Commonwealth Department of Health and Aged Care

TGA THERAPEUTIC GOODS ADMINISTRATION

CMEC 28

Complementary Medicines Evaluation Committee

Extracted Ratified Minutes
Twenty Eighth Meeting
27 July 2001

Abbreviations:

ADEC	Australian Drug Evaluation Committee
ADRAC	Adverse Drug Reactions Advisory Committee
ADRU	Adverse Drug Reactions Unit (of TGA)
ANZFA	Australia New Zealand Food Authority
ARTG	Australian Register of Therapeutic Goods
ASMI	Australian Self Medication Industry
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
GBR	Geographical Risk of BSE
JHTF	Joint Herbal Task Force
MEC	Medicines Evaluation Committee
NDPSC	National Drugs and Poisons Schedule Committee
OCM	Office of Complementary Medicines
PBS	Pharmaceutical Benefits Scheme
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TSEs	Transmissible spongiform encephalopathies

The twenty-eighth meeting of the Complementary Medicines Evaluation Committee was held at the Ansett Conference Rooms, Sydney Airport, between 9:30 am and 4.00 pm on Friday 27 July 2001.

Members of CMEC present were:

Prof David Roberts (Chair)
Mr Nick Burgess
Dr Roberta Chow
Dr Colin Duke
Dr Joachim Fluhrer
Ms Val Johanson
Prof Stephen Myers
Mr Kevin Ryan
Prof Bill Webster
Dr Heather Yeatman

Present from the TGA were:

Dr Susan Alder
Dr David Briggs
Mr Geoff Newman-Martin
Ms Allison Rosevear
Dr John McEwen (Friday morning only).

Apologies were received from:

Dr Fiona Cumming
Prof Tony Smith

1. Procedural Matters

1.1 Opening of Meeting

Professor Roberts opened the meeting at 9.30 am on Friday 27 July.

1.2 Apologies

Apologies were received from Dr Fiona Cumming and Prof Tony Smith.

1.3 Conflict of Interest

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

2. Confirmation of Minutes of CMEC 27 (14-15 June 2001)

- The minutes of the meeting of CMEC 27 were accepted as an accurate record of proceedings, subject to minor amendments.

Recommendation 28.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 27, 15-17 March 2001), 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* (the 'Guidelines')

There were no matters for formal consideration under this item. However, there was a brief discussion on issues arising from the guidelines.

4. Stakeholder consultation paper: review of the regulation of herbal medicinal substances

There were no matters for consideration under this item.

5. Action Arising from Previous Meetings

5.1 Action arising from CMEC 27 (15-17 June 2001)

5.1.1 Draft policy on sponsor comment on evaluation papers (item 6.1 of CMEC 27 refers)

At CMEC 27 (June 2001) members requested that, at the next meeting, the Office of Complementary Medicines (OCM) provide information regarding the options available to sponsors for commenting on Evaluation Reports.

In the spirit of increased transparency and accountability, the OCM provides sponsors of applications for new registered complementary medicines and new substances for inclusion in Schedule 4 of the *Therapeutic Goods Regulations* with a copy of the evaluation report prepared by OCM prior to its consideration by CMEC. Sponsors, if they so wish, may provide written comment to assist CMEC in dealing with their application or to correct any factual errors or omissions that they may identify in the report.

The evaluation report is provided approximately two weeks prior to the CMEC meeting scheduled for consideration of the application and sponsors are allowed one week to return their comments to the OCM. Comments must be brief and returned by the due date in order to be considered by the Committee at the scheduled meeting. In general, data requiring further evaluation will not be accepted at this stage.

It is not essential that sponsors respond to the Evaluation Report; their application will still be considered by the Committee at the nominated meeting should they decide not to respond. The sponsor response need not address all issues raised in the report; minor issues can be resolved separately after the meeting provided they do not effect the basis on which CMEC made their recommendation.

The major elements of the procedure and options for sponsor comment are identical to those available to sponsors of applications being considered by the Medicines Evaluation Committee (MEC).

As an interim measure, in the absence of specific guidelines for complementary medicines, sponsors may request additional time to comment on Evaluation Reports. The request will be considered, on a case-by-case basis. Extra time may be permitted (with consequent deferral of the item from the CMEC agenda) subject to negotiation of a satisfactory timeframe and other conditions for response by the sponsor.

Present discussion

A member asked whether CMEC will receive copies of sponsors' comments ahead of the CMEC meeting. A TGA officer advised that these documents would be received by CMEC members prior to the meeting, but would be sent as late papers. A members noted the desirability of such papers being received a week before the meeting, although the time constraints were noted.

The question was raised as to how much extra time should be allowed for a sponsor to respond. A TGA officer indicated that generally a response would be expected within 30 days, with an allowance for further extension should the circumstances warrant.

6. Evaluation of new substances

6.1

A recommendation was made under this agenda item.

6.2

Recommendation 28.3

CMEC recommends to the TGA that when a recognized pharmacopoeial or other appropriate monograph exists for a new excipient, the matter need not be referred to CMEC for consideration. For new excipients for which there is no recognised pharmacopoeial or other appropriate monograph, and/or where the OCM has identified safety concerns, an evaluation should be referred to CMEC for their consideration.

7. Safety reviews

7.1 Quercetin

At the request of the Complementary Healthcare Council of Australia the OCM has undertaken a review of the safety of quercetin with a view to "switching" its regulatory status from 'registrable' to 'listable'.

Quercetin is a flavonol with the CAS name of 2-(3,4-dihydroxypheny1)-3,5,7-trihydroxy-4H-1-benzopyran-4-one. Glycosides of quercetin are the most abundant flavonoids present in food. Quercetin occurs in nature with sugars (mono-, di-, tri- and tetrasaccharides) attached mainly at the heterocyclic-3 position. The estimated daily intake of flavonoids from food calculated on the basis of the aglycones ranges from approximately 3-70 mg in different countries, and may well exceed these values in regions with a very high intake of tea and vegetables.

Present discussion

Members noted that quercetin and rutin are ingredients of a large number of multivitamin preparations and herbal remedies. Information available in 1995 indicated that quercetin was available in Brazil, Germany, Japan, Spain, Switzerland, the United Kingdom and the United States. Quercetin and rutin are sold as dietary supplements in the USA.

Members noted that quercetin-rich herbal teas and plant extracts (e.g. from buckwheat) are therapeutically used in the treatment of chronic venous insufficiency in certain countries. Quercetin and rutin are used in many countries to relieve capillary impairment and to treat venous insufficiency of the lower limbs. Flavone glycosides are also considered to be efficacious compounds of phytomedicines used in the therapy of infections of the lower urinary tract as frequently used in Western European countries.

It was noted that quercetin is frequently used for allergic conditions, including asthma and hay fever, eczema, and hives. Additional clinical uses include treatment of gout, pancreatitis and prostatitis. Quercetin is a recognised antioxidant and has been studied for its gastro-protective effects, inhibition of carcinogenicity either alone or in combination with chemotherapeutic agents, reducing risk of cataract.

Members were advised that seventeen products containing quercetin are registered on the ARTG for supply in Australia. All products are grandfathered. All products contain multiple ingredients generally with smaller amounts of quercetin for products containing a large number of ingredients. The amount of quercetin in products varies from 10 mg to 300 mg per capsule or tablet with an average of 106 mg.

Members noted that most animal and human trials of oral dosages of quercetin show absorption in the vicinity of 20 percent. It appears that absorption of dietary quercetin and the aglycone is reasonably efficient. Because of the long half-lives of elimination, repeated consumption of quercetin will probably cause accumulation of quercetin in blood and increase the antioxidant capacity of blood plasma. Studies indicate that quercetin aglycone is absorbed from the upper duodenum or possibly from the stomach, whereas quercetin glycosides are mainly absorbed from the distal parts of the small intestine or the colon.

Quercetin and rutin have been found in plasma as glucuronides and/or sulfates of quercetin and as unconjugated quercetin aglycone.

The results of toxicity studies were noted. Carcinogenicity was seen in only two studies in rats; quercetin increased the incidences of intestinal and urinary bladder tumours in one study, but this effect was not seen in subsequent studies. Quercetin produced a low but significant increase in the incidence of renal tubular neoplasms, primarily adenomas in male rats, which was observed only after step-sectioning of renal tissue. However, there was only a small number of adenomas, which only occurred at high dose levels, and the results were not reproducible. When tested in several two-stage models of organ carcinogenesis, quercetin did not significantly enhance tumour incidence, except that of renal tumours induced by oestradiol in a model in hamsters. Although the metabolism of quercetin appears to be similar in humans and rabbits (the same three metabolites were identified in urine), no information on rats or mice was available for comparison. No information was available on the toxicity of quercetin in humans.

Members also noted that quercetin increased the frequency of DNA damage and lipid peroxidation in liver nuclei of rats *in vitro.* In long-term studies in rats, there were no treatment-related clinical signs of toxicity, but renal hyperplasia occurred in males. Quercetin inhibited cytochrome P450 enzymes in both human and rodent microsomes *in vitro.* Foetal growth retardation was observed in a study in rats exposed to quercetin by oral gavage. No data were available on the genetic and related effects of quercetin in humans. It was not genotoxic in experimental systems *in vivo.* It produced cytogenetic damage in human and rodent cells *in vitro,* but conflicting results were obtained in assays for gene mutation.

Members were advised that flavonoid data have been used in a number of prospective cohort studies and in one prospective cross-cultural study on the relation between flavonol and flavone intake and cancer and cardiovascular disease. No association with cancer mortality was found in two cohort studies, whereas in only one cohort study a reduction of lung cancer risk was apparent. A protective role for flavonols in cardiovascular disease was found in three out of five prospective cohort studies, in addition to one cross-cultural study. One prospective cohort study showed no association, and one a weakly positive association between flavonol intake and coronary heart disease. So far, the epidemiological evidence points to a protective effect of antioxidant flavonols in cardiovascular disease but it is not conclusive.

Members also noted that only four clinical trials employing quercetin were found in the literature. The objective of one was to characterise and compare the absorption and pharmacokinetics of quercetin from quercetin aglycone and rutin. The others investigated the use of quercetin in the treatment of serious diseases. They furnish information on dose toleration and adverse reactions. Three studies used oral administration and one used intravenous administration. Oral doses up to 500 mg twice a day for one month were well tolerated and there were no serious adverse reactions. Intravenous administration used in the Phase I clinical trial is not appropriate for a listable substance, but the trial indicated that high doses of quercetin can be tolerated and that quercetin may be useful in cancer patients.

Members were advised that no adverse reactions have been reported for quercetin in the Australian Adverse Drug Reactions Database system. There were three adverse reaction reports in the SN/AEMS (FDA) reporting system for products containing quercetin. The reports involve multi-ingredient products, so it was not possible to determine adverse reactions to quercetin alone. There are no known drug interactions. Human studies have not

shown any serious adverse reactions associated with oral administration of quercetin in single doses up to 4 g or after one month of 500 mg twice daily. Intravenous infusions of quercetin up to 1400 mg/m^2 showed no serious adverse reactions.

In discussion, it was concluded that quercetin appears to be well tolerated when taken orally in clinical trials. There have been large carcinogenicity studies in animals, with results which are not reproducible from study to study. However, there was no evidence of carcinogenicity in human studies, and there were positive effects in terms of reducing cardiovascular disease. Information on its metabolites was limited. The low number of reported adverse reactions, and the lack of serious adverse reactions in humans, together with the extensive worldwide usage of quercetin, and taking into account that there is no scientific evidence that the levels of manufactured quercetin would have adverse effects different from quercetin found in foods, tend to indicate a satisfactory level of safety in use. There is a wide safety margin for human consumption of quercetin compared to doses in animal studies. On this basis, members considered that quercetin is suitable for use as an active ingredient in listable therapeutic goods.

Members made the following recommendation to the TGA:

Recommendation 28.4

CMEC recommends to the TGA that quercetin is suitable for use as an active ingredient in listable therapeutic goods.

7.2 Tryptophan

Tryptophan is a neutral amino acid which can also be classified as an aromatic amino acid because the 'side-chain' group is an aromatic structure, indole. L-tryptophan has the chemical name *(S)*-2-amino-3-(1*H*-indol-3-yl)propanoic acid, or *(S)*-α-amino-1H-indole-3-propanoic acid. This is the form of tryptophan which occurs naturally.

Present discussion

Members noted that at its 19th and 20th meetings, CMEC considered a report prepared by the Office of Complementary Medicines concerning the suitability of L-tryptophan for inclusion in listable therapeutic goods. At present, under the Therapeutic Goods Regulations, tryptophan, together with some other amino acids, is specifically excluded from use in listable goods. Further, when supplied in doses above 100 mg, tryptophan is included in Schedule 4 of the *Standard for the Uniform Scheduling of Drugs and Poisons* (SUSDP), and therefore requires a medical, dental or veterinary prescription before it can be supplied in Australia. However there are a number of grandfathered, registered goods eligible for supply in Australia that contain tryptophan as an active ingredient.

The evaluation report prepared for members had considered only the naturally-occurring isomer of tryptophan, L-tryptophan. Members noted that although tryptophan is a normal component of dietary protein, synthetic tryptophan consumed in medicinal/supplement form has been associated with the occurrence of eosinophilia-myalgia syndrome (EMS), resulting in 38 reported deaths in the US since 1989. While the 1989 outbreak appears likely to have been linked to the introduction of a contaminant associated with a new manufacturing

process, the exact cause of the outbreak, or the identity of causative agent unequivocally identifed. Prior to the 1989 outbreak of EMS and the introduction of the new manufacturing process, tryptophan was also tentatively linked to a related disorder, eosinophilic fasciitis (EF). Therefore, the evaluators had concluded that it was not possible to be certain that the demonstrated human toxicity of tryptophan is associated only with a particular manufacturing process.

Members also noted that there have been 18 reports of adverse reactions associated with tryptophan ingestion in Australia, of which eleven reported tryptophan as the sole suspected agent. Some of the reported symptoms are also encountered in subjects suffering from EMS. Five adverse reactions have been reported since September 1997, and of these, three had involved concurrent use of selective serotonin reuptake inhibitors.

Members were advised that the Complementary Healthcare Council (CHC) of Australia had provided information on population exposure to tryptophan in Australia and overseas. Only one sponsor provided Australian sales data for products containing tryptophan. Two multi-ingredient products, each containing 25 mg tryptophan/tablet, had total sales figures of 44,383,301 units (presumably tablets) for the 11 years since being launched. Sales data for an S4 product containing 500 mg tryptophan, launched in 1994, was 1,033,900 units Three other sponsors that responded to the request from CHC for usage data stated either that they did not have any products containing tryptophan, or that sales volumes were negligible.

It was noted that the Pharmaceutical Evaluation Section of the Pharmaceutical Benefits Branch, Department of Health and Aged Care, had reported that they are seeing no prescription use of tryptophan on their database, which provides an estimate of all prescriptions dispensed through community pharmacy. However, data on prescription use of non-subsidised drugs, such as tryptophan, come from a small sample of pharmacies that may miss complementary medicine hot spots for example, and provide only broad estimates of commonly use drugs.

It was noted that the evaluator had conducted a search of the web sites of overseas regulatory agents and regulatory databases, but failed to find any further information on the regulatory status of tryptophan overseas. In the USA, tryptophan is available as a dietary supplement only under special dietary circumstances, i.e. in special infant formulas and enteral products. However, it can be purchased in the USA with a prescription over the internet.

Members noted that a bulletin issued by the FDA in 1996 had concluded that the L-tryptophan-associated EMS was caused by several factors and was not necessarily related to a contaminant in a single source of L-tryptophan. Based on the scientific evidence that is available at the present time, the FDA could not determine with certainty that the occurrence of EMS in susceptible persons consuming L-tryptophan supplements derives from the content of L-tryptophan, an impurity contained in the L-tryptophan, or a combination of the two in association with other, as yet unknown, external factors. A search of all FDA documents available on their web site has not provided any evidence that their position on the safety of L-tryptophan has changed since this time.

It was also noted that tryptophan is not authorised as a medicinal product in Sweden, and can only be prescribed in the context of clinical trials as a supplementary medication for sleeping disorders or depression. Availability in Canada, the UK and Switzerland was said to be “limited” in one literature report, although exact details were not provided.

Tryptophan for human therapeutic use is included in Schedule 4 (PRESCRIPTION ONLY MEDICINES) of the *Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP)* except in preparations labelled with a daily dose of less than 100 mg. As result, exempted preparations were not included in an Australia-wide recall of products containing tryptophan. The chair of the National Drugs and Poisons Scheduling Committee during the period concerned had been contacted to determine the basis on which this decision was made. According to his recollection, it was believed at the time that the lower doses were not considered to be associated with the occurrence of EMS.

A member advised that 5-hydroxytryptophan also has the purported toxic contaminant, but not in sufficient concentration in most samples to cause the EMS syndrome, although it was recognised that the risk would be higher with higher doses. There had been much lower usage of tryptophan since its banning in the USA, and in the last 10 years there had not been many reported cases of EMS. However, its relative infrequency of this adverse effect needed to be considered against its severity.

Members discussed whether the 100 mg cutoff was now appropriate for tryptophan given that the scheduling exemption was based on a safe dose level of tryptophan which may no longer be the case. It was noted that only unscheduled products are eligible for listing. A member advised that the lower dosages are not considered by complementary healthcare practitioners to be very effective.

Members then considered whether tryptophan is suitable for use as an active ingredient in listable therapeutic goods. Members made the following recommendation to the TGA:

Recommendation 28.5

CMEC recommends to the TGA that tryptophan is not suitable for use as an active or excipient ingredient in listable therapeutic goods as there is insufficient evidence to support its safety in listable goods.

7.3 Kava

Kava is the common name of the plant *Piper methysticum*, a member of the pepper family (Piperaceae) and is used to refer to the drink prepared from the ground rhizome (root) of that plant, as well as to other preparations from *P. methysticum* (such as powdered kava for use in capsules and tablets). Kava has a long history of use as a beverage in social ceremonies and as a medicine in several cultures.

The constituents of kava are kavalactones (or kava α-pyrones), which are believed to be the pharmacologically active compounds in the kava plant. However, the nature and density of psychosomatic effects are determined by the relative proportions and potencies of the kavalactones from one variety to another. Eighteen kava lactones have been isolated from the kava root, of which six are the major constituents of kava. The content of kavalactones in the root of the plant is between 3 and 4% of the dried material.

Present discussion

Members noted that CMEC had previously considered kava at its 3rd, 4th, 5th, 13th and 14th meetings, in March, April and May, 1998, and June and July 1999 respectively.

It was also noted that a search in May 2001 indicated that there are currently 109 products listed on the ARTG containing *Piper methysticum.* All of these entries have occurred since 1995, with the most recent entry occurring in April 2001.There were various dosage forms, and a range of indications. As the kavalactones are restricted in all products containing kava, all sponsors must state the amount of these constituents in all applications containing *Piper methysticum* as an active ingredient.

Members noted a summary of the current situation with regard to importation of kava in Australia, which had been prepared by a TGA officer.

Attention was drawn to a paper which had recently been published in the *British Medical Journal*, which described a case of liver failure, associated with oral administration of kava, which occurred in Switzerland. A 50-year-old male patient who had been taking three to four capsules daily of a kava preparation containing 210-280 mg kavalactones (maximum recommended dose being three capsules). suffered fulminant liver failure, and received a liver transplant, recovering uneventfully. Histology showed extensive and severe liver damage. The authors stated that the relationship between kava ingestion and liver failure was supported by the chronology, histological findings and exclusion of other causes. Assessment of causality according to WHO definitions was 'probable'.

Members were advised that advice has been received from the Swiss Interkantonale Kontrollstelle (IKS) Pharmacovigilance-Zentrum that IKS has withdrawn the marketing authorisation of Laitan (trade name), an acetonic kava extract used as an anxiolytic. This decision has been taken following 10 reports of liver injury under kava therapy. Eight reports were considered serious, with jaundice reported in all cases, coagulopathy in 3 cases and encephalopathy in one patient, necessitating a liver transplant. While Laitan has been withdrawn from the market, alcoholic kava extracts are still marketed but their status has been changed from OTC to OTC - pharmacy only (Schedule 2 medicine). IKS has stated that "This is because alcoholic extracts have been incriminated in one case only so far and marketing through pharmacies should help detect further potential risks".

Members noted that associations between kava use and signs of poor health, found in previous studies, were also found in a recent study of a remote Aboriginal community, conducted by researchers at the Menzies School of Health Research, Northern Territory University. While there is evidence across the indigenous population in East Arnhem Land of markers of increased cardiovascular risk, which may be linked to infectious pathogen burden, these were not greater in kava users. The research also indicated that kava users and non-users were functionally equivalent on neurocognitive tests, although there were acute effects but no long term neurocognitive effects. Evidence of the acute effects in humans suggests that kava disrupts motor and coordination systems and in extreme cases can cause severe dystonic reactions. There is also considerable evidence to suggest that the neurotransmitter systems underlying behaviour are affected. Psychophysiological measures suggest that attentional and memory systems are also disrupted. The subjective experiences and performance deficits that occur when alcohol is administered alone appear to be increased when kava is taken in combination with alcohol.

The researchers have submitted papers on various aspects of the research to *Psychopharmacology* and *ANZ Public Health*. In the research group's clinical work on kava, all cases with elevated liver enzymes have shown return to normal levels upon ceasing kava or reducing consumption, which agrees with earlier published observations. No cases of serious liver failure or irreversible effects had been noted, and it is understood that this would be commented upon in a paper submitted for publication in the *Medical Journal of Australia*.

It was considered that the TGA should continue to monitor adverse effects associated with the use of kava and that no action be taken at this stage. Members made the following unanimous recommendation (with one absentee):

Recommendation 28.6

CMEC recommends that the TGA continue to monitor adverse effects associated with the use of kava and that no action be taken at this stage.

8. Registration applications

There were no items for consideration under this agenda item.

9. Variation to a registered product

There were no items for consideration under this agenda item.

10. Matters referred from within the TGA

10.1 Report from the 252nd meeting of ADRAC

Members noted a report from the 252nd meeting of the Adverse Drug Reactions Advisory Committee (ADRAC) on recent consideration of adverse reactions associated with the use of complementary medicines. The reports concerned possible interactions between venlafaxine and *Hypericum perforatum*; flavonoids in *Passiflora incarnata* and warfarin; and cisplatin and melatonin. Melatonin was also possibly associated with another adverse reaction. Possible hypersensitivity reactions were associated with products containing a mixture of *Gelsemium, Daphne mezereum*, *Paris quadrifolia* and other materials; silica; *Echinacea*; and a mixture of herbal materials. Possible neurological reactions were noted in association with products containing a mixture of herbal materials including *Piper methysticum*, *Passiflora incarnata* and *Hypericum perforatum*; and beta carotene. Possible skin reactions had been reported in association with a products containing *Serenoa serrulata*. In another case a skin reaction was considered more likely to have been caused bupropion than *Acidophilus*. Possible psychiatric reactions had been reported in products containing evening primrose oil and other materials; and levocarnitine and other materials. A member commented that in the case of possible hypersensitivity reaction to silica, the product base was lactose, and there was a possibility that the reaction may have been due to a trace of milk protein.

10.2 Transmissable spongiform encephalopathies update

Members noted an update on actions taken to date by the Office of Complementary Medicines to minimise the risk of exposure to transmissible spongiform encephalopathies (TSEs), particularly, bovine spongiform encephalopathy (BSE) through the use of complementary medicines. It was recalled that the TGA had written to sponsors in a staged manner based on a preliminary assessment of relative risk of certain products being associated with TSE infective agents.

A number of products had been identified about which there were negligible TSE concerns. This group includes products with no animal/human derived components involved in their manufacture, or containing animal components that were both sourced and processed exclusively from countries currently considered highly unlikely, or unlikely to have domestic cattle infected with the BSE agent. (Geographical Risk of BSE (GBR) level I or II, respectively). A number of other products had been identified where there were some TSE concerns. The concerns are varied. Examples of concerns and follow-up included, for example, verification that no cross-contamination has occurred in the manufacturing plant; assurance that products containing ruminant ingredients from countries which have reported BSE will not be used in the manufacture of products that will be supplied to the Australian market, and clarification whether levocarnitine in a product is synthetic or animal-derived. Information yet to be received from a number of sponsors.

It was noted that the level of TSE risk associated with the use of lanolin had not yet been evaluated by the TGA.

10.3 Status of substances presented as homoeopathic preparations

One matter was considered by CMEC under this agenda item.

Recommendation 28.7

CMEC made a recommendation to TGA concerning action in relation to certain products.

Recommendation 28.8

CMEC made a recommendation to TGA concerning action in relation to certain products.

Recommendation 28.9

CMEC recommends to the TGA that the definition of 'homoeopathic preparation' be amended to more clearly reflect the principles of homoeopathic medicine.

10.4 Royal jelly

- Members noted previous discussion at earlier CMEC meetings

Present discussion

Members noted that the main issue was whether the word "fatalities" is justified in the warning on the labels of goods containing royal jelly. It was noted that prescription products containing royal jelly would not require a label of this type, although the Product Information needs to contain a warning to draw the attention of prescribers to this severe potential adverse reaction. It was noted that the level of reports of severe adverse reactions to royal jelly in Australia and New Zealand was high, and that the level per head of population reported in New Zealand, which was the highest in the world, was twice that in Australia.

Details of the report of a New Zealand working party on royal jelly were noted.. A member pointed out that almost any product can cause anaphylactic reactions, some of which may be fatal, and that they were not required to carry warning labels of this type; aspirin was quoted as an example. However, a TGA officer commented that aspirin is not a listable substance and is regulated differently to listable substances such as royal jelly. A member responded that consumers would not necessarily see the difference, which was based on regulatory procedures about which most consumers probably knew very little. A member noted that if the decision was based on a risk-benefit analysis, there would be no reason to change CMEC's previous decision on the wording of the label warning. It was also noted that any subsequent decision made by the ANZFA would take into consideration CMEC's recommendation.

It was noted that ADRAC had established that three deaths were attributable beyond reasonable doubt to royal jelly. Deaths occurred in mild to moderate asthma, as a one-off catastrophic event. Allergic reactions in asthmatics were fairly identifiable. As death due to royal jelly was a known entity, CMEC was under some obligation to provide this information to consumers. Reference was made to allergy to peanuts, and to the facts that peanuts were not required to be labelled as causing fatalities, However, individuals with peanut allergy know to avoid peanuts, asthmatics may not be aware that they have an allergy to royal jelly.

CMEC recommended that products containing royal jelly should continue to carry the warning statements that had previously been recommended. Any request from a sponsor to vary these warning statements should include a risk-benefit analysis. CMEC members made the following recommendation:

<u>Recommendation 28.10</u>

CMEC recommends to TGA that royal jelly-containing products should continue to carry the warning statements:

> **"This product contains royal jelly which has been reported to cause severe allergic reactions and in rare cases, fatalities, especially in asthma and allergy sufferers" (in 3 mm type)**
> **OR**
> **"Not to be taken by asthma and allergy sufferers" (in 3 mm type), combined with "Royal jelly may cause severe allergic reactions and in rare cases, fatalities" (in 1.5 mm type).**

11. Recommendation record

CMEC members adopted the following as a summary of the recommendations made at its 27th meeting.

Item 2 Minutes of CMEC's 26th meeting

Recommendation 27.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 26, 23 March 2001), as amended, are a true and accurate record of that previous meeting.

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

Recommendation 27.2

CMEC endorsed the revised Guidelines (May 2001 version) and recommended some minor revisions. Members supported the Guidelines being placed on the TGA website.

Item 4 Draft stakeholder consultation paper: *Review of the regulation of herbal medicinal substances*

Recommendation 27.3

CMEC agreed that the draft consultation paper could be released for stakeholder comment, subject to minor revisions. The consultation paper will be examined with a view to formulating an overview document relevant to consumers, to assist with consumer consultation on this matter.

Item 5.1.1 (*S*)-S-Adenosylmethionine ('SAMe') – report on claims SAMe can produce a 'legal high'

Recommendation 27.4

CMEC recommends to the TGA, based on an extensive literature and electronic media review, that the recent media promotions of SAMe as a 'legal high' appear to be without foundation and do not preclude the use of SAMe as an active ingredient in listable therapeutic goods. However CMEC recommends that all therapeutic goods containing SAMe should carry the following label statement:

> "Individuals who are using prescription anti-depressants or suffer from bipolar depression should not use this product unless under the supervision of a health practitioner" (or words to that effect).

CMEC also recommends that the TGA should advise relevant health practitioner organisations of the potential for 'switching' from depressive to manic states, where SAMe is taken by people with bipolar disorder.

AANs and label AANs that have been assigned for SAMe sources.

A draft compositional guideline has been developed for (*S*)-S-Adenosylmethionine

Item 6.2 Tall oil phytosterols

Recommendation 27.6

CMEC recommends to the TGA that the substance 'tall oil phytosterols' is suitable for use as an active ingredient in listable therapeutic goods.

Note: an Australian Approved Name is yet to be approved for this substance and the final name approved may vary from the name used in this summary.

Item 6.3 *Azadirachta indica* ('neem') cold-pressed seed oil

Recommendation 27.7

CMEC recommends to the TGA that cold-pressed neem (*Azadirachta indica*) seed oil is suitable for use in listable therapeutic goods, provided it is restricted to topical application on the skin only and that the following conditions are met:

- therapeutic goods containing the substance are supplied with label warnings that these goods are for external use only and should be kept out of the reach of children; and
- the containers of therapeutic goods containing this substance are fitted with child-resistant closures.

Item 6.4 Black boned chicken

Recommendation 27.8

CMEC recommends to the TGA that black boned chicken (a variety of *Gallus gallus domesticus* Brisson) is suitable for use as an active ingredient in listable therapeutic goods, subject to inclusion of appropriate limits for antibiotic residues and hormones in the compositional guideline for this substance.

Note: an Australian Approved Name is yet to be approved for this substance and the final name approved may vary from the name used in this summary.

Item 7.2 *Tricosanthes kirilowii*

Recommendation 27.10

CMEC recommends to the TGA that *Tricosanthes kirilowii* should be maintained as a listable active substance and considers that, based on available evidence, no substance-specific restrictions should be placed on its use at this time.

Item 8 Registration applications

CMEC made recommendations to the TGA in relation to two matters under this agenda item.

Item 9 Registration variations

CMEC made a recommendation to the TGA in relation to a matter under this agenda item.

12. For Information

12.1 Chamomile tea enema anaphylaxis (Letter – *MJA* 2 July 2001)

Members noted a report in the *Medical Journal of Australia* concerning anaphylaxis associated with chamomile tea enema.

13. Action list from previous CMEC meetings

The Action List for CMEC Meetings was included in the agenda papers but not discussed at this meeting.

14. Other business

The Chairman drew attention to a product which appeared not to comply with Australian regulations and it was suggested that appropriate action should be taken. A TGA officer undertook to follow up this matter with the relevant authorities.

The meeting closed at 4.00 pm on Friday 27 July 2001. The next meeting is to be held on Friday 14 September 2001.