	Adverse Drug Reactions Advisory Committee
ADRU	Adverse Drug Reactions Unit (of TGA)
AQIS	Australian Quarantine Inspection Service
ARTG	Australian Register of Therapeutic Goods
ASMI	Australian Self Medication Industry
BP	British Pharmacopoeia
BPC	British Pharmaceutical Codex
BSE	Bovine spongiform encephalopathy
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicines Evaluation Committee
DSEB	Drug Safety and Evaluation Branch
ELF	Electronic Lodgement Facility
EP	European Pharmacopoeia
FSANZ	Food Safety Australia and New Zealand
LOAEL	Lowest Observable Adverse Effect Level
MEC	Medicines Evaluation Committee
NDPSC	National Drugs and Poisons Schedule Committee
NOAEL	No Observable Adverse Effect Level
OCM	Office of Complementary Medicines
PBS	Pharmaceutical Benefits Scheme
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TGAL	Therapeutic Goods Administration Laboratory Branch
TSE	Transmissible spongiform encephalopathies

The forty-eighth meeting of the Complementary Medicines Evaluation Committee (CMEC) was held in Conference Room 1, Therapeutic Goods Administration, 136 Narrabundah Lane, Symonston, Canberra from 9.30 a.m. to 4.30 p.m. on Friday 15 October 2004.

Members of CMEC present were:

Professor Tony Smith (Chair)

Dr Vicki Kotsirilos
Associate Professor Douglas Moore
Professor Stephen Myers
Dr John Ryan
Mr Kevin Ryan
Professor Gillian Shenfield
Dr Iggy Soosay
Associate Professor Heather Yeatman

Present from the Therapeutic Goods Administration (TGA) were:

Dr David Briggs
Dr John McEwen
Dr John Hall
Mr Karl Skewes

Attending from TGA for the presentation of papers or verbal reports:

Ms Christianna Cobold
Dr Barry Fankhauser
Dr Anne Field
Ms Michelle McLaughlin
Dr Nagendram Nandapalan
Dr Bogdan Sikorski
Ms Diane Wilkinson

1. Procedural Matters

1.1 Opening of Meeting

The Chair opened the meeting at 9.30 a.m. and welcomed CMEC Members and TGA staff.

1.2 Apologies

The Secretariat received an apology from Professor Bill Webster.

The Chair noted that the CMEC Secretariat had received comments from Professor Webster on specific agenda items *in absentia* for consideration during the meeting

1.3 Conflict of Interest

Members submitted conflict of interest declarations specific to agenda items for this meeting to the Chair.

1.4 Meeting dates for 2005

The Chair asked Members to note the proposed meeting dates for CMEC in 2005. These are as follows:

CMEC Meeting Number	Meeting date	Meeting location
50	Friday 11 February	Sydney
51	Friday 8 April	Melbourne
52	Friday 10 June	Sydney

2. Confirmation of Minutes of CMEC 47 (13 August 2004)

Members accepted the minutes of the forty-seventh meeting of CMEC as an accurate record of proceedings, subject to several minor amendments:

CMEC Recommendation:
Members made the following recommendation:

Recommendation 48.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 47, 13 August 2004), as amended, are a true and accurate record of that previous meeting.

3. Guidelines on levels and kinds of evidence to support claims for therapeutic goods (Guidelines)

CMEC did not consider any matters under this agenda item.

4. CMEC Working Party on Herbal Medicine Issues

CMEC did not consider any matters under this agenda item.

5. Action Arising from Previous Meetings

5.1 Safe Access to Chinese Medicines

Background
At CMEC47 (August 2004) Members considered the discussion paper *Safe Access to Chinese Herbs* prepared by the Chinese Medicine Registration Board of Victoria (CMRBV) and the Victorian Department of Human Services. This document provided an overview of how the Victorian legislative scheme intended to regulate prescribing and dispensing of otherwise restricted Traditional Chinese Medicine (TCM) herbs.

The CMRBV has:

- proposed TCM herbs for inclusion into Schedule 1 of the Victorian Poisons List;
- requested that stakeholders provide specific feedback in a questionnaire on the proposals and issues raised in the discussion paper;
- to provide feedback to the Victorian Minister for Health before the Board finalised its report and recommendations.

The CMRBV sought advice from CMEC since the Committee is probably recognised as one of the major group of experts in the herbal medicine area in the country. Hence the request that CMEC provide advice on a matter that is technically outside the purview of the Committee.

Responses to the discussion paper were due in early September. However following initial consideration at CMEC47, the OCM requested an extension from the CMRBV so that a draft response could be prepared for endorsement by CMEC at this meeting.

TGA referred CMEC Members to the draft response which had been put together to address the questionnaire in the discussion paper. Members had raised several issues at the last meeting.

Present Discussion
The Chair reminded Members that the response to the CMRBV discussion paper was from CMEC, and not TGA. Therefore, it was important that Members had the opportunity to comment on each of the responses put forward in the draft response paper.

CMEC Members made a number of further observations and comments on the proposed response to the CMRVB and asked for a final response to be prepared then cleared out of session for return to the CMRBV by Friday 22nd October 2004.

6. Evaluation of New Substances

6.1 *Canarium indicum* seed oil

Background
The Office of Complementary Medicines (OCM) received an application for the evaluation of a new complementary medicine substance known colloquially as ngali nut oil for use in Listed medicines. The oil is derived from the nuts of a variety of *Canarium indicum*, notably *C. indicum* var. *indicum*, which is a rainforest tree native to Melanesia, and particularly the Solomon Islands.

The applicant has foreshadowed the use of the oil in topical creams and oral liquids for indications relating to the relief of pain and discomfort caused by arthritis and related conditions.

Characterisation of the substance
Canarium is a large genus of trees of the family Burseraceae found in the tropics from Malaysia to Melanesia with one species in the West Indies. Common names for the fruit from the trees includes ngali nut, canarium almond, canarium nut, and galip.

The application contained a detailed description of the process used to obtain the oil from the *C. indicum* nuts. The process involves the following steps:

- harvesting of the fruit;
- baking or cooking the fresh fruit to loosen the flesh from the nut shell;
- cracking and removal of the seed from the nut shell;
- grinding and pressing of the seed; and
- filtering of oil from the pressed seed.

The total oil content of the nuts is about 75% and the free fatty acid content equals 0.2%. Ngali nut oil contains mainly the following fatty acids: palmitic (34%), stearic (13%), oleic (38%), and linoleic (14%). The nut oil appears to be stable for at least a year and this could be longer with proper storage. TGA has been developing a draft compositional guideline for ngali nut oil with the sponsor.

History and pattern of use
From its distribution, *C. indicum* appears to be one of the oldest domesticated species in Melanesia. As a consistent source of animal protein in the local diet has not always been available the nuts play an essential, as well as traditional, role in a balanced diet for Melanesian islanders. The present estimated consumption in the Solomon Islands is about 70 g/person/day.

The oil from the ngali nut is used as a flavoured cooking oil in the Solomon Islands. Recently, ngali nut oil has been exported from the Solomon Islands to the United Kingdom, New Zealand, and the USA and is used as an emollient in hair care, bath, lotion and sun care products and also as a substitute for cocoa butter.

The present applicant has been granted patents in South Africa, the United States of America, and Australia for the treatment of arthritis and other similar conditions using ngali nut oil. The therapeutic product for topical application is very simple. Oil pressed from *Canarium* nuts is mixed with sorbolene and the mixture is then applied to the skin. The manufacturer purports that ngali nut oil can be used in all forms of arthritis. Further, the sponsor has also proposed the use

of ngali nut oil for both topical and oral routes of administration. The total dose per day for ngali nut oil in the dermal cream is approximately 0.8 g and about 0.2 g for oral drops.

Biological activity
The active constituents in *Canarium indicum* nut oil are unknown.

Potent food allergens are usually water-soluble glycoproteins with molecular weights of 10 – 60 kD that are stable at low pH. For people with tree nut allergy, consuming nuts can lead to, at the least, itching or swelling in the mouth, and, at the worst, anaphylaxis and death. Tree nuts are one of main foods responsible for food-induced allergic reactions, and they are one of the foods associated with more severe reactions. Although high rates of *in vitro* and skin test cross-sensitisation have been shown to exist in patients allergic to peanuts when assayed for IgE to various tree nuts this does not translate into clinical cross-reactivity.

In vitro and skin studies have shown cross-reactivity between tree nuts. This has provided a theoretical basis for clinical cross-reactivity. It must be considered, too, that just as peanut allergy and tree nut allergy appears to co-exist as separate entities, allergies to separate tree nuts may exist without cross-reactivity. However, there is the concern that tree nut sensitivity appears to be severe and lifelong.

In a study to investigate the risk of cross-allergenicity in subjects to ngali nuts with allergies to other nuts, no significant cross-reactivity was found against peanut. Cross reactivity was observed in one case out of five for hazel and cashew nuts and in all five cases for pistachio nut. This study points to a possible risk of cross-allergenicity between ngali nuts and pistachio nut. Another study evaluated the clinical and serological relevance of cross-reactivity between ngali nut and pollen allergens. There was prevalence for reactivity against ngali nut in the group of pollen allergic patients. Three out of 12 patients tested with ngali nut were positive upon open challenge, but using double blind placebo controlled food challenge this could not be confirmed in two patients. The biological effects of ngali nut on allergic patients were confirmed using histamine release test and skin prick test. As the investigators only looked at the cross-reactivity between IgE specific to ngali nut and other allergens it is still unknown to what extent ngali nut could act as a primary sensitising allergen.

Highly processed oils do not contain nut protein and can be safely consumed by allergic persons. However, crude oils can cause allergic reactions. Ngali nut oil could be termed a crude oil and as such possibly contains a small quantity of nut protein. Therefore, there would be a low probability that a consumer could experience an allergic response to the oil.

Toxicology
Canarium indicum seed oil is made up essentially of triacylglycerols, which contain simple fatty acids. Although triacylglycerols have a lower toxicity than individual fatty acids, acute oral toxicity values indicate fatty acids that are found in ngali nut oil are of low oral toxicity in rodents.

There were no data on *Canarium indicum* seed oil available for chronic toxicity, genotoxicity, carcinogenicity, or reproductive toxicity. However, as ngali nut oil is edible oil with a long tradition of use no toxic effects would be expected.

Adverse reactions
No reports could be found for adverse reactions to the consumption of *Canarium indicum* var. *indicum* nut or seed oil. The nuts have been consumed for several thousand years. Allergies to peanuts and tree nuts are among the most common food allergies, affecting about 1% of the population in developed countries.

The presence of nuts and nut products (like oils) as an active ingredient in medicines would be declared automatically under the general provisions of the Therapeutic Goods Order Number 69 *General Requirements for labels for medicines* (TGO 69). However TGO 69 has a specific requirement that peanuts and peanut products (including peanut oil) always be declared when used as excipients in medicines. The provisions ensure that those with peanut sensitivities are able to avoid certain products.

Present discussion
One Member questioned whether TGA required sponsors to declare the fatty acid composition of oils on therapeutic goods for oral consumption. The Member noted that ngali nut oil contained 60 % saturated fats, which was a potential safety concern. Other Members, however, suggested that the proposed doses were clearly small compared to dietary sources, especially in comparison to the Island peoples who consumed large amounts of this oil as well as animal fats in their diet.

In view of the long history of use by Melanesian islanders, CMEC unanimously supported a recommendation to the TGA that *Canarium indicum* var. *indicum* seed oil (ngali nut oil) was suitable for use as an active ingredient in Listed medicines. On the basis of potential for allergy, as with other nut products, CMEC also recommended that any product that contained the oil should also carry a label advisory statement that the oil is derived from nuts.

CMEC Recommendation:
Members made the following recommendation:

Recommendation 48.2

CMEC recommends to the TGA that *Canarium indicum* seed oil is suitable for use as active ingredient in Listed medicines subject to inclusion of a label advisory statement indicating that the material is derived from nuts.

The Committee considered one further matter under this item

7. Safety or Efficacy Reviews

The Committee considered two matters under this item.

8. Registration Applications

CMEC did not consider any matters under this agenda item.

9. Variation to a Registered Product

CMEC did not consider any matters under this agenda item.

10. Matters referred from within the TGA

10.1 ADRAC Matters - Adverse Drug Reaction Advisory Committee report (ADRAC) Meeting 278

A Member introduced this item to the Committee.

Members noted the adverse drug reaction reports from 278th meeting of ADRAC.

CMEC specifically discussed two reports that ADRAC had asked the Office of Complementary Medicines to comment on.

10.2 Definition of complementary medicines

Background
The Australian and New Zealand governments have agreed to establish a Trans Tasman regulatory agency for therapeutic products (the Joint Agency). Complementary medicines will also be regulated within the Joint Agency and it had raised the need to develop an appropriate and workable definition of a 'complementary medicine' to guide the Joint Agency. An appropriate definition would assist in determining which products would be evaluated by the Centre for Complementary Medicines.

At its meetings in April 2004 (CMEC 45) and June 2004 (CMEC 46), Members provided the TGA with comments on a number of options for a definition of a complementary medicine and discussed the important elements which it would need to include. The main elements considered by CMEC included:

- The need to allow for traditional methods of manufacture of complementary medicines but also to permit the use of more modern methods in their manufacture provided other conditions are met. Members considered that 'tradition of use' was an important concept to retain in the definition of a complementary medicine and that this could be adequately covered if the various forms of 'traditional preparation' were retained in the definition;

- The need for the definition to allow for innovation by the complementary medicines industry;
- The need to ensure that substances which fell within the definition, but which needed control over their access and the involvement of a qualified healthcare professional, were adequately catered for;
- The need to ensure that new chemical entities, which are not related to complementary medicines as they are commonly understood, are not permitted by the definition;
- The need to ensure that the definition is enduring in that it allows for the fact that, with time, complementary medicines may become conventional, orthodox medicines once their efficacy is established through research and public acceptance;
- That, ideally, a definition of 'complementary medicines' for regulatory purposes should not diminish or limit the way 'complementary medicines' and 'complementary medicine' are understood and practised respectively in the wider community;
- That in cases where the definition is inappropriate for a particular substance or product, there are discretionary powers available to the regulator to ensure public safety and/or an appropriate means of evaluation; and
- That the part of the definition of homoeopathic medicine or "a medicine based on a related paradigm" be accompanied by an explanatory note elsewhere which refers to these related paradigms as "energetic medicines."

Present discussion
A TGA officer tabled a document detailing the proposed definitions for complementary and homoeopathic medicines and provided an overview of the definitions. The officer worked through a number of examples of how certain substances fell into or out of the draft definition. The CMEC Secretariat took on notice a number of comments from Members, including the need to attach these sorts of worked examples with the definition when it went to industry for consultation. CMEC agreed that the proposed new definition for complementary medicines appeared to adequately define those substances promoted as complementary medicines. The Committee recommended that TGA should take the proposed new definition for consultation with industry in both Australia and New Zealand.

CMEC Recommendation:
Members made the following recommendation:

Recommendation 48.3

CMEC recommends to the TGA that the proposed new definition of a complementary medicine be made available for stakeholder consultation in Australia and New Zealand.

The Committee considered three further matters under this item.

11. For Information

11.1 Trans-Tasman update

TGA officers provided the Committee with verbal updates on the progress of key elements of the new joint regulatory agency, and the Permitted Ingredient List Project.

11.2 Recent journal article - Use of herbal drugs in pregnancy: a survey among 400 Norwegian women *Pharmacoepidemiology and Drug Safety* (2004)

Members noted a recent journal article relating to the use of herbal drugs by pregnant Norwegian women.

12. Sponsor representations to CMEC

CMEC did not consider any matters under this agenda item.

13. Other business

There was no other business for consideration by CMEC.

14. Recommendation record

Item 2 Minutes of CMEC's 47th Meeting

Recommendation 48.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 47, 13 August 2004), as amended, are a true and accurate record of that previous meeting.

Item 6.1 Application for the Evaluation of a New Substance – *Canarium indicum* seed oil

Recommendation 48.2

CMEC recommends to the TGA that *Canarium indicum* seed oil is suitable for use as active ingredient in Listed medicines subject to inclusion of a label advisory statement indicating that the material is derived from nuts.

Item 10.2 Definition of a Complementary Medicine

Recommendation 48.3

CMEC recommends to the TGA that the proposed new definition of a complementary medicine be made available for stakeholder consultation in Australia and New Zealand

The Chair closed the meeting at 4.30 p.m.