



Report On The Findings Of The Bee Product Warning Scientific Review Working Group

16/17 August 1999

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EXECUTIVE SUMMARY

PROPOLIS

The Working Group concluded that risk management should be limited to ingredient labelling of all products containing propolis by whatever means. This may be through voluntary labelling and a self-regulated industry code of practice, or through mandatory labelling.

BEE POLLEN

The Working Group concluded that risk management should be limited to ingredient labelling of all products containing bee pollen by whatever means. This may be through voluntary labelling and a self-regulated industry code of practice, or through mandatory labelling.

ROYAL JELLY

The Working Group concluded that as with other bee products, ingredient labelling of all products containing royal jelly is a necessary risk management activity. This may be through voluntary labelling and a self-regulated industry code of practice, or through mandatory labelling.

The Working Group estimated that the risk of adverse health effects in the general population from ingestion of royal jelly was higher than that for other bee products, and also identified that asthmatics represent a population group with higher susceptibility to adverse health effects than the general population. The Working Group recommends the following statement on all food products/dietary supplements containing royal jelly:

"Royal jelly may cause serious allergic reactions. Most reports have been in asthma sufferers."

INTRODUCTION AND BACKGROUND

Members introduced themselves and provided information on their backgrounds, conflicts of interest and any previous experience with bee products.

Cliff Van Eaton provided some general background and history for the Working Group on the products under consideration (propolis, bee pollen and royal jelly) and explained how the products were collected etc. Mr Van Eaton also presented members of the group with research reviews of various bee products. There was a short discussion on the properties, uses of the products and quality control processes of these products. Mr Van Eaton explained that bee products were considered as therapeutic goods in Australia, but not in New Zealand (where they are considered to be dietary supplements).

Mr Van Eaton introduced a submission from Mr Ron Law of the National Nutritional Food Association (NNFA) which provided an NNFA analysis of information provided to the Working Group.

Dr Glenn Buchan was unable to attend the meeting on 17 August 1999.

PART ONE - RISK ANALYSIS FRAMEWORK

Dr Hathaway proposed a risk analysis framework for addressing the issues before the Working Group. The risk analysis framework would be applied in a similar manner to that advocated by Codex Alimentarius and AS/NZS4360:1999. The three bee products under consideration are different in their derivation, make-up, proposed therapeutic effects and potential allergic effects and, therefore, a separate risk analysis is required for each product.

Risk Assessment:

Risk assessment is an important part of an overall risk analysis approach to manage risks to public health (Appendix I). The Working Group applied a risk assessment process consisting of:

- Hazard identification
- Hazard characterisation
- Exposure characterisation
- Risk characterisation

All data supplied to the Working Group, especially that related to individual reported cases and the nature of adverse health effects (hazard characterisation) was validated to the extent practicable in the time frame available. Exposure characterisation included pathways in addition to dietary exposure.

Due to the quality of the data available, Dr Hathaway suggested that the risk analysis should be based on qualitative rather than quantitative approaches.

The Working Group agreed to the following risk assessment policy decisions in assessing risk.

- There are established differences in derivation, biochemical nature and biological activity of propolis, bee pollen and royal jelly. There is also potential for different exposures and adverse health effects. For these reasons, the principles of risk assessment and risk management would be applied to each product separately.
- Adverse health effects described in the hazard characterisation would be classified according to the WHO framework, i.e. 'severe'¹, 'serious'² and 'other'. The definitions of 'severe' and 'serious' differ from the definitions used both by the Australia New Zealand Food Authority (ANZFA) and in early documents from the Ministry of Health.
- Only serious adverse reactions would be considered in the risk characterisation for each product.
- Due to the extensive consumer and political interest in the three reported deaths resulting from ingestion of royal jelly, these case reports would be individually reviewed by the Working Group.

¹ Severe is defined as "the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (e.g. "severe headache")."

² Serious is defined as "death, hospitalisation, persistent/significant disability, life threatening".

- The Working Group applied a "weight-of-evidence" approach in considering the disproportionate reporting of adverse reactions to bee products in New Zealand/Australia compared with the rest of the world
- All reported cases considered in the risk characterisation were validated to the extent possible.

(1) Risk Assessment of Propolis

◆ Product Description and Use

Propolis - a resinous substance collected by worker honey bees from the growing parts of trees and shrubs, modified by the bees and, then, used by the bees to seal their hive. Propolis is antimicrobial and has a range of other bioactive effects.

Propolis is available in syrup and lozenges. It is also available in a variety of creams and soaps. For the purpose of this risk assessment, propolis was considered in its oral and in its topical form.

◆ Hazard Identification

A search of world literature (up to 1997) indicated 47 papers on possible adverse reactions to propolis.

◆ Hazard Characterisation

Propolis was identified as a possible cause of bronchospasm urticaria/angioedema, mucositis and contact dermatitis.

In reviewing 'serious' cases the Working Group examined five case reports (reports no. 023651/ 027189/ 032247/ 034890/ 035632) provided from New Zealand (CARM³) and three case reports from Australia (ADRAC⁴).

Bronchospasm: Three reported cases of bronchospasm

Angioedema: Four cases reported.

Two CARM case reports indicated serious adverse health effects of propolis in its **oral** form.

There was no data available to suggest a dose-response relationship for propolis.

There was no evidence to suggest a population group with a higher susceptibility to propolis.

³ CARM - Centre for Adverse Reactions Monitoring - the national reporting centre for adverse drug reactions in New Zealand

⁴ ADRAC - Adverse Drug Reactions Advisory Committee - the national reporting centre for adverse reactions in Australia

Table 1: Hazard Characterisation for Propolis

Adverse Health Effects	Categorisation	Cases
Topical contact dermatitis (including mucositis)	Severe but rarely serious	0.64% population allergic to propolis. 2.5% contact dermatitis of patients attending contact dermatitis clinic in NZ were allergic to propolis ⁵ World literature – 1 to 47 papers
Angioedema/urticaria	Potentially serious depending on severity	NZ (CARM database) – 4 cases Aust. (ADRAC database) – 3* WHO database ⁶ – reports not collected World literature – no reports
Bronchospasm	Potentially serious depending on severity	NZ (CARM database) – 1 case Aust. (ADRAC database) – 3* WHO database – reports not collected World literature – no reports

* The Working Group concluded that these reports were of the same patients.

The Working Group concluded from an analysis of all reported cases that there is some evidence of serious adverse health effects linked to ingestion of propolis, but this is very limited in extent.

◆ Exposure Characterisation

Dr Rademaker reported that 6 out of 207 patients (2.5%) who presented to a contact dermatitis clinic in New Zealand tested positive for allergic reactions to propolis.

Despite indications from industry of high daily doses of propolis in New Zealand and Australia, there is insufficient data available to generate an estimate of exposure. The Working Group suspects that there is a large exposure on a per capita basis, with even greater exposure in some other countries e.g. China, Japan.

The Working Group noted that daily dose values as supplied by industry were insufficient to generate exposure estimates on a per capita basis.

◆ Risk Characterisation

Only 8 cases of serious adverse effects have been reported in Australia/ New Zealand since 1992. Despite the probability of high levels of exposure on a world-wide and Australasian basis there are an extremely small number of cases. Therefore, on any qualitative scale the risk is extremely low.

The Working Group recognised that topical application does result in adverse health effects. These adverse effects are considered unlikely to be serious and that those which are serious are unlikely to be life threatening.

⁵ Personnel communication from Dr Marius Rademaker

⁶ WHO - World Health Organisation database of adverse drug reactions. Note: WHO does not collect data of adverse reactions to propolis or bee pollen)

(2) Risk Assessment of Bee Pollen

◆ Product Description and Use

Bee Pollen - pollen grains collected by worker bees from flowering plants, modified - by the bees and, then, used as the honey bee colony's only source of protein. Bee pollen has nutritive value and also has a range of bioactive effects.

Bee pollen is available in granules, tablets, capsules, creams, soap and shampoo.

◆ Hazard Identification

Bee pollen (ingestion) was identified as a possible cause of anaphylaxis, gastro-intestinal symptoms, asthma, angioedema/urticaria and hypoglycaemia.

The Working Group identified that topical application of bee pollen could cause adverse effects but that these effects were unlikely to pose a significant health risk and were therefore not considered further.

◆ Hazard Characterisation

Gastro-intestinal symptoms: The Working Group identified that exposure to high doses of bee pollen can result in gastro-intestinal symptoms⁷ but that these were not serious and could be avoided by ensuring that initial exposure was at a low dose. Thus these health effects were not further considered in risk characterisation.

Hypoglycaemia: There was a report of a single case of bee pollen-related hypoglycaemia.⁸ The Working Group considered that the potential for hypoglycaemia-related adverse health effects was speculative and, further, would not be characterised as serious.

Anaphylaxis: The Working Group identified anaphylaxis to be the predominant adverse health effect reported from ingestion of bee pollen.

Asthma: The Working Group noted that there was tenuous evidence to indicate that the 'worsening of asthma' was an adverse effect of bee pollen.

Angioedema/urticaria: Available data indicated that angioedema and urticaria were possible adverse effects from bee pollen.

⁷ No. 57: Appendix III

⁸ CARM report - Other drugs identified in the report in addition to bee pollen were insulin and insulin zinc, possibly suggesting insulin-dependent diabetes. The Working Group believed that the reaction could have been caused by insulin as there was no rechallenge.

⁹ The Working Group was unable to determine from the reports whether these cases were anaphylaxis or angioedema/urticaria and were unable to ascertain from literature if the two reported adverse effects reported the same case.

Table 2: Hazard Characterisation of Bee Pollen

Adverse Health Effects	Categorisation	Cases
Gastro-intestinal	Possibly severe, but not serious	NZ (CARM database) – 1 case Aust. (ADRAC database) - n/a WHO database - reports not collected World literature - between 12 and 30% of patients, especially with higher initial doses.
Hypoglycaemia	Not serious	NZ (CARM database) – 1 case Aust.(ADRAC database) – no cases WHO database – reports not collected World literature – no reports found
Asthma/worsening of asthma	Serious if severe	NZ (CARM database) – Unable to determine from reports Aust. (ADRAC database) – Unable to determine from reports WHO database – 1 case World literature – unable to establish whether are of asthma or anaphylaxis
Anaphylaxis	Serious	NZ (CARM database) – no cases Aust (ADRAC database) – 1 (+2) ^{9*} WHO database – reports not collected World literature – 9 cases
Angioedema/urticaria	Serious	NZ (CARM database) – 5 cases Aust (ADRAC database) – (2)* WHO database – reports not collected World literature – (several)
Contact dermatitis	Not serious	NZ (CARM database) – no cases Aust.(ADRAC database) – no cases WHO database – reports not collected World literature – no reports found

*Adverse reaction reports have been appointed to a country of origin to avoid duplication with WHO reports

There does not appear to have been any deaths associated with the use of bee pollen.

There was no data available to suggest a dose-response relationship for bee pollen.

There was no evidence to suggest a population group with a higher susceptibility to adverse health effects from bee pollen. However, the Working Group noted a reported association between anaphylaxis and atopic individuals from the world literature.

◆ Exposure Characterisation

There are strong indications of a high level of exposure on a per capita basis in the general population. The Working Group noted that despite indications from industry of high daily doses of bee pollen in New Zealand and Australia there was insufficient data to generate exposure estimates on a per capita basis.

◆ Risk Characterisation

Over an 8 year period there is one validated report (and possibly two further reports) of anaphylaxis (from Australia) but no such reports from New Zealand. There are very few reports of anaphylaxis in the international literature and the actual frequency of anaphylaxis following ingestion of bee pollen cannot be assessed. Notwithstanding this, the world literature indicates that the frequency of serious adverse health effects following ingestion of bee pollen is extremely low.

No more than 5 cases of angioedema/urticaria have been reported in New Zealand and possibly two in Australia over an eight-year period. Similarly, there are extremely few reports of angioedema/urticaria in the literature following ingestion of bee pollen.

The Working Group concluded that despite evidence of high levels of exposure on a world-wide and Australasian basis there are an extremely small number of cases of serious (and potentially life-threatening) adverse effects. Therefore, on any qualitative scale the risk is extremely low.

(3) Risk Assessment of Royal Jelly

◆ Product Description and Use

Royal Jelly - a substance produced by special glands in worker honey bees and used as both a food for developing larval bees and to feed the queen bee. Royal jelly is high in protein and has a range of bioactive effects.

Royal jelly is available in raw form and in capsules, tablets, vials, creams, soaps and shampoos.

◆ Hazard Identification

Royal jelly was identified as a possible cause of contact dermatitis, bronchospasm anaphylaxis, gastro-intestinal symptoms, asthma, urticaria, and rhinitis.

◆ Hazard Characterisation

Contact dermatitis: there is one case report in the world literature¹⁰ but the Working Group did not categorise contact dermatitis as a serious adverse reaction to ingestion of royal jelly.

Rhinitis: three cases have been reported in Australia/New Zealand and a small number have been reported in world literature. Rhinitis was not categorised as a serious adverse health effect.

Gastro Intestinal Symptoms: There are at least 2 case reports in world literature¹¹ 1 of serious gastroenteritis or haemorrhagic colitis. Although these adverse effects would be considered as serious, there was insufficient data available for the Working Group to reasonably establish an association with royal jelly. The extremely low number of reports meant that these potential adverse effects were not further considered.

¹⁰ No. 69: Appendix III

¹¹ No. 63 & 68: Appendix III

Bronchospasm/Asthma: Bronchospasm/Asthma was identified as a serious adverse health effect consequential to ingestion of royal jelly. Thirty-two reports of serious adverse health effects were validated. The Working Group noted that two papers¹² refer to the same set of patients and have been acknowledged as such in a notice of duplicate publication.

Table 3: Hazard Characterisation of Royal Jelly

Adverse Health Effect	Categorisation	Cases
Rhinitis	Not serious	NZ (CARM database) – no cases Aust (ADRAC database) – 6 cases* WHO database – several reports * World literature – no cases
Contact dermatitis	Not serious	NZ (CARM database) – no cases Aust. (ADRAC database) – no cases WHO database – 1 case ** World literature – 1 report **
Bronchospasm/ Asthma	Severe and serious	NZ (CARM database) – 1 case Aust. (ADRAC database) – 16 cases WHO database – 3 to 6 cases World literature – 12 reports
Angioedema/Urticaria	Severe and serious	NZ (CARM database) - no cases Aust. (ADRAC database) – 2 cases WHO database – 2 cases World literature – 5 reports
Gastro-intestinal	Serious	NZ (CARM database) – no cases Aust. (ADRAC database) – 1 case WHO database – 1 case *** World literature – 2 reports***
Anaphylaxis	Serious	NZ (CARM database) – no cases Aust. (ADRAC database) – 1 case WHO database – no cases World literature – 4 reports

* The cases from Australia could include the cases reported to WHO

** This could be the same case

*** The cases from world literature could include the case reported to WHO

There was no data available to suggest a dose-response relationship for royal jelly.

The Working Group noted a reported association between anaphylaxis and atopic individuals from world literature.

¹² Royal Jelly-induced asthma and anaphylaxis: clinical characteristics and immunological correlations by Leung, Thien, Baldo and Czarny, - 1995 and the study entitled "Asthma and Anaphylaxis Induced by Royal Jelly " by Thien, Leung, Baldo et al, - 1996. The same set of patients was also discussed in a third paper (Thien, F. et al], 1993. Royal jelly induced asthma - The Medical Journal of Australia. 159:639).

◆ **Asthmatics as a Susceptible Population Group**

A Hong Kong study on asthmatics¹³ reports positive skin prick tests for 16.8% of a Hong Kong asthmatic population tested for allergy to royal jelly (this paper estimated that 30% of the Hong Kong population used royal jelly). This followed an earlier population survey in Hong Kong¹⁴ showing 7% of asthmatics had a positive skin prick test to royal jelly. 0.6% of respondents in the second study reported an adverse reaction to royal jelly.

In total there have been 37 reports of serious adverse reactions (anaphylaxis/bronchospasm/asthma) to royal jelly. Due to duplication in scientific literature and different reporting methods in different countries, these figures are considered to be indicative only.

◆ **Evaluation. of Three Reported Deaths Linked to Royal Jelly**

In categorising adverse health effects as "serious" or otherwise for the purposes of risk assessment policy, the Working Group did not place a different status on death as an outcome compared with other manifestations of "serious" adverse health effects.

However, the Working Group recognised that risk perception is an important issue in stakeholder evaluation (and participation) in risk management decisions. In particular, the public is likely to view death as a more important risk event than other "serious" adverse health effects, even though all "serious" adverse health effects may result in death in different circumstances. For this reason, the Working Group placed considerable emphasis on evaluating the three reported cases of death linked to oral ingestion of royal jelly.

The Working Group evaluated the three reported deaths associated with royal jelly in Australia, to the extent practicable in the time available.

Death of 31 Year Old Surfer. The Working Group was unable to assess the claimed association with the ingestion of the royal jelly and the death of the 31 year old surfer but notes the comments made by Dr Alain Rohan (Head of the ADRS) -Who states; "It would not be fair or scientifically defensible, to pin this death on the product."¹⁵ The Working Group, therefore, excluded this report from the risk characterisation.

Death of 11 Year Old Girl. Inadequate information was available to support the finding of the coroner on the claimed association between the ingestion of the royal jelly and the death of the 11 year old girl. In particular, this was because of the retrospective and anecdotal evidence of exposure and the lack of supporting analytical data. The Working Group, therefore, excluded this report from the risk characterisation.

Death of 23 Year Old Woman: The Working Group considered the evidence on the death of the 23 year old woman and concluded that there is a strong association between the ingestion of royal jelly and the development of an acute asthmatic episode with a fatal outcome.

¹³ No. 67: Appendix III

¹⁴ No. 60: Appendix III

¹⁵ "Severe/fatal asthma or other allergic reactions associated with ingestion of Royal jelly" Dr Alain Rohan, Head, Adverse Drug Reactions System (ADRS), Australia, June 12, 1997.

In itself, the possibility of one reported death does not alter the risk characterisation performed by the Working Group, as death is a potential outcome of any serious adverse reaction. As stated above, the Working Group did not distinguish between serious reactions where the outcome was death or recovery.

◆ **Exposure Characterisation**

Despite indications from industry of high daily doses of royal jelly in New Zealand, Australia and overseas there is insufficient data available to generate actual estimates of exposure on a per capita basis.

◆ **Risk Characterisation**

Table 4: Summary of Reported Cases of Serious Adverse Health Effects from Ingestion of Royal Jelly

World Literature (excluding NZ, Aust and WHO reports)	New Zealand CARM	Australia ADRAC	WHO Database	Total
12 reports of bronchospasm/asthma (including 5 cases of angioedema)	1 case of asthma	16 cases asthma (including 1 death and 2 cases of angioedema)	3 – 6 cases asthma	32 cases (including 7 cases of angioedema)
4 reports of anaphylaxis	-	1 case of anaphylaxis	-	5 cases of anaphylaxis

The Working Group identified that there was clear evidence of an association between ingestion of royal jelly and the potential for serious adverse health effects. Thirty-two cases of asthma/bronchospasm and 5 cases of anaphylaxis were validated from the available data.

There was insufficient information to establish a quantitative risk estimate but serious adverse health effects (including 'fatal outcome'), while very uncommon, appear to occur at a frequency considerably higher than that for other bee products. Thus, a qualitative risk characterisation ranks royal jelly as a bee product presenting higher risk, both in terms of probability of occurrence and seriousness of reactions, compared to propolis or bee pollen.

The Working Group notes that a disproportionate number of serious cases have been reported from Australia and this should be taken into consideration when assessing the comparative risk on a world-wide basis of ingestion of royal jelly.

PART TWO - RISK MANAGEMENT

Risk management involves a combination of risk evaluation and risk management option assessment to reach decisions on the management of risks to public health (Appendix II). It must include an evaluation of the likely impact of different risk management options on reducing risks to human health. In most cases, it will also include an evaluation of the likely impact of different risk management options on "other legitimate factors" that may be appropriately considered.

Following the qualitative characterisation of risk for each bee product the Working Group identified a number of risk management options. These were:

- ◆ Ban all bee products
- ◆ Change formulation of bee products to mitigate risks
- ◆ Make bee products prescription products with regulatory controls
- ◆ Restrict supply of bee products
- ◆ Label bee products (e.g. ingredient labelling, warning labelling, at risk group labelling):
 - Mandatory -
 - Voluntary and supported by an industry agreed code of practice -
 - Voluntary -
- ◆ Educate stakeholders
 - All consumers or targeted at-risk group -
 - Retailer -
- ◆ Take no risk management action to reduce risks

These possible options were then examined from a viewpoint of feasibility and practicality and summarised in Table 5.

Table 5: Options for Risk Management of Bee Products

Option	Feasible	Practical
ban	yes	no
change formulation	no	no
prescription only	?	no
restrict supply	no	no
ingredient labelling -mandatory	yes	yes
ingredient labelling- voluntary/code	yes	yes
ingredient labelling- voluntary	yes	yes
warning labelling –mandatory	yes	yes
warning labelling –voluntary/code	yes	yes
warning labelling –voluntary	yes	yes
high susceptibility group labelling - mandatory	yes	yes
high susceptibility group labelling -voluntary/ code	yes	yes
high susceptibility group labelling - voluntary	yes	yes
educate consumer	yes	no
educate groups with high susceptibility	yes	no
educate retailer	yes	no
no risk management action	yes	yes

The risk management options that were available and which could reasonably be applied were judged by the Working Group to be:

- ◆ **Mandatory labelling** (ingredient labelling, warning labelling, susceptible group labelling)
- ◆ **Voluntary labelling with code of practice** (ingredient labelling, warning labelling, susceptible group labelling)
- ◆ **Voluntary labelling** (ingredient labelling, warning labelling, susceptible group labelling)
- ◆ **No action**

Risk Management Safety Standards

The Working Group considered several risk management safety standards that could be applied to arrive at decisions on acceptable levels of risk.

Zero-risk: Achievement of "notional zero risk"

Threshold: Specification of a quantitative limit for an acceptable level of risk

Comparative: Determination of an acceptable level of risk based on comparative decisions taken in other comparable situations

Balancing: Balancing of risks and benefits to arrive at an acceptable level of risk.

As-Low-As-Reasonably-Achievable (ALARA): Reducing risks to the greatest extent practicable given available controls.

Given the risk management options for bee products that were judged to be reasonable and practicable, the Working Group decided to apply a balancing risk management safety standard. A threshold standard is not available and achievement of a "zero risk" environment was not considered practicable. ALARA is not appropriate, primarily due to the qualitative nature of the risk characterisation.

Factors Included In Decision Making

The Working Group had an extensive discussion on the factors that would be systematically considered in application of a balancing safety standard for risk management.

Public health was clearly identified as the primary determinant in decision-making.

Other legitimate factors that were considered are:

- ◆ World Trade Organisation (WTO) obligations
- ◆ ANZFA obligations
- ◆ Consumer expectations (Choice/ Demand)
- ◆ Economic impact on bee products industry
- ◆ Possible regulation as food in the case of pollen, so as to mitigate any risk

Precautionary Approach

Application of a "precautionary approach" in public policy decision-making has recently been the subject of widespread international debate. In the area of food safety, this has largely been due to various interpretations by different national governments in respect of implementation of the WTO SPS¹⁶ Agreement. In the absence of a working definition applicable to food safety (including dietary supplements), The Working Group noted reference to the precautionary approach in various Ministry of Health public policy documents.

In its deliberations, the Working Group applied a general understanding of the "precautionary principle" as it relates to risk management decision-making in the absence of sufficient scientific information. The Working Group did not apply the "precautionary approach" as a routine response to uncertainties inherent in all risk assessments, as this is considered to be an integral part of the risk characterisation process.

(1) Risk Management of Propolis

The estimated risk to the population is considered to be extremely low and no population with increased susceptibility could be identified. There was no statistical evidence of an emerging trend of serious health effects, despite the preponderance of reports in New Zealand and Australia. The Working Group had no reason to apply the precautionary approach because the data available did not support this.

Ingredient labelling was considered to be a systematic, low-cost risk management activity appropriate to the circumstances. Although the Working Group does not anticipate any measurable reduction in the already extremely low level of risk as a consequence of this activity, it is a measure that is consistent with general public health expectations.

In considering other risk management options, the use of mandatory health warnings was examined. It was assessed that any benefits to public health from mandatory health warnings (i.e. reducing the number of serious cases of adverse health effects in the consumer population) would be negligible. Furthermore, there were a number of negative consequences:

- ◆ The considerable costs of mandatory warning labels (borne by industry)
- ◆ Mandatory health warnings could act as an unjustified restriction to trade under the terms of the WTO and ANZFA
- ◆ Such warnings would create negative consumer perception disproportionate to the possible risks.

¹⁶ Agreement on the Application of Sanitary and Phytosanitary Measures

Risk Management Decision

For propolis, the Working Group concluded that the only risk management activity required was ingredient labelling of all products containing propolis. This could be through voluntary labelling and a self-regulated industry code of practice, or through mandatory labelling.

This is a low-cost risk management option that may mitigate an already extremely low level of risk without significant negative impact on other legitimate factors appropriately considered in risk management.

Because of the known frequency of allergic contact dermatitis to topical preparations containing propolis, the Working Group recommends that such products contain the statement:

"Propolis may cause allergic skin reactions".

(2) Risk Management of Bee Pollen

The estimated risk to the population from ingestion of bee pollen is extremely low. Case reports indicate a possible increased risk of anaphylaxis in atopic individuals, i.e. a population with a higher than normal susceptibility, but this was not a robust scientific finding. There was no statistical evidence of an emerging trend of serious adverse health effects. The Working Group concluded that the public health data available did not support the use of a precautionary approach.

Ingredient labelling was considered to be a systematic, low-cost risk management activity appropriate to the circumstances. Although the Working Group does not anticipate any measurable reduction in the already extremely low level of risk as a consequence of this activity, it is a measure that is consistent with general public health expectations.

In considering other risk management options, the use of mandatory health warnings was examined. It was assessed that any benefits to public health from mandatory health warnings (i.e. reducing the number of serious cases of adverse health effects in the consumer population) would be negligible. Furthermore, there were a number of negative consequences:

- ◆ The considerable costs of mandatory warning labels (borne by industry)
- ◆ Mandatory health warnings could act as an unjustified restriction to trade under the terms of the WTO and ANZFA
- ◆ Such warnings would create negative consumer perception disproportionate to the possible risks.

Due to the high consumer intake of bee pollen it was suggested that this bee product could be regulated as a food but this risk management option was not explored further by the Working Group.

Risk Management Decision

For bee pollen, the Working Group concluded that the only risk management activity required was ingredient labelling of all products containing bee pollen. This could be through voluntary labelling and a self-regulated industry code of practice, or through mandatory labelling.

This is a low-cost risk management option that may mitigate an already extremely low level of risk without significant negative impact on the other legitimate factors appropriately considered in risk management.

(3) Risk Management of Royal Jelly

The estimated risk to the normal population from ingestion of royal jelly is low. The estimated risk to the atopic population from ingestion of royal jelly is higher and the effects of adverse health reactions are more serious. There was no statistical evidence of an emerging trend of serious adverse health effects, despite the preponderance of reports from New Zealand and Australia. The Working Group concluded that the public health data available did not support the use of a precautionary approach.

The Working Group considered that although risks were low, they could be significantly reduced by implementation of appropriate risk management measures.

There was insufficient comparative information available to compare royal jelly to other dietary supplements when assessing the "proportionality" of different management options. The Working Group did note that for food there have been 141 admissions to New Zealand hospitals for anaphylactic shock (page 42 of the NNFA submissions to the Regulation Review Committee) but believe that consumers have a greater expectation for safety of ingested goods presented in packaged form. This is considered to be particularly true for dietary supplements.

The Working Group was not in a position to evaluate claimed benefits of royal jelly and therefore this was not included in benefit parameters in the risk management framework. The Working Group also do not believe that categorisation of these benefits would have altered their risk management decision.

Ingredient labelling was considered to be a systematic, low-cost risk management activity appropriate to the circumstances. Although the Working Group does not anticipate any measurable reduction in the already low level of risk as a consequence of this activity, it is a measure that is consistent with general public health expectations.

In considering other risk management options, the use of mandatory health warnings was thoroughly examined. It was assessed that any benefits to public health from mandatory health warnings in terms of the general population would be negligible.

However, the risk assessment process applied by the Working Group identified that asthmatics represent a population that is more susceptible to serious adverse health effects than the general population. A specific mandatory health warning label for products containing royal jelly could qualitatively be expected to reduce this risk. The only factor legitimately representing a negative impact of this risk management option was the cost of mandatory warning labels.

Risk Management Decision

For royal jelly the Working Group concluded that risk management should include ingredient labelling of all products containing royal jelly. This could be through voluntary labelling and a self-regulated industry code of practice, or through mandatory labelling.

To reduce the risk to population sub-groups more susceptible to adverse health effects than the general population following oral ingestion of products containing royal jelly, the Working Group recommends the following statement on all food products/ dietary supplements containing royal jelly:

"Royal jelly may cause serious allergic reactions. Most reports have been in asthma sufferers."

PART THREE - TERMS OF REFERENCE

The Working Group makes the following comments regarding the Terms of Reference provided by the Minister. In meeting the Terms of Reference provided by the Minister, the Working Group carried out a risk analysis on the bee products in question using an established and internationally recognised risk analysis framework.

No.1: To advise the Minister of Health on whether the precautionary approach is appropriate for decisions related to mandatory warning labels for dietary supplements

Application of principles of risk analysis to any food safety issue should, wherever appropriate, include consideration of the precautionary approach. Application of the approach is most likely to be necessary when there is insufficient scientific information for decision making. In the case of bee products, the Working Group considered that they had sufficient information to reach a well-founded risk management decision.

No.2: To advise the Minister of Health on whether there are any circumstances where the decision of a coroner on cause of death should be further investigated

The New Zealand Coroners Act clearly states, "If satisfied that since an inquest was completed new facts have been discovered that make it desirable to hold another the Solicitor General may order another to be held."

No.3: To advise the Minister of Health on whether the quality of advice used for the decisions related to the mandatory warning labels is adequate and consistent with the health implications of using the products

The data available to the Working Group was systematically evaluated within a risk analysis framework and was sufficient to reach a well-founded risk management decision.

No.4: To advise the Minister of Health if the quality of evidence is not considered adequate, what improvements to the quality of advice is needed/recommended and whether the additional resources should be publicly or privately funded.

In the instance of bee products, the Working Group felt that the evidence was adequate. However, as a general principle, the Working Group recommends consideration be given to the more systematic collection of adverse reaction reports from food, dietary supplements and complimentary health products similar to reporting systems for prescribed medications (CARM).

No.5: To advise the Minister of Health on whether the quality and extent of the risk assessment, consultation and consideration of submissions was adequate and appropriate to reach the decision to require warning statements on products containing royal jelly, bee pollen or propolis in light of the health implications of using the products.

The Working Group systematically applied a risk analysis framework appropriate to the public health problem identified to arrive at its risk management decisions. This included a functionally separate risk assessment process, validation of available data to the extent practicable, and detailed evaluation of submissions from stakeholders on relevant factors applying to risk management.

The Working Group notes the efforts of the Ministry of Health in co-ordinating the consultative process and aggregating submissions from stakeholders. However, systematic evaluation of available information by the Ministry of Health using a risk analysis framework may have led to different risk management decisions in respect of mandatory warning labels for all of the products considered.

The health statement arrived at by the Working Group for royal jelly is a specific outcome of the risk analysis that is different to that arrived at by the Ministry of Health.

Appendix I - Risk Assessment

Risk assessment has been defined for the purposes of food safety as "a scientifically based process consisting of the following steps: hazard identification, hazard characterisation, exposure assessment, and risk characterisation (Codex Alimentarius Commission, 1997). This definition was used as the basis for risk assessment by the Working Group.

Risk assessment is the primary scientific process in risk analysis and represents an evaluation of the probability of occurrence (likelihood) and severity (magnitude) of known or potential adverse health effects resulting from human exposure to hazards. Although the ideal goal is a quantitative estimate of risk, qualitative expressions of risk are common in many situations. A qualitative risk estimate would be based on non-numerical categorisation e.g. ranking of levels of risk as high, medium or low.

A risk assessment should ideally contain four analytical elements:

- Hazard identification; the possible presence of biological, chemical or physical agents capable of causing adverse health effects
- Exposure assessment; the intake of hazards that is likely to occur
- Hazard characterisation; the nature of adverse health effects, and may include a dose/response assessment
- Risk characterisation; integration of the above elements into an estimation of the probability and severity of adverse effects likely to occur in a given population.

Hazard identification is essentially a qualitative exercise that utilises a weight-of-evidence approach, and may include ranking of multiple hazards in order of their likely importance. (Low-ranking hazards may not be included in the risk assessment because of resource implications). Information should be gained from as many sources as possible so as to qualitatively estimate the 'likelihood of adverse health effects occurring in the population that is exposed. In the case of chemicals in food, hazard identification may include quantitative evaluation of toxicological data from animal studies, and consideration of mechanistic and pharmacokinetic/dynamic data. In the case of biological hazards in food, surveillance and epidemiological data on food-borne disease in the particular consumer population is essential.

Exposure assessment may utilise qualitative analyses alone, however it is now well recognised that inadequate estimates of intake and incomplete knowledge on distribution/level of hazards within the ingested product at the point of consumption will severely limit the ability to conduct quantitative risk assessments. In this context, many countries are strengthening their databases so as to better serve risk management decisions. Hazard characterisation includes a qualitative description of the nature of adverse health effects, and in the ideal situation will include a dose/response assessment. Dose-response studies in either animal models or humans contain both quantitative and qualitative elements, and the latter is particularly apparent in extrapolation of data from high-dose chemical toxicity studies in animals to low-dose exposures in humans. Where microbiological hazards occur in food, accurate dose/response data at the point of consumption is very difficult to obtain and risk assessments will often rely on qualitative hazard characterisations based on the initial contamination level of the food, process treatment and microbiological growth characteristics.

The final step in the risk assessment process is the risk characterisation. Both qualitative and quantitative analytical processes contribute to the estimate of risk, and the level of uncertainty in a quantitative estimate will reflect the quality of the data series utilised. If a key step in the process involves a qualitative analysis e.g. dose/response, then the output of the risk characterisation will reflect this. As an example, setting of standards for chemical residues in foods is often regarded as a quantitative risk assessment process with the ADI representing an upper limit of exposure associated with a zero level of risk. However, the utilisation of arbitrary safety factors in arriving at ADIs is a qualitative element that has a marked impact on the hazard characterisation step.

- Dr Steve Hathaway

Appendix I - Risk Management

Risk management has been defined for the purposes of food safety as "the process, distinct from risk assessment, of weighing policy alternatives, in consultation with all interested parties, considering risk assessment and other factors relevant to health protection of consumers and the promotion of fair trade practices, and, if needed, selecting appropriate prevention and control options" (Codex Alimentarius Commission, 1999). This definition was used as the basis for risk management decisions by the Working Group.

Elements of risk management

Risk evaluation

- Identification of problem
- Establishment of a risk profile i.e. qualitative information on the nature, extent and context of possible risks
- Ranking of the hazard for risk assessment and risk management priority
- Establishment of risk assessment policy for conduct of risk assessment
- Commissioning of a risk assessment, either qualitative or quantitative
- Consideration of output of the risk assessment.

Risk management option assessment

- Identification of available risk management options
- Selection of preferred management option, including consideration of an appropriate safety standard e.g. balancing standard
- Final management decision.
- Implementation of management decision.

Monitoring and review

- Assessment of the effectiveness of measures taken
- Review decisions as appropriate.

- Dr Steve Hathaway

Appendix III: - International Literature Considered by the Working Group

PROPOLIS:

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Hansson-C, Ezzelarab-M, Steiner-O
Acta-Derm-Venereol. 1995 Jan; 75(1): 34-6
2. **Propolis allergy (iv) Studies with further sensitizers from propolis and constituents common to propolis, popular buds and balsam of Peru.**
Hausen-BM, Evers-P, Stuwe- HT; Konig-WA; Wollenweber-E
Contact-Dermatitis. 1992 Jan; 26(1): 34-44
3. **Propolis allergy**
Hegy-E; Suchy-V; Nagy-M Hautarzt.
990 Dec; 41(12): 675-9
4. **Propolis allergy: a cause of oral mucositis with ulceration.**
Hay-KD; Greig-DE
Oral-Surg-Oral-Med-Oral-Pathol. 1990 Nov; 70(5): 584-6
5. **Contact dermatitis from propolis**
Raton-JA; Aguirre-A; Diaz-Perez-JL
Contact-Dermatitis. 1990 Mar; 22(3): 183-4
6. **Propolis allergy: synthesis and patch testing of gamma, gamma-dimethylallyl caffeic acid ester and its o-methyl derivatives**
Ginanneschi-M; Acciai-MC; Sertoli-A; Bracci-S
Contact-Dermatitis. 1989 Oct, 21(4): 267-9
7. **Propolis-induced contact allergy**
Schuler-TM; Frosch-PJ
Hautarzt. 1988 Mar; 39(3):139-42
8. **Allergic reaction to propolis. Case record**
Slezak-R
Prakt-Zubn-Lek. 1988 Sep; 36(7): 208-11
9. **Propolis allergy .(III). Sensitization studies with minor constituents.**
Hausen-BM; Wollenweber-E
Contact-Dermatitis. 1988 Oct, 19(4): 296-303
10. **Sensitivity to propolis in Japan.**
Nakamura-T
Contact-Dermatitis. 1988 May; 18(5): 313
11. **The incidence of allergy to propolis in 605 consecutive patients patch tested in Prague.**
Machackova-J
Contact-Dermatitis. 1988 Apr; 18(4): 210-2
12. **Current contact allergens**
Frosch-PJ
Z-Hautkr. 1987 Dec 1; 62(23): 1631-4. 1637-8
13. **Psoriasis and contact allergy to propolis**
Angelini-G; Vena-GA; Meneghini-CL
Contact-Dermatitis 1987 Oct 17(4) 251-3
14. **Airborne contact dermatitis due to propolis.**
Kleinhans-D
Contact-Dermatitis. 1987 Sep; 17(3): 187-8
15. **Sensitivity to propolis.**
Young-E
Contact-Dermatitis. 1987 Jan; 16(1): 49-50

16. **Propolis allergy. (I). Origin, properties, usage and literature** review. Hausen-BM, Wollenweber-E; Senff-H; Post-B
Contact-Dermatitis. 1981 Sep, 17(3): 163-170
17. **Propolis allergy. (11). The sensitizing properties of 1, 1-dimethylallyl caffeic acid ester.** Hausen-BM; Wollenweber-E; Senff-H; Post-B
Contact-Dermatitis. 1987 Sep; 17(3): 171-177
18. **Primary and secondary allergy to propolis]**
Rudzki-E; Grzywa-Z
Przegl-Dermatol. 1987 Jan-Feb, 74(1):11-4
19. **Hypersensitivity to propolis, sensitization method and cross reactions**
Rudski-E; Grzywa-Z
Pol-Tyg-Lek. 1987 Jan 12; 42(2): 40-2
20. **Contact dermatitis from propolis.**
Cirasino-L; Pisati-A; Fasani-F
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21. **Contact dermatitis from propolis: role of gastrointestinal absorption.**
Trevisan-G; Kokelj-F
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22. **New data on dermatitis from Propolis.**
Rudzki-E; Grzywa-Z; Pomorski -Z
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23. **Role of allergens causing skin lesions in humans In the development of allergy in dogs. IV. Contact allergens)**
Pomorski-Z; Rudzki-E
Przegl-Dermatol. 1985 May-Jun; 72(3): 253-6
24. **Contact dermatitis to propolis.**
Machackova-J
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25. **Propolis contact dermatitis.**
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26. **Contact dermatitis from propolis.**
Ayala-F; Lembo-G; Nappa-P; Balato-N
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27. **Allergic dermatitis caused by propolis: an Increasing pathology**
Bedello-PG; Goitre-M; Cane-D; Alovise-V,
G-Ital-Dermatol-Venereol. 1984 Nov-Dec; 11 9(6): 43 1-2
28. **Dermatitis from propolis.**
Valsecchi-R; Cainelli-T
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29. **Propolis: incidence of hypersensitization in an at risk population**
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30. **Contact dermatitis from propolis**
Pincelli-C; Motolese-A; Pincelli-L
Contact-Dermatitis. 1984 Jul; 11 (I): 49
31. **Occupational dermatitis in a bee-keeper.**
Melli-MC; Giorgini-S; Sertoli-A
Contact-Dermatitis. 1983 Sep; 9(5): 427-8
32. **Occupational and cosmetic dermatitis from propolis.**
Monti-M; Berti-E; Carininati-G; Cusini-M
Contact-Dermatitis. 1983 Mar; 9(2):163

33. **Dermatitis from propolis.**
Rudzki-E; Grzywa-Z
Contact-Dermatitis. 1983 Jan; 9(1): 40-45
34. **Possibility of allergy during treatment with propolis**
Grzywa-ZA
Wiad-Lek. 1983 Jun 15; 36(12): 999-1002
35. **Contact dermatitis from propolis,**
Kokelj-F; Trevisan-G
Contact-Dermatitis. 1983 Nov; 9(6): 518
36. **Contact dermatitis due to honeybee royal jelly**
Takahashi-M; Matsuo-I; Ohkido-M
Contact-Dermatitis. 1983 Nov; 9(6): 452-5
37. **A new cause of contact dermatitis: propolis (letter))**
Proserpio-G
G-Ital-Dermatol-Venereol. 1982 Sep-Oct; 117(5): 316-7
38. **A new cause of contact dermatitis: Propolis**
Monti-M; Berti-E; Carminati-G; Cusini-M
G-Ital-Dermatol-Venereol. 1982 Mar-Apr; 117(2): 119-22
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Przepl-Dermatol. 1980; 67(6): 747-52
40. **Sensitivity to Propolis**
Grzywa-Z; Rudzki-E
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41. **Hypersensitivity to propolis.**
Petersen-HO
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44. **Contact dermatitis from propolis.**
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64. **Anaphylaxis caused by royal jelly**
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