

**13 March 2002**  
**08/02**

**INITIAL / DRAFT ASSESSMENT**  
**[PRELIMINARY ASSESSMENT / FULL ASSESSMENT - SS.13/15] - S.37**

**APPLICATION A445**

**MAXIMUM RESIDUE LIMITS**

**DEADLINE FOR PUBLIC SUBMISSIONS** to the Authority in relation to this matter: **10 April 2002** (See “Invitation for Public Submissions” for details)

## **THE AUSTRALIA NEW ZEALAND FOOD AUTHORITY**

The Australia New Zealand Food Authority's (ANZFA) role is to protect the health and safety of people in Australia and New Zealand by maintaining a safe food supply. ANZFA is a partnership between the Commonwealth Government, Australian States and Territories governments and the New Zealand Government.

As an independent expert body, ANZFA is responsible for developing and reviewing food standards for both Australia and New Zealand. ANZFA makes recommendations to change the food standards to the Australia New Zealand Food Standards Council, a Ministerial Council made up of Commonwealth, State and Territory and New Zealand Health Ministers. If the Council approves the recommendations made by ANZFA, the food standards are automatically adopted as regulations into the food laws of the Australian States and Territories and New Zealand.

### **ANZFA's OBJECTIVES**

In developing or varying a food standard, ANZFA is required by its legislation to meet three primary objectives which are set out in Section 10 of the *Australia New Zealand Food Authority Act 1991*. These are:

- the protection of public health and safety;
- the provision of adequate information relating to food to enable consumers to make informed choices; and
- the prevention of misleading or deceptive conduct.

In developing and varying standards, ANZFA must also have regard to:

- the need for standards to be based on risk analysis using the best available scientific evidence;
- the promotion of consistency between domestic and international food standards;
- the desirability of an efficient and internationally competitive food industry; and
- the promotion of fair trading in food.

### **OTHER REGULATORY OBJECTIVES**

At the same time ANZFA must ensure that the regulations it develops are the most efficient and effective possible. It does this by looking at the possible impact that the regulation might have on consumers, business and other groups in our community or whether there are alternative options to formal regulations such as codes of practice. In addition, as Australia and New Zealand are members of the World Trade Organization (WTO), ANZFA must ensure that the regulations are consistent with the obligations of both countries as members of the WTO.

## **INVITATION FOR PUBLIC SUBMISSIONS**

On 31 August 2001, the draft variations for Application A445 were recommended to Council under s.37 of the ANZFA Act as a matter of urgency to avoid compromising the objectives set out in subsection 10(1)(a) of the Act, namely the protection of public health and safety.

The Ministerial Council amended the draft variations as recommended by ANZFA to include permission for dried vegetable seasonings to contain residues of ethylene oxide, provided the

residues did not exceed 20 mg/kg. The Ministerial Council then adopted the draft variations as amended.

In accordance with s.37 of the ANZFA Act, ANZFA invites submissions for the purposes of holding an inquiry into the draft variations as amended and adopted by Council.

Written submissions containing technical or other relevant information that will assist the Authority in preparing the Final assessment for this Application are invited from interested individuals and organisations. Technical information presented should be in sufficient detail to allow independent scientific assessment.

The processes of the Authority are open to public scrutiny, and any submissions received will ordinarily be placed on the public register of the Authority and made available for inspection. If you wish any information contained in a submission to remain confidential to the Authority, you should clearly identify the sensitive information and provide justification for treating it as commercial-in-confidence. The *Australia New Zealand Food Authority Act 1991* requires the Authority to treat in confidence trade secrets relating to food and any other information relating to food, the commercial value of which would be, or could reasonably be expected to be, destroyed or diminished by disclosure.

Submissions must be made in writing and should be clearly marked with the word 'Submission' and quote the **correct project number and title**. Submissions may be sent by mail to the **Standards Liaison Officer** at one of the following addresses:

Australia New Zealand Food Authority  
PO Box 7186  
Canberra BC ACT 2610  
AUSTRALIA  
Tel (02) 6271 2258  
email: [slo@anzfa.gov.au](mailto:slo@anzfa.gov.au)

Australia New Zealand Food Authority  
PO Box 10559  
The Terrace  
WELLINGTON 6036 NEW ZEALAND  
Tel (04) 473 9942  
email: [anzfa.nz@anzfa.gov.au](mailto:anzfa.nz@anzfa.gov.au)

Submissions should be received by the Authority **by 10 April 2002**.

Submissions may also be sent electronically through the submission form on the ANZFA website [www.anzfa.gov.au](http://www.anzfa.gov.au). Electronic submissions should also include the full contact details of the person making the submission on the main body of the submission so that the contact details are not separated.

Queries on this matter and other Standards matters can be directed to the Standards Liaison Officer at the above address or by email on [slo@anzfa.gov.au](mailto:slo@anzfa.gov.au). Requests for more general information on the Authority can be directed to the Information Officer at the above addresses.

**DEADLINE FOR PUBLIC SUBMISSIONS** to the Authority in relation to this matter:

**24 APRIL 2002**

(see 'Invitation for Public Submissions' for details)

## **1. APPLICANT'S REQUEST**

The Australia New Zealand Food Authority (ANZFA) received **Application A445** on 6 July 2001, from the Australian Food and Grocery Council (AFGC) seeking to amend the *Food Standards Code* to extend the expiry date for the maximum residue limit (MRL) of 20 mg/kg for ethylene oxide in herbs, spices, and to extend the existing MRL to include dried seasoning vegetables. The MRL for herbs and spices is due to expire on 30 September 2001 and the application sought to extend the expiry date to 30 September 2006.

The Applicant has sought the extension to allow:

- further investigation of the toxicology of the breakdown products of ethylene oxide;
- development of commercially viable alternatives to ethylene oxide sterilisation; and
- consumers to become informed about the benefits of alternative technologies.

The Applicant has also stated that the 'maintenance of the temporary MRLs for ethylene oxide will allow the continued use of ethylene oxide as a fumigant and thereby ensure availability of safe herbs, spices and dried seasoning vegetables, free of unsafe levels of microbial contamination.'

On 21 August 2001, the Applicant amended the Application and requested:

- the ethylene oxide MRL be reduced below 20 mg/kg ('possible to less than 10 mg/kg');
- a three-year extension of the expiry date for the MRL;
- development and implementation of a Code of Practice requiring a withholding period of 21 days following treatment; and
- establishment of a Working Group to monitor the transition period, monitor use of ethylene oxide and adoption and implementation of alternative technologies.

## **2. SECTION 37 CONSIDERATION**

It is proposed that this Application be considered as a matter of urgency, under section 37 of the *Australia New Zealand Food Authority Act 1991* in order to avoid compromising the objective set out in subsection 10(1)(a) of the Act, namely the protection of public health and safety.

### **3. BACKGROUND TO THE APPLICATION**

#### **3.1 The Use of Agricultural and Veterinary Chemicals**

In Australia, the National Registration Authority for Agricultural and Veterinary Chemicals (NRA) is responsible for registering agricultural and veterinary chemical products, granting permits for use of chemical products and regulating the sale of agricultural and veterinary chemical products. Following the sale of these products, the use of the chemicals is then regulated by State and Territory 'control of use' legislation.

#### **3.2 Maximum Residue Limits**

The MRL is the highest concentration of a chemical residue that is legally permitted or accepted in a food. The MRL does not indicate the amount of chemical that is always present in a treated food but it does indicate the highest residue that could possibly result from the registered conditions of use. The concentration is expressed in milligrams per kilogram (mg/kg) of the food.

#### **3.3 Previous Consideration of Ethylene Oxide MRL**

##### *PACSC Consideration*

In 1983 and 1985, the National Health and Medical Research Council (NHMRC) Pesticides and Agricultural Chemicals Standing Committee (PACSC) considered requests for Maximum Residue Limits for ethylene oxide in a range of foods. The Committee agreed that no MRL could be set for ethylene oxide because of its extremely toxic nature.

##### *NFA Consideration*

The issue of ethylene oxide was raised with the then National Food Authority (NFA) in March 1993 as a result of a New Zealand initiative to review the use of ethylene oxide on herbs and spices with a view to phasing out the use of ethylene oxide. It was noted by the NFA at the time that ethylene oxide was used in Australia on imported herbs and spices and that this use may be inconsistent with Commonwealth, State and Territory food legislation. However, it was also considered at that time that ethylene oxide was necessary to reduce the microbial contamination of some herbs and spices and that one of the alternatives to ethylene oxide use, namely, irradiation, was not available. The NFA agreed to review the continued use of ethylene oxide in cooperation with the New Zealand Ministry of Health and the spice industry.

At this time, NFA staff also had discussions with the Spice Association of Australasia and with Australian Quarantine and Inspection Service (AQIS). It was recognised that there were little data on the extent and level of residues of ethylene oxide on herbs and spices. To address this matter, AQIS was directed to place ethylene oxide on the Imported Food Inspection Program's active surveillance list to obtain more data. In cases where residues were detected, AQIS was to use an action level of 50ppm that was consistent with the tolerance used in the USA for ground spices. This action level was to apply only for 6 months from 10 June 1993. This position was formally advised in a letter from the NFA Chairperson to AQIS in June 1993 advising that an action of 50 ppm for herbs and spices under the Imported Food Program was to apply.

Following discussions with NFA staff, the Spice Association agreed to provide:

- (i) the results of residue trials on both local and imported products;
- (ii) toxicity data on residues of ethylene oxide from the American Spice Traders Association (ASTA); and
- (iii) other information on alternatives to the use of ethylene oxide.

While some data were provided, only limited information was obtained from the Spice Association. The issue of establishing an MRL for ethylene oxide was not pursued by the NFA in the expectation that alternative treatments would make the use of ethylene oxide obsolete.

#### *ANZFA Consideration*

In January 2000 AQIS sought advice from ANZFA about the status of ethylene oxide in relation to the *Food Standards Code* and was informed that there was no MRL for ethylene oxide and that therefore no detectable residues of ethylene oxide (or its breakdown products) were permitted in foods imported into or produced in Australia.

Subsequently, the NRA received an application for an emergency use permit for ethylene oxide treatment of herbs and spices (Application No. 3589). They granted this permit on 20 April 2000. Prior to this date, ethylene oxide on herbs and spices was not registered for use in Australia.

ANZFA received **Application A412** on 27 April 2000 from NRA seeking to amend the *Food Standards Code* to establish a maximum residue limit (MRL) of 20 mg/kg for ethylene oxide in herbs and spices.

ANZFA, pursuant to section 37 of the *Australia New Zealand Food Authority Act 1991*, progressed this application as a matter of urgency in order to avoid compromising the objective set out in subsection 10(1)(a) of the Act, namely the protection of public health and safety. Accordingly, ANZFA completed a Full Assessment of the application, prepared draft variations to the *Food Standards Code*, and proposed recommendations to be considered by the Australia New Zealand Food Standards Council (ANZFSC).

On 28 July 2000, ANZFSC agreed to the recommendations to amend Standard A14 – Maximum Residue Limits, and agreed also that the date of implementation of the amendment would coincide with the date of gazettal of the variation to the standard. The variation commenced on the 17 August 2000, the date of gazettal, with an expiry date of 30 September 2001. This expiry date was set to allow the phasing out of ethylene oxide and its replacement by alternative methods of decontamination.

### **3.4 Treatment of herbs and spices**

Selected herbs and spices (particularly paprika, pepper and cinnamon) imported into Australia can be contaminated with *Salmonella* and may require treatment prior to sale and use. AQIS test for *Salmonella* in imported herbs and spices and, if found, require decontamination or re-export of the shipment. Until the recent expiry of the NRA permit for the use of ethylene oxide (31 July 2001 – see below), treatment with ethylene oxide was the standard method to control microbial contamination of herbs and spices.

In addition, some segments of the food industry routinely sterilised herbs and spices with ethylene oxide as part of their production processes.

### **3.5 Consideration of Ethylene Oxide in New Zealand**

New Zealand food legislation, until recently, permitted herbs and spices to contain residues of ethylene oxide of 50 ppm. There has been on-going concern regarding ethylene oxide in New Zealand since 1993. Following consideration of a recent report entitled *Cancer Risk Assessment of Ethylene Oxide Residues in New Zealand Spices* prepared by the New Zealand Institute of Environmental and Scientific Research (ESR), the New Zealand Ministry of Health recommended an MRL of 20 ppm for ethylene oxide residues in spices. This regulation came in force on 23 April 2000. This MRL only applies to residues of ethylene oxide and does not include residues associated with its major breakdown products ethylene chlorohydrin and ethylene bromohydrin.

The agreement between the Commonwealth of Australia and the Government of New Zealand, 1995 to establish a system for the development of joint food standards (the Treaty) excluded MRLs for agricultural and veterinary chemicals in food from the joint Australia New Zealand food standards setting system. Australia and New Zealand separately develop MRLs for agricultural and veterinary chemicals in food.

Following the commencement of the Trans Tasman Mutual Recognition Arrangement (TTMRA) between Australia and New Zealand on 1 May 1998:

- food produced in Australia that complies with volume 1 (Standard A14) or Volume 2 (Standard 1.4.2) of the *Food Standards Code* can be legally sold in New Zealand; and
- food produced in New Zealand that complies with the *New Zealand (Maximum Residue Limits of Agricultural Compounds) Mandatory Food Standard, 1999* can be legally sold in Australia.

### **3.6 Ethylene Oxide as a Processing Aid**

Based upon the previous application from the NRA to include an MRL for ethylene oxide in herbs and spices, ethylene oxide has been regarded as an agricultural chemical and regulated as such in the Food Standards Code. However, the residues of ethylene oxide resulting from use of ethylene oxide to treat herbs and spices to reduce microbial contamination could be regulated in the *Food Standards Code* as an agricultural chemical or as a processing aid. It would also allow for the further treatment of herbs and spices with ethylene oxide and limited further usage of ethylene oxide may be necessary for a short period in order to protect public health and safety. Therefore, the applicant's request for an extension of the expiry date for the MRL is equivalent to a request for a limit for ethylene oxide residues resulting from its use as a processing aid. This approach would overcome any confusion as to whether the use of ethylene oxide is as an agricultural chemical or a processing aid.

## **4. OBJECTIVE OF THE APPLICATION**

The applicant has sought the extension to allow the continued use of ethylene oxide for fumigation of herbs and spices while:

- the toxicology of the breakdown products of ethylene oxide is further investigated;
- commercially viable alternatives to ethylene oxide sterilisation are developed; and
- consumers become informed about the benefits of alternative technologies.

The applicant has also stated that the ‘maintenance of the temporary MRLs for ethylene oxide will allow the continued use of ethylene oxide as a fumigant and thereby ensure availability of safe herbs, spices and dried seasoning vegetables, free of unsafe levels of microbial contamination.’

The inclusion of a limit on ethylene oxide residues in the *Food Standards Code* permits the sale of herbs and spices that contain ethylene oxide up to that limit. Depending upon the claims made about ethylene oxide products, other regulatory agencies may need to approve the use of ethylene oxide products.

As the objective of the applicant’s request is to allow the legal sale of herbs and spices that contain detectable residues of ethylene oxide, ANZFA has considered the applicant’s request of an extension of the expiry date for the MRL as being equivalent to a request for a limit for ethylene oxide residues resulting from its use as a processing aid. This will overcome any confusion as to whether the use of ethylene oxide is as an agricultural chemical or a processing aid.

## **5. MICROBIOLOGICAL ASSESSMENT**

The applicant has claimed that the MRL needs to be extended to allow the legal sale of herbs, spices and dried seasoning vegetables that have been treated with ethylene oxide to reduce microbial contamination. To determine the extent of this contamination, the Authority has conducted an assessment of the risk to public health of microbiological contamination of herbs and spices. The Authority’s assessment of the microbiological assessment is at Attachment 2.

The risks to human health and safety resulting from the possible association of pathogens with herbs and spices falls into several classes. Firstly, the assessment demonstrates that spices can sometimes have a high incidence of microbial contamination. It is likely that herbs will sometimes also be contaminated with microorganisms, because of the similarity of growing and processing conditions for herbs and spices. However, there is limited evidence to verify this assumption.

If the herbs and spices are included in a food product prior to a cooking or other high heat processing step, then even contaminated herbs and spices do not pose a risk to public health and safety. This type of heat treatment kills potential pathogens.

However, the risk associated with herbs and spices is potentially higher in those cases where they are added to food that does not undergo further processing and/or are consumed without cooking or high heat treatment. In these cases, the microorganisms associated with the herbs and spices may proliferate, and then may pose a risk to public health and safety. However, the risks vary significantly between foods that provide different environments for growth of various microorganisms and because of the different impacts of various processing steps adopted. Therefore, not all foods in this category can be considered to be ‘at risk’ because of the addition of herbs and spices.



However, there will be some ‘at risk’ foods that, in the absence of a suitable treatment for herbs and spices should either: be withdrawn from the food supply; require changes in processing procedures to incorporate a suitable ‘kill’ step; or require changes in reformulation.

The risks posed by different pathogens also vary. There is evidence to demonstrate that for two potential spore forming pathogens (*Clostridium* and *Bacillus* spp), the public health risk is relatively low. The risk posed by these pathogens is best managed by food processors excluding significantly contaminated material through ingredient specification and by the appropriate management of post processing cooling steps. A third pathogen (*Salmonella*) has been mostly associated with specific dried spices (eg pepper and paprika). These spices, and particularly pepper, are often added to food without a heat treatment. This group of spices pose the highest risk where they are used without a heat treatment.

A number of factors reduce the risk posed by untreated, but potentially contaminated herbs and spices. First, the current microbiological requirements and the high frequency testing requirements for imported products for *Salmonella* in pepper, paprika and cinnamon help ensure that the risk to public health and safety from this organism is kept to a minimum. However, it is recognised that end product testing can be an insensitive tool for the detection of low level and non homogenous contamination. Thus some contaminated spices may not be detected.

Second, the use of HACCP in the production, transport and handling of herbs and spices plays a major role in reducing levels of contamination. It is recognised internationally that appropriate procedures should be in place to protect raw herbs and spices from contamination by human, animal and other waste. The international standard setting body, the Codex Alimentarius Commission, has developed guidance for the production, harvesting and handling of herbs and spices under hygienic conditions.

Further reduction in contamination can be achieved through good manufacturing practice. Manufacturers who use spices can utilise other tools to minimise the risk posed by potentially contaminated, but untreated, spices (eg examining the microbiological profile of the spices, use of appropriate processing procedures).

Third, herbs and spices are used in very small quantities in individual products. It is notable that the levels are so small that they are not recorded in ANZFA’s database of food recipes, limiting ANZFA’s ability to estimate dietary intake and more accurately estimate the risk posed by potential contaminants. The dose of pathogens required to cause disease in most cases will be high. Therefore, although herbs and spices may be contaminated with a particular microorganism, this may not occur at a sufficient level, nor have the appropriate virulence factors to cause disease.

Finally, it is noted that chemical decontamination processes have been banned in some countries, including the European Union and Japan, for many years. There is no documented evidence to suggest that this has led to an increase in food borne illness from herbs and spices in these countries.

## 6. TOXICOLOGY ASSESSMENT

### *Available toxicology reports*

ANZFA has not undertaken an independent assessment of the toxicology of ethylene oxide and its breakdown products, ethylene chlorohydrin and ethylene bromohydrin. Based on the fact that it was an emergency standard, the temporary MRL put in place in July 2000 was based on the report prepared by New Zealand Institute of Environmental and Scientific Research (ESR) in December 1999 entitled *Cancer Risk Assessment of Ethylene Oxide in New Zealand Spices* in December 1999 (see Attachment 4).

This report concluded that:

1. The current monitoring and risk assessment has indicated that there is negligible cancer risk to both upper-end and worst-case scenario consumers associated with ethylene oxide (EtO) residues in spices.
2. There are no known significant cancer risks associated with the consumption of ethylene chlorohydrin and ethylene bromohydrin at the levels found in retail spices. Neither compound is a known carcinogen. However, there is a significant degree of scientific uncertainty in this advice as some key toxicological studies have not been done for these compounds.
3. An MRL of 20 ppm of EtO in spices is sufficient to take account of residues found in retail spices. This is consistent with the policy of maintaining residues as low as practically achievable.

The ESR report uses a quantitative risk assessment approach to analyse the cancer risk associated with exposure to the levels of EtO and its breakdown products found in New Zealand spices. This approach, while not used in Australia to analyse cancer risks, is widely used in the USA, and forms the basis of many regulatory decisions associated with exposure to chemicals in that country. This was considered by ANZFA to be an acceptable analysis of the risk associated the EtO and an adequate justification for the temporary MRL of 20 mg/kg in herbs and spices in the Food Standards Code. However, the issue of the breakdown products could not be fully addressed due to the paucity of the available data.

A second report on the safety of ethylene oxide and its breakdown products was prepared on 12 June 2001 by the Chemical and Non-Prescription Drugs Branch of the Therapeutic Goods Administration (Australia) in response to an application to the National Registration Authority for Agricultural and Veterinary Chemicals (NRA) to extend the temporary permission for both the use and the MRL for ethylene oxide (see Attachment 5).

This report concluded that:

1. Ethylene oxide is a potent genotoxic carcinogen. Furthermore, the breakdown products likely to be found as components of the residues are also genotoxic and potentially carcinogenic. The TGA considers that while quantitative estimates of cancer risk may be low, there is no threshold to the risk, and exposure to clearly genotoxic chemicals is to be avoided where suitable alternatives exist.

Accordingly, the approval of a permit to use ethylene oxide to fumigate imported herbs and spices is not supported from a toxicological perspective.

2. The advise of NOHSC should be sought for any occupational health and safety implications of the use of ethylene oxide.
3. Current recommendations on poison scheduling are appropriate.
4. An ADI will not established for ethylene oxide since it is considered to be a genotoxic carcinogen and therefore there is no acceptable threshold for exposure.
5. ADIs will not be established for either ethylene chlorohydrin or ethylene bromohydrin because of the absence of sufficient toxicological data. In addition, the available data raises some concerns with respect to the genotoxic and carcinogenic potential of these compounds.

This report has examined the same data as the ESR report but has not used quantitative risk assessment to examine the cancer risk from exposure to EtO and its breakdown products. Instead, it has examined whether the data would support the establishment of an acceptable daily intake (ADI). In the case of EtO, the report concludes that an ADI cannot be established for a genotoxic carcinogen. In the case of the breakdown products, the report concludes an ADI cannot be established because of the absence of data.

#### *Conclusions from the available toxicology reports*

Taken together, these reports agree that EtO is a genotoxic carcinogen and therefore exposure at any level presents a potential health risk. In the ESR report, it is concluded that this risk is negligible at the level of EtO in spices. In the TGA report, no assessment of risk at low levels of exposure is undertaken. Instead, the report concludes that “exposure to clearly genotoxic carcinogens is to be avoided where suitable alternatives exist”. On the basis of these two reports and in the absence of an independent analysis of the data by ANZFA, it may be concluded that exposure to EtO is undesirable and that the health risk is difficult to quantify.

In relation to the breakdown products, ethylene chlorohydrin and ethylene bromohydrin, both reports agree that the toxicological database is insufficient to reach any definite conclusions regarding the risk associated with these compounds. Both reports agree that they are weak genotoxins, giving positive results only in *in vitro* assays. The ESR report, however, concludes “neither compound is a known carcinogen” while the TGA report concludes “the available data raises some concerns with respect to the genotoxic and carcinogenic potential of these compounds”. On the basis of these two reports and in the absence of an independent analysis of the data by ANZFA, it may be concluded that the data available does not allow any definite conclusions to be drawn.

The regulatory approach that has previously been adopted, in the amendment of the *Food Standards Code*, is not to allow the use of genotoxic chemicals that are intentionally added to food.

## **7. DIETARY EXPOSURE ASSESSMENT**

In relation to MRLs, ANZFA's role is to ensure that the potential residues in treated food associated with the MRL do not represent an unacceptable risk to public health and safety.

On the basis of the toxicology assessment, ethylene oxide is a genotoxic carcinogen and there is no level of exposure which is without some, albeit small, health risk. Therefore, ANZFA has not proceeded to conduct a formal dietary exposure assessment. In addition, there are insufficient toxicological data on the breakdown products of ethylene oxide, namely ethylene chlorohydrin and ethylene bromohydrin, to establish an acceptable daily intake and as a result ANZFA is not able to undertake a formal dietary exposure assessment for the breakdown products of ethylene oxide.

Herbs and spices are generally used in low amounts in food, resulting in extremely low levels of consumption. The 1995 National Nutrition Survey and the 1997 National Nutrition Survey reports consumption of a limited number of herbs and spices and do not include these ingredients in recipes for mixed foods due to the extremely low contribution per 100g of product. Therefore, these food consumption data do not reflect actual consumption levels of herbs and spices.

Although a formal dietary exposure estimate cannot be undertaken it should be noted that the food industry has stated that it is possible that some treated herbs and spices would be used in food without further processing. On this basis and given the potentially high residues in treated herbs and spices, these foods may contain finite residues of ethylene oxide or its breakdown products despite herbs and spices only being a minor ingredient of many foods.

In conclusion, the available toxicology and food consumption data do not enable a formal dietary exposure assessment to be undertaken. Although levels of consumption of herbs, spices and dried vegetable seasonings are generally low, the high residues of ethylene oxide and the extremely high residues of its break down products in treated herbs and spices means it is likely that finite residues of ethylene oxide, particularly the ethylene chlorohydrin, would remain in minimally processed foods containing even low amounts of treated herbs, spices and dried vegetable seasonings.

## **8. RISK CHARACTERISATION**

On the basis of the toxicological reports available, it is clear that ethylene oxide is a strong genotoxic carcinogen. For the breakdown products, ethylene chlorohydrin and ethylene bromohydrin, there is evidence of weak genotoxicity and inadequate data to reach a firm conclusion on the carcinogenicity potential. It is not possible to establish an acceptable daily intake (ADI) for either ethylene oxide or its breakdown products. When ethylene oxide is used on herbs and spices, there is a small and unavoidable health risk to consumers through the presence of residues of ethylene oxide and its breakdown products.

There is no precedent in the *Food Standards Code* for continuing approval of a genotoxic carcinogen that is intentionally added to food, or to the granting of an MRL in the absence of an ADI where finite residues remain in the treated food. In view of the inadequacy and nature of the toxicological data and associated scientific uncertainty, and the high levels of persistent residues following treatment, a conservative approach to the management of the risk posed by these residues is appropriate.

## **9. REGULATORY IMPACT ASSESSMENT**

The applicant has applied for an extension of the expiry date for the MRL for ethylene oxide in herbs, spices and dried vegetable seasonings. An extension of the expiry date would have the effect of allowing the legal sale of herbs, spices and dried vegetable seasonings that contain up to 20 mg/kg of ethylene oxide residues. For brevity, any reference in this assessment to ‘herbs and spices’, other than the conclusion, is to be taken as a reference to herbs, spices and dried seasoning vegetables.

Residues of ethylene oxide result from treatment of herbs and spices with ethylene oxide to reduce microbial contamination. Therefore, the objective of the application is to protect public health and safety by facilitating treatment of herbs and spices with ethylene oxide to reduce microbial contamination.

### **9.1 Identification of Affected Parties**

The parties affected by this application include:

- manufacturers including those that currently use ethylene oxide treated herbs and spices and those that do not;
- consumers, including domestic and overseas customers;
- importers of herbs and spices; and
- Commonwealth, State and Territory agencies involved in monitoring agricultural and veterinary chemicals in food.

The inclusion of a limit on ethylene oxide residues in the *Food Standards Code* permits the sale of herbs and spices that contain ethylene oxide up to that limit. Depending upon the claims made about ethylene oxide products, other regulatory agencies may need to approve the use of ethylene oxide products.

As the objective of the applicant’s request is to allow the legal sale of herbs and spices that contain detectable residues of ethylene oxide, ANZFA has considered the applicant’s request of an extension of the expiry date for the MRL as being equivalent to a request for a limit for ethylene oxide residues resulting from its use as a processing aid. This will simplify the regulatory impact assessment.

### **9.2 Possible options**

ANZFA has identified four main options for addressing the objective of the application:

1. extend the expiry date of the existing limit for ethylene oxide residues for a transition period. This would allow the sale of herbs and spices containing residues up to the limit and facilitate the use of ethylene oxide;
2. not to extend the expiry date of the limit for ethylene oxide residues thereby prohibiting the sale of herbs and spices that contain detectable residues of ethylene oxide;
3. extend the expiry date of the existing limit for ethylene oxide residues for a transition period in a limited range of herbs and spices. This would allow the sale of herbs and spices containing residues up to the limit and facilitate the use of ethylene oxide; or
4. remove the expiry date for the existing limit for ethylene oxide residues thereby meaning that the limit would not have an expiry date.

### 9.3 Assessment of Options

#### 1. *Extend the expiry date of the existing limit for a transition period*

The costs of this option would be:

- an indeterminate public health cost for government and consumers in exposing consumers, for a limited time, to residues of ethylene oxide that is a potent genotoxic carcinogen and residues of suspected genotoxic breakdown products. The estimates of risk may be low and this cost would extend for only a limited period;
- commercially disadvantaging, for a limited time, those suppliers and manufacturers that are already using herbs and spices that have been treated with alternative technologies or who have developed procedures to reduce the contamination; and
- potential adverse impact on exports of produce if foods containing detectable residues of ethylene oxide were detected in the European Union where ethylene oxide has not been permitted since the 1980s, although there is no evidence of this difficulty.

The benefits of this option would be that:

- the industry, including small business could continue for a limited time to trade herbs and spices containing detectable residues of ethylene oxide thereby providing the industry with a further opportunity to seek alternatives to ethylene oxide treated herbs and spices;
- consumers would have access to products with reduced microbial contamination following sterilisation with ethylene oxide with the consequent public health benefit of a small reduction in the incidence of food-borne disease;
- products from North America where ethylene oxide residues are permitted in herbs and spices, would be permitted entry to Australia.

#### 2. *Not to extend the expiry date for the limit*

The costs of this option would be that:

- There would be potential for a small increase in food-borne illness as a result of some businesses unwittingly using contaminated herbs and spices that may potentially contain human pathogens.
- Based upon representations from industry, substantial transition costs would be immediately incurred by manufacturers that currently use herbs and spices containing detectable residues of ethylene oxide. These costs could include:
  - Supply problems in obtaining herbs and spices that do not contain detectable residues of ethylene oxide or unacceptable microbial contamination, although ANZFA has been informed that steam sterilised herbs and spices are available;
  - suspension of product manufacturing with consequent loss of employment and social costs to the community;
  - reformulation of products as a result of the different flavour profiles of herbs and spices treated with alternative technologies;
  - changes to food processing techniques to account for herbs and spices containing higher microbial load that is currently the case with sterilised herbs and spices (e.g. differing food processing techniques to reduce microbial load during processing); and

- the possible recalls of products that have recently been produced that may contain up to 20 mg/kg of ethylene oxide but which would no longer comply with food legislation after 30 September 2001. However, a 'stock-in-trade' provision may address this concern.
- Consumers would potentially bear the above transition costs of industry in increased food prices and may have less access to foods containing herbs and spices as some manufacturers may choose not to produce products until they could be satisfied that their products were safe.
- Products from North America where ethylene oxide residues are permitted in herbs and spices, would not be permitted entry, although there is no evidence of this difficulty.

The benefits of this option would be that:

- Consumers would be protected from the exposure to the residues of ethylene oxide with known genotoxic carcinogenic properties and the suspected genotoxic residues of its breakdown products;
  - Suppliers and manufacturers who are already using herbs and spices that have been treated with alternative technologies, could continue to market their products at a commercial advantage to those products containing ethylene oxide residues.
  - Products produced in Australia could continue to be exported to the European Union where ethylene oxide has not been permitted since the 1980s.
3. *Extend the expiry date of the existing limit for a transition period in a limited range of herbs and spices.*

The costs of this option would be:

- an indeterminate public health cost for government and consumers in exposing consumers, for a limited time in a limited range of herbs and spices, to residues of ethylene oxide with known genotoxic properties and residues of suspected genotoxic breakdown products;
- commercially disadvantaging, for a limited time and for a limited range of herbs and spices, those suppliers and manufacturers that are already using herbs and spices that have been treated with alternative technologies;
- potential impact on trade if foods containing detectable residues of ethylene oxide were detected in the European Union where ethylene oxide has not been permitted since the 1980s, although there is no evidence of this difficulty;
- difficulties in determining the precise range of herbs and spices to which the MRL should apply with consequent public health costs if some businesses unwittingly using untreated herbs and spices that may potentially contain human pathogens; and
- costs to industry and consumers of not being permitted to use herbs and spices containing ethylene oxide residues similar to those indicated in Option 2 but for a limited range of herbs and spices.

The benefits of this option would be that:

- the industry, including small business could continue for a limited time to trade some herbs and spices containing detectable residues of ethylene oxide thereby providing the industry with an opportunity to rapidly seek alternatives to ethylene oxide treated herbs

- and spices;
  - consumers would have access to products with reduced microbial contamination following sterilisation with ethylene oxide with the consequent public health benefit of a small reduction in the incidence of food-borne disease;
  - products from North America where ethylene oxide residues are permitted in herbs and spices, would be permitted entry.
4. *Remove the expiry date for the limit.*

The costs and benefits of this option would be the same as Option 1 but would be on an ongoing basis, rather than for a limited period of time.

#### **9.4 Conclusion**

In considering the industry's transition costs, ANZFA has noted that until recently, there was no permission for herbs and spices to contain detectable residues of ethylene oxide and that manufacturers who were using herbs and spices containing detectable residues of ethylene oxide, were doing so illegally. This has resulted in a slight commercial disadvantage to those businesses that have incurred transition costs and been complying with food law and potentially paying higher prices for alternative sources of herbs and spices.

In addition, ANZFA has noted that the industry has been asked on a number of occasions in the past to provide additional information about ethylene oxide, with insufficient information being provided. The food industry has had substantial warning and opportunity to discontinue the use of herbs and spices containing residues of ethylene oxide but alternatives have not been developed partly because of the lack of approval (food irradiation) and partly because of technical difficulties (steam sterilisation). Based upon past experiences, it is questionable whether the industry would move to alternatives unless ethylene oxide use was monitored and the limit was limited to a short period of time.

Overall, ANZFA considers that the public health benefits of reduced microbial contamination combined with the high transition costs for industry and consumers of immediately seeking alternatives to ethylene oxide treated herbs and spices would outweigh the public health costs of permitting residues of ethylene oxide in food for a limited time. On this basis, ANZFA considers that the expiry date of the existing limit for ethylene oxide residues in herbs and spices should be extended for a limited time to allow industry to rapidly develop alternative sources.

Given the carcinogenic properties of ethylene oxide, any extension should be limited to the shortest feasible time. Taking into account the treated herbs and spices that are already part of stock in trade and the time that would be required to source alternative sources of herbs and spices or commission new equipment, a transition period of two years is considered appropriate with a total ban on ethylene oxide residues to apply after this time.

The existing limit was included as a Maximum Residue Limit (MRL) because ethylene oxide was used as an 'agricultural chemical'. The intended use of ethylene oxide is to control human pathogens, however, there are questions as to whether this use is regulated as an 'agricultural chemical' use.



Given that existing chemicals with similar biocidal use are included in the processing aid standards, it is considered more appropriate to limit the residues of ethylene oxide by regarding it as a processing aid and including the necessary limits in the standards relevant to processing aids in the *Food Standards Code*.

The applicant also requested that the existing temporary limit be extended to also apply to dried vegetable seasonings. No data on the residues in dried vegetable seasonings were provided and given the genotoxic nature of ethylene oxide residues, ANZFA considers that it would not be appropriate to extend the range of foods that might contain ethylene oxide residues. On this basis, the limit should only apply to herbs and spices.

On 21 August 2001, the applicant amended its application and requested the ethylene oxide MRL be reduced below 20 mg/kg ('possible to less than 10 mg/kg'). Reducing the limit would require the recall of stock in trade that contained residues above 10 mg/kg and would not be consistent with the 20 ppm limit that already applies in New Zealand legislation. On this basis, it was considered appropriate to retain 20 mg/kg.

On 21 August 2001, the applicant amended their application and proposed the development of a Code of Practice requiring a withholding period of 21 days following treatment. As a period between treatment and sale could result in the reduction of residues, it was considered appropriate to include this condition in the *Food Standards Code*.

## **9.5 Review**

In an amendment to their application, the applicant has proposed the establishment of a Working Group to monitor the reduction in the use of ethylene oxide. The residues of ethylene oxide are a function of the use of ethylene oxide. On this basis, a programme that focuses on reducing the use of ethylene oxide on herbs and spices would result in an orderly reduction of ethylene oxide residues in the food supply and would complement the limit proposed for inclusion in the *Food Standards Code*.

This program would need to be agreed and instituted before any change in the expiry date for the limit is gazetted and include consideration of:

- restrictions on the use of ethylene oxide that would minimise residues including, using ethylene oxide only where strictly necessary, minimising applications rates and times to the minimum required to control microbial contamination and ensuring sufficient time (withholding period) between treatment and use to allow maximum dissipation of residues;
- industry proposals as to how ethylene oxide treated herbs and spices will be replaced with alternative sources of herbs and spices; and
- three-monthly public reporting by industry on the industry's progress towards the replacement of ethylene oxide treated herbs and spices, including on an industry-wide basis, the percentage of major individual herbs and spices that are treated with ethylene oxide and the approximate ranges of all remaining residues in these treated herbs and spices.

recognising that ethylene oxide is currently regulated as an agricultural compound in New Zealand and agricultural compounds are outside the scope of the Treaty, the scope of the

Working Group will initially be limited to industry use in Australia, although New Zealand industry would not necessarily be excluded.

In addition, ANZFA will continue to monitor the results from the inspection of imported herbs and spices to determine if more stringent measures are required to ensure the protection of public health and safety.

### **CONSIDERATION OF ISSUES UNDER SECTION 13 OF THE AUSTRALIA NEW ZEALAND FOOD AUTHORITY ACT 1991**

Subsection 13(1) of the *Australia New Zealand Food Authority Act, 1991* (ANZFA Act) requires ANZFA to make a preliminary assessment of an application. In making that preliminary assessment, subsection 13(2) requires ANZFA to have regard to a number of matters set out in paragraphs 13(2)(a) to (e). Each of these matters is discussed below.

#### **Paragraph 13(2)(a)**

This Application relates to a matter that may warrant a variation to a food regulatory measure, because the Application seeks an amendment of a standard. Under the ANZFA Act, a standard, by definition, is a food regulatory measure.

#### **Paragraph 13(2)(b)**

This Application is not so similar to a previous application that it ought not be accepted.

#### **Paragraph 13(2)(c)**

Overall, ANZFA considers that the small public health benefits of reduced microbial contamination combined with the high transition costs for industry and consumers of immediately seeking alternatives to ethylene oxide treated herbs and spices would outweigh the small public health costs of permitting residues of genotoxic substances in food for a limited time. On this basis, ANZFA considers that the limit for ethylene oxide in herbs and spices should be extended for a limited time to allow industry to develop alternative sources but that residues should be banned after this time.

#### **Paragraph 13(2)(d)**

The nature of the Application is such that the objective of protecting public health and safety could be brought about by implementing, in part, the request of the applicant to extend the expiry date for the limit on ethylene oxide residues in herbs and spices. The existing limit was included as an MRL because ethylene oxide was used as an 'agricultural chemical'. However, given the intended use of ethylene oxide to control human pathogens and doubts as to whether this use is strictly an 'agricultural chemical' use, it is considered more appropriate to limit the residues of ethylene oxide by regarding it as a processing aid and including the necessary limits in the standards relevant to processing aids in the *Food Standards Code*. This approach would be similar to the approach used for a number of biocidal substances that are already included in the processing aid standards.

### **Paragraph 13(2)(e)**

Other relevant matters for consideration by ANZFA are as follows.

#### *World Trade Organization Notification*

As a member of the World Trade Organization (WTO) Australia is obligated to notify WTO member nations where proposed mandatory regulatory measures are inconsistent with any existing or imminent international standards and the proposed measure may have a significant effect on trade.

The limits prescribed in the *Australia New Zealand Food Standards Code* constitute a mandatory requirement applying to all food products of a particular class whether produced domestically or imported. Food products exceeding the limits set out in the *Food Standards Code* cannot legally be supplied in Australia.

This application contains variations to limits that are not addressed in the international Codex standard. Limits in this application also relate to chemicals used in the production of heavily traded agricultural commodities which may indirectly have a significant effect on trade of derivative food products between WTO members. A WTO notification for this application will therefore be made following the endorsement of the Full Assessment.

The application **will be** notified as a Sanitary and Phytosanitary (SPS) measure in accordance with the WTO SPS agreement as the primary objective of the measure is to minimise residues of ethylene oxide to protect human, animal and plant health and the environment.

### **CONSIDERATION OF ISSUES UNDER SECTION 15 OF THE AUSTRALIA NEW ZEALAND FOOD AUTHORITY ACT 1991**

Subsection 15(1) of the *Australia New Zealand Food Authority Act, 1991* requires ANZFA to make a Full Assessment of an application. In making that Full Assessment, subsection 15(3) requires ANZFA to have regard to a number of matters set out in paragraphs 15(3)(a) to (e). Each of these matters is discussed below.

#### **Paragraph 15(3)(a)**

No public consultation was undertaken in making this Full Assessment as it is proposed that this Application be considered as a matter of urgency, under section 37 of the Act in order to avoid compromising the objective set out in subsection 10(1)(a) of the Act, namely the protection of public health and safety.

#### **Paragraph 15(3)(b)**

Section 10 (1), paragraphs (a) to(c) of the Act) set out ANZFA's objectives in developing food regulatory matters and variations to food regulatory matters. Each of these matters is discussed below.

*(a) The protection of public health and safety*

On the basis of the toxicology reports available, when ethylene oxide is used there is a small but unavoidable health risk to consumers due to the presence of residues of ethylene oxide and its breakdown products, ethylene chlorohydrin and ethylene bromohydrin. While the microbiological risks associated with most dried herbs and spices are relatively low, the risk associated with some spices, including pepper, paprika and cinnamon may be potentially higher. This higher relative risk could be argued on the basis that these products are consumed more often without further heating (cooking), there is a higher reported, although variable, incidence of microbial contamination, and associations with a small number of outbreaks have been recorded.

Overall, ANZFA considers that the public health benefits of reduced microbial contamination would outweigh the public health risks of permitting residues of ethylene oxide and its breakdown products in food for a limited time. On this basis, the Authority considers that the expiry date of the existing limit for ethylene oxide residues in herbs and spices should be extended for a limited time to allow industry to develop alternative sources but that residues should be banned after this time.

*(b) The provision of adequate information relating to food to enable consumers to make informed choices*

This is not relevant for this application.

*(c) Prevention of misleading or deceptive conduct*

This is not relevant for this application.

In addition to these main objectives, subsection 10(2) requires ANZFA to have regard to a number of matters set out in paragraphs 10(2)(a) to (d). Each of these matters is discussed below.

*(a) The need for standards to be based on risk analysis using the best available scientific evidence*

The procedures used by ANZFA and the TGA rely on the comprehensive examination of detailed scientific information, including a rigorous toxicological, microbiological and dietary exposure assessment.

*(b) The promotion of consistency between domestic and international food standards*

The limit of 20 mg/kg for ethylene oxide in herbs and spices is consistent with the level currently prescribed in the *New Zealand (Maximum Residue Limits for Agricultural Compounds) Mandatory Food Standard 1999*. This application contains variations to limits that are not addressed in the international Codex standard.

(c) *The desirability of and efficient and internationally competitive food*

The limits are necessary to allow the legal sale of herbs and spices that have been treated with ethylene oxide to reduce microbial contamination. Varying the *Food Standards Code* to include the proposed limit would alleviate industry's costs.

(d) *The promotion of fair trading in food*

As the limits in the *Food Standards Code* apply to all food produced or imported for sale or in Australia, the inclusion of the limits would benefit all producers equally.

**Paragraph 15(3)(c)**

Overall, ANZFA considers that the public health benefits of reduced microbial contamination combined with the high transition costs for industry and consumers of immediately seeking alternatives to ethylene oxide treated herbs and spices would outweigh the public health risk of permitting residues of ethylene oxide and its breakdown products in food for a limited time. On this basis, ANZFA considers that the limit for ethylene oxide in herbs and spices should be extended for a limited time to allow industry to rapidly develop alternative sources but that residues should be banned after this time.

**Paragraph 15(3)(d)**

The nature of the application is such that the objective of protecting public health and safety could be brought about by implementing in part the request of the applicant to extend the expiry date for the limit on ethylene oxide residues in herbs and spices. The existing limit was included as an MRL because ethylene oxide was regulated as an 'agricultural chemical'. However, given the intended use of ethylene oxide to control human pathogens and questions as to whether this use is regulated as an 'agricultural chemical' use, it is considered more appropriate to limit the residues of ethylene oxide by regarding it as a processing aid and including the necessary limits in the standards relevant to processing aids in the *Food Standards Code*. This approach would be similar to the approach used for a number of biocidal substances that are already included in the processing aid standards.

**Paragraph 15(3)(e)**

Other relevant matters for consideration by ANZFA under Section 15 are as stipulated above under the Section 13 consideration.

**CONCLUSIONS**

The Application fulfils the requirements of an application as stipulated in the *Australia New Zealand Food Authority Act 1991*. ANZFA has completed a Full Assessment of the Application and prepared draft variations to Volumes 1 and 2 of the *Food Standards Code*.

ANZFA has decided, pursuant to section 37 of the *Australia New Zealand Food Authority Act 1991*, to progress this application as a matter of urgency in order to avoid compromising the objective set out in subsection 10(1)(a) of the Act, namely the protection of public health and safety.

ANZFA recommends the adoption of the draft variations to Standard A16 and Standard 1.3.3 for the following reasons:

- Ethylene oxide treated herbs and spices have reduced microbial contamination including less contamination with human pathogens and viable alternative sources are not yet readily available to all sectors of the industry.
- On the basis of the reports prepared by the Institute of Environmental and Scientific Research, New Zealand, and by the Chemicals and Non-prescriptions Medicines Branch of the Therapeutic Goods Administration (TGA) when ethylene oxide is used there is a small but unavoidable health risk to consumers due to the presence of residues of ethylene oxide which is a potent genotoxic carcinogen and its breakdown products, ethylene chlorohydrin and ethylene bromohydrin which are weakly genotoxic and potentially carcinogenic.
- Ethylene oxide and residues of this substance should not be permitted in the food supply any longer than necessary. Accordingly, residues of ethylene oxide and its breakdown products in food should be allowed for no longer than two years.
- A limit of 20 mg/kg for ethylene oxide in herbs and spices has previously been recommended by the NRA after the granting of an Emergency Use Permit for fumigant use of ethylene oxide on herbs and spices on 20 April 2000 and is consistent with the level currently prescribed in the *New Zealand (Maximum Residue Limits for Agricultural Compounds) Mandatory Food Standard 1999*.
- On the basis of representations from industry, the transition costs for industry and ultimately consumers, of letting the limit for ethylene oxide in herbs and spices expire at the end of September would be extensive. Therefore the expiry date needs to be extended.
- While industry develops alternative decontamination techniques to remove human pathogens from herbs and spices, a temporary limit of 20 mg/kg for ethylene oxide in herbs and spices should be retained but should cease to have effect after 30 September 2003.
- Recognising that stipulating a limit with an expiry date has not previously prompted industry to undertake sufficient timely work to develop alternatives to ethylene oxide, an industry Working Group should be established to encourage, monitor and publicly report on the reduction in the use of ethylene oxide.
- The inclusion of a limit for ethylene oxide residues in dried vegetable seasonings is not recommended because data on the residues of ethylene oxide in dried vegetable seasonings were not provided and, given the genotoxic nature of ethylene oxide residues, ANZFA considers that it would not be appropriate to extend the range of foods that might contain ethylene oxide residues. This would mean that dried vegetable seasonings would not be permitted to contain detectable residues of ethylene oxide beyond 30 September 2001.

The inclusion of a limit on ethylene oxide residues in the Food Standards Code permits the sale of herbs and spices that contain ethylene oxide up to that limit. Depending upon the claims made about ethylene oxide products, other regulatory agencies may need to approve the use of ethylene oxide products.

In an amendment to their application, the applicant has proposed the establishment of a Working Group to monitor the reduction in the use of ethylene oxide. The residues of ethylene oxide are a function of the use of ethylene oxide. On this basis, a program that focuses on reducing the use of ethylene oxide on herbs and spices would result in an orderly reduction of ethylene oxide residues in the food supply and would complement the limit proposed for inclusion in the *Food Standards Code*.

This program would include consideration of:

- restrictions on the use of ethylene oxide that would minimise residues including, using ethylene oxide only where strictly necessary, minimising applications rates and times to the minimum required to control microbial contamination and ensuring sufficient time (withholding period) between treatment and use to allow maximum dissipation of residues;
- industry proposals as to how ethylene oxide treated herbs and spices will be replaced with alternative sources of herbs and spices; and
- three-monthly public reporting by industry on the industry's progress towards the replacement of ethylene oxide treated herbs and spices, including on an industry-wide basis, the percentage of major individual herbs and spices that are treated with ethylene oxide and the approximate ranges of all remaining residues in these treated herbs and spices.

Recognising that ethylene oxide is currently regulated as an agricultural compound in New Zealand and agricultural compounds are outside the scope of the Treaty, the scope of the Working Group will initially be limited to industry use in Australia, although New Zealand industry would not necessarily be excluded.

In addition, ANZFA will continue to monitor the results from the inspection of imported herbs and spices to determine if more stringent measures are required to ensure the protection of public health and safety.

### **Ministerial Council Consideration**

On 31 August 2001, the draft variations for Application A445 were recommended to Council under s.37 of the ANZFA Act as a matter of urgency to avoid compromising the objectives set out in subsection 10(1)(a) of the Act, namely the protection of public health and safety.

The Ministerial Council amended the draft variations as recommended by ANZFA to include permission for dried vegetable seasonings to contain residues of ethylene oxide, provided the residues did not exceed 20 mg/kg. The Ministerial Council then adopted the draft variations as amended.

In accordance with s.37 of the ANZFA Act, ANZFA invites submissions for the purposes of holding an inquiry into the draft variations as amended and adopted by Council.

**Attachments**

1. Draft variation to the *Food Standards Code*.
2. Statement of Reasons
3. Microbiological Risk Assessment of Dried Herbs and Spices
4. ESR Report: *Cancer Risk Assessment of Ethylene Oxide Residues in New Zealand Spices*
5. Toxicology Evaluation on Ethylene Oxide from Chemicals and Non-Prescription Medicines Branch of the Therapeutic Goods Administration.



**ATTACHMENT 1****DRAFT VARIATIONS TO THE FOOD STANDARDS CODE AS ADOPTED BY THE MINISTERIAL COUNCIL****To commence: On gazettal**

[1] *Standard A16 of Volume 1 of the Food Standards Code is varied by inserting into Table III immediately after Ethylene diamine tetraacetic acid –*

Ethylene Oxide  This permission ceases to have effect on 30 September 2003. This permission is an Australia Only Standard	Sterilisation of herbs, spices and dried vegetable seasonings – herbs and spices sterilised by the application of ethylene oxide may only be sold or imported into Australia 21 days after such sterilisation	20
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[2] *Standard 1.3.3 of Volume 2 of the Food Standards Code is varied by inserting into the Table to clause 14 immediately after Ethylene diamine tetraacetic acid –*

Ethylene Oxide  This permission ceases to have effect on 30 September 2003. This permission is an Australia Only Standard.	Sterilisation of herbs, spices and dried vegetable seasonings – herbs and spices sterilised by the application of ethylene oxide may only be sold or imported into Australia 21 days after such sterilisation	20
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**STATEMENT OF REASONS**

The Australia New Zealand Food Authority received Application **A445** (on 6 July 2001), from the Australian Food and Grocery Council to amend the Australian *Food Standards Code* to extend the expiry date for the maximum residue limit (MRL) of 20 mg/kg for ethylene oxide in herbs and spices, and to extend the existing MRL to include dried seasoning vegetables to 30 September 2006.

The application fulfils the requirements of an application as stipulated in the *Australia New Zealand Food Authority Act 1991*. ANZFA has completed a full assessment of the application and prepared draft variations to the Australian *Food Standards Code*.

ANZFA has decided, pursuant to section 37 of the *Australia New Zealand Food Authority Act 1991*, to progress this application as a matter of urgency in order to avoid compromising the objective set out in subsection 10(1)(a) of the Act, namely the protection of public health and safety.

ANZFA recommends the adoption of the draft variations to Standard A16 and Standard 1.3.3 for the following reasons:

- Ethylene oxide treated herbs and spices have reduced microbial contamination including less contamination with human pathogens and viable alternative sources are not yet readily available to all sectors of the industry.
- On the basis of the reports prepared by the Institute of Environmental and Scientific Research, New Zealand, and by the Chemicals and Non-prescriptions Medicines Branch of the Therapeutic Goods Administration (TGA) when ethylene oxide is used there is a small but unavoidable health risk to consumers due to the presence of residues of ethylene oxide which is a potent genotoxic carcinogen and its breakdown products, ethylene chlorohydrin and ethylene bromohydrin which are weakly genotoxic and potentially carcinogenic.
- Ethylene oxide and residues of this substance should not be permitted in the food supply any longer than necessary. Accordingly, residues of ethylene oxide and its breakdown products in food should be allowed for no longer than two years.
- A limit of 20 mg/kg for ethylene oxide in herbs and spices has previously been recommended by the NRA after the granting of an Emergency Use Permit for fumigant use of ethylene oxide on herbs and spices on 20 April 2000 and is consistent with the level currently prescribed in the *New Zealand (Maximum Residue Limits for Agricultural Compounds) Mandatory Food Standard 1999*.
- On the basis of representations from industry, the transition costs for industry and ultimately consumers, of letting the limit for ethylene oxide in herbs and spices expire at the end of September would be extensive. Therefore the expiry date needs to be extended.

- While industry develops alternative decontamination techniques to remove human pathogens from herbs and spices, a temporary limit of 20 mg/kg for ethylene oxide in herbs and spices should be retained but should cease to have effect after 30 September 2003.
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The inclusion of a limit on ethylene oxide residues in the *Food Standards Code* permits the sale of herbs and spices that contain ethylene oxide up to that limit. Depending upon the claims made about ethylene oxide products, other regulatory agencies may need to approve the use of ethylene oxide products.

In an amendment to their application, the applicant has proposed the establishment of a Working Group to monitor the reduction in the use of ethylene oxide. The residues of ethylene oxide are a function of the use of ethylene oxide. On this basis, a programme that focuses on reducing the use of ethylene oxide on herbs and spices would result in an orderly reduction of ethylene oxide residues in the food supply and would complement the limit proposed for inclusion in the *Food Standards Code*.

This program would include consideration of:

- restrictions on the use of ethylene oxide that would minimise residues including, using ethylene oxide only where strictly necessary, minimising applications rates and times to the minimum required to control microbial contamination and ensuring sufficient time (withholding period) between treatment and use to allow maximum dissipation of residues;
- industry proposals as to how ethylene oxide treated herbs and spices will be replaced with alternative sources of herbs and spices; and
- three-monthly public reporting by industry on the industry's progress towards the replacement of ethylene oxide treated herbs and spices, including on an industry-wide basis, the percentage of major individual herbs and spices that are treated with ethylene oxide and the approximate ranges of all remaining residues in these treated herbs and spices.

Recognising that ethylene oxide is currently regulated as an agricultural compound in New Zealand and agricultural compounds are outside the scope of the Treaty, the scope of the Working Group will initially be limited to industry use in Australia, although New Zealand industry would not necessarily be excluded.

In addition, ANZFA will continue to monitor the results from the inspection of imported herbs and spices to determine if more stringent measures are required to ensure the protection of public health and safety.

### **Ministerial Council Consideration**

On 31 August 2001, the draft variations for Application A445 were recommended to Council under s.37 of the ANZFA Act as a matter of urgency to avoid compromising the objectives set out in subsection 10(1)(a) of the Act, namely the protection of public health and safety.

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In accordance with s.37 of the ANZFA Act, ANZFA invites submissions for the purposes of holding an inquiry into the draft variations as amended and adopted by Council.

### **DRAFT VARIATIONS**

See Attachment 1 to the Full Assessment Report.



**AUSTRALIA NEW ZEALAND FOOD AUTHORITY**

**MICROBIOLOGICAL RISK ASSESSMENT OF  
DRIED HERBS AND SPICES**

**AUGUST 2001**

## **OBJECTIVES**

The objectives of this assessment are to identify and qualitatively characterise the public health risks arising from microbiological contamination of dried herbs and spices as food ingredients. The microbiological assessment is largely based on the risk assessment ‘Dried Foods and ingredients of plant origin’ conducted during the *Review of Microbiological Standards* (ANZFA, 1999a; ANZFA 1999b) as part of the establishment of the joint Food Standards Code for Australia and New Zealand (the Code).

## **BACKGROUND**

Spices are any of the various aromatic plant products used primarily to season, flavour, or to impart an aroma to foods. The term applies equally to the spices in the whole, broken or ground form. Herbs are generally defined as leafy parts of soft-stemmed plants (e.g. oregano, marjoram, basil, curry leaves, mints, rosemary and parsley) (ICMSF, 1998).

With respect to current microbiological standards for herbs and spices, Standard 1.6.1 – Microbiological Limits for Food, of Volume 2 of the *Food Standards Code* -sets a zero tolerance standard for *Salmonella* in the spices pepper, paprika, and cinnamon. This Standard was the outcome of a comprehensive risk assessment conducted for the development of microbiological standards for the joint *Australia New Zealand Food Standards Code*. There are no microbiological standards for herbs and spices in Volume 1 of the *Food Standards Code* or in the *New Zealand Food Regulations* (NZFR).

Pepper, paprika and cinnamon, if imported, are tested at 100% for the presence of *Salmonella* prior to being released for sale in Australia. If contamination is detected, products are refused entry onto the market. Other spices and all herbs are only tested at a random rate of 5% for microbiological contamination, as they are considered to present a lower risk of contamination.

Under the Imported Food Program (IFP), importers have several options available to them once a product has been failed for non-compliance. One option in response to finding positive microbial contamination is for an importer to treat the failed product by disinfection with ethylene oxide (ETO). If an importer chooses to use ETO treatment, the Australian Quarantine and Inspection Service (AQIS) is obliged to test for ETO residues, and ensure that they conform to the Maximum Residue Limit (MRL) listed in the *Food Standards Code*.

## **RISK ASSESSMENT**

### **1. General considerations**

Food-borne diseases are generally defined as diseases caused by the consumption of food or water containing unsafe levels of pathogenic microorganisms or their toxins.

Microorganisms generally associated with food-borne disease include various species of bacteria and viruses, particularly human enteric viruses, as well as parasitic protozoa and helminths. Spices contain large numbers of microorganisms that occasionally may cause spoilage or more rarely, disease, when introduced into food (ICMSF, 1998).

## 2. Hazard identification

Microorganisms of concern identified in the literature for herbs and spices are:

*Bacillus* spp;  
*Clostridium perfringens*;  
*Escherichia coli*;  
*Salmonella* spp;  
*Klebsiella pneumoniae*; and  
*Staphylococcus aureus*

Appendix 1 provides descriptions of the above pathogens.

Examples of outbreaks of illness due to consumption of dried spices or foods containing these ingredients are:

- an estimated 1000 cases of salmonellosis due to consumption of paprika or paprika-powdered potato chips contaminated with *S. Saintpaul*, *S. Rubislaw* and *S. Javiana*, Germany, April - Sept 1993 (Lehmacher *et al.*, 1995);
- an outbreak of salmonellosis due to consumption of black pepper contaminated with *S. Oranienburg*, Norway, 1981-82 (Gustarsen & Breeno, 1984);
- 4 cases of gastroenteritis due to consumption of spices contaminated with *B. cereus* and *B. thuringiensis*, Canada, 1995 (Jackson *et al.*, 1995); and

In addition, a large number of cases of *B. cereus* food poisoning have been associated with consumption of meat and meat dishes seasoned with spices (AIFST, 1997).

The presence of *C. perfringens* (Kneifel and Berger, 1994), *E. coli*, *K. pneumoniae* (Satchell *et al.*, 1989) and *S. aureus* (Leitao *et al.*, 1973-1974; Al-Jassir, 1992) have been detected during analysis of dried foods, however, examples of illness due to these pathogens are not readily available in the literature.

## 3. Hazard characterisation

Dried herbs and spices can become contaminated with potentially dangerous microorganisms because of the way they are grown and handled. Sources of contamination may be dust, insects, faecal material from birds and rodents, and possibly processing water. Contamination can occur at any stage during harvesting, drying and preparation, transport and storage of products. Preventing contamination is not always possible, and despite all efforts at good agricultural practice, dried herbs and spices may still become contaminated with pathogenic microorganisms.

While salmonellae are primarily associated with animals, infected animals including humans will excrete large numbers of bacteria which may contaminate soil and water. *Salmonella* are thus ubiquitous organisms found throughout the environment as contaminants and dried herbs and spices may become contaminated either prior to or post harvesting.

In countries with high levels of environmental contamination with *Salmonella* and poor sanitation and sewage disposal, the opportunity for herbs and spices to become contaminated during the harvesting, transport and drying process will be significant.

An additional potential route of contamination for dried herbs and spices is through the colonisation of processing equipment. Equipment used for processing herbs and spices may not be designed to meet modern requirements for plant sanitation. As exposure to water or heat during processing and drying of herbs and spices may damage the properties of the material, equipment sanitation may be difficult.

While salmonellae are not spore formers, they may display a high degree of tolerance to environmental stress, including drying. They may survive and remain viable for years in dried herb or spice. If added to a moist substrate the bacteria resuscitate and may multiply. Thus a hazard may be presented by processed foods containing contaminated plant material, especially spices, unless a bactericidal process is applied.

Spore forming organisms that are capable of causing gastroenteritis when ingested in large populations are found in spices, but usually in small populations. To cause illness, they would have to multiply to  $10^5$ - $10^6$  cfu/g of food to which the spice is added (ICMSF, 1998).

An assessment of the microbiological quality of spices and herbs found that *B. cereus* counts ranged from less than  $1.0 \times 10^2$  cfu /g to  $1.0 \times 10^5$  cfu/g, with most being less than  $1.0 \times 10^3$  cfu/g (Pafumi, 1986). *Bacillus* sp. are commonly associated with plant material. Thus the presence of low numbers of *Bacillus* spores is not unexpected in dried herbs and spices. When added to moist foods, often as a seasoning or garnish, the time and temperature conditions may allow spore germination and toxin production.

A relatively high incidence of *Cl. perfringens* has also been found in several spices, however the number per gram is usually less than 500 and is rarely over 1000 (ICMSF, 1998).

*Staphylococcus aureus* is rarely found in dry spices (ICMSF, 1998).

The incidence of microbial contamination of spices may be high and this can include pathogenic bacteria such as *Salmonella* species that have the potential to cause food-borne infections (ICMSF, 1998). Pafumi (1986) reported the incidence of *E. coli* in approximately 30% of peppercorns and in 42% of a range of herbs and spices that were tested. The incidence of salmonella contamination in black peppercorn was reported at 8.2%, and at 2% for white pepper (Pafumi, 1986).

Analysis of spices imported into NZ found 1 out of 197 (0.5%) samples of peppercorns positive for *Salmonella* and 16 out of 328 paprika (4.9%) (Hudson and Hasell, 1998).

Analysis of Australian import data shows a similar failure rate to that of the NZ data, with 1.6% of all pepper and 4.5% of all paprika tested for *Salmonella* in the IFP, not meeting the specified requirements (Table 1). However, current sampling regimes may not detect all *Salmonella* positive shipments. Sampling and testing regimes cannot detect low levels of contamination with a high degree of confidence. In addition, Salmonellae are not homogeneously distributed throughout a food. Shipments of spices can be sourced from a number of different spice manufactures, and therefore shipments may also not be homogenous.



**Table 1.** *Salmonella* test results for spices in the risk surveillance category from 1995 – 1999.

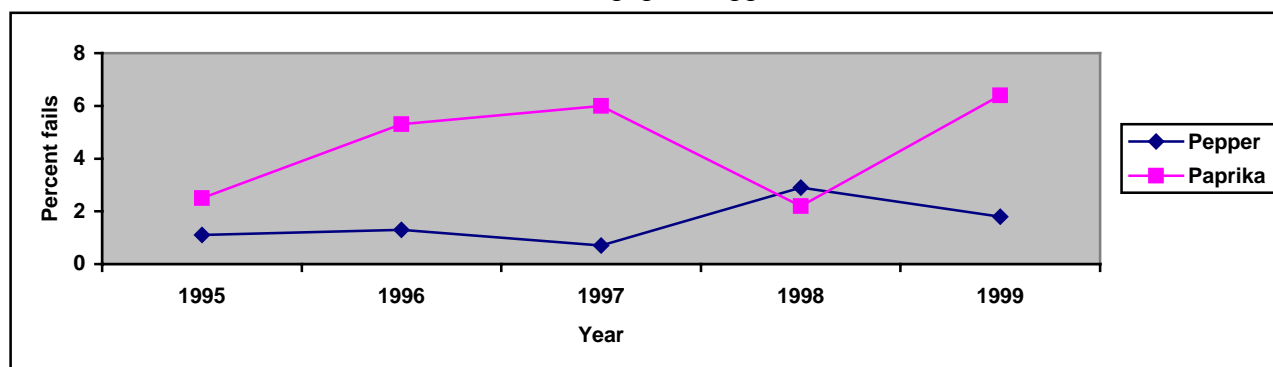
Spice	Failed tests	Passed tests	Total tests	Percent fails
Cinnamon	0	102	102	0
Paprika	15	320	335	4.5
Pepper	26	1558	1584	1.6
All spices	41	1980	2021	2.0

Testing of spices in the random surveillance category for high levels of coliforms has recently changed to the testing for *Salmonella* only. Spices tested at the random surveillance level (that is 5% of all shipments) under the Australian IFP include peppers (capsicum and pimento), vanilla, cinnamon, cloves and nutmeg. These spices were previously only tested for high levels of coliforms, but some testing for the presence of *Salmonella* has occurred. The results in Table 2 show that there were no failures for high levels of coliforms from 147 tests, but *Salmonella* testing yielded failures in 2.7% of pimento and chilli and 1.9% of other spice samples (including vanilla, cloves, nutmeg, coriander, cumin, curry and basil seed).

**Table 2.** Coliform and *Salmonella* test results for spices in the random surveillance category from 1999 – January 2001.

Test	Spice	Failed tests	Passed tests	Total tests	Percent fails
Coliforms	Pimento or chilli	0	13	13	0
	Spice	0	134	134	0
	All spices	0	147	147	0
Salmonella	Pimento or chilli	6	214	220	2.7
	Spice	6	307	313	1.9
	All spices	12	521	533	2.3

Analysis of IFP data for *Salmonella* failures of pepper and paprika for the years 1995 to 1999 is represented in Figure 1. Overall, *Salmonella* failure rates for pepper have remained consistent, whereas *Salmonella* failure rates for paprika appears to be variable.



**Figure 1:** Failure rates for *Salmonella* 1997 – 1999 for pepper and paprika

Surveys conducted elsewhere have found significant levels of *Salmonella* in spices, in particular peppers and paprika (D'Aoust, 1994).

Contamination can occur during the harvesting, drying and preparation of spices. Complete control of these contamination sources is often difficult given the conditions under which they are harvested and dried.

Dried teas and herbs are an increasing feature of the Australian and New Zealand scene. *Salmonella* and faecal coliforms are frequently isolated world-wide from plant material intended for production of infusions. *Salmonella* have been isolated from herbal teas and other plant materials used for infusing increasingly in recent years as the range of plant materials being marketed in this category increases. Harvesting and drying of these plants may be undertaken as a cottage or peasant industry allowing *Salmonella* contamination to occur.

#### **4. Exposure assessment**

Herbs and spices may be incorporated into processed foods or may be added to food as an ingredient, condiment or made into an infusion in the home. While in many cases the food or infusion will be subjected to sufficient heat to inactivate the microbial hazards present, in some circumstances the bacteria may survive. Where bacteria are not inactivated, their continued survival and potential to cause illness will depend on subsequent conditions relating to the food matrix and storage conditions, in particular moisture and temperature.

Spores from either *B. cereus* or *Cl. perfringens* may survive the cooking temperatures and will grow in many foods at temperatures between 3 and 50°C. Spices harbouring these spores must be considered as a potential health hazard if the foods in which the spices are added are not properly prepared and handled.

The presence of *Salmonella* is of concern when spices are used on foods that are consumed raw, or when they are added to foods after cooking such as a garnish or condiments.

Tea and herb infusion are consumed on a regular basis by adults.

Results of the Australian National Nutrition Survey (1995) (Appendix) for the consumption of herbs and spices showed that a relatively low proportion of people surveyed consumed the food group.

Consumption data does not identify where herbs and spices are incorporated into other foods, therefore the validity of this data is limited.

#### Decontamination treatments

Spices have frequently been treated to reduce microbiological contamination. Until recently, the most widely used method to destroy microorganisms in dry food ingredients was fumigation, i.e. treatment with ethylene oxide (ETO).

Irradiation, at a variety of dose levels, has been shown to significantly reduce levels of micro-organisms present on herbs and spices (ANZFA, 2001). In addition, irradiation has been shown to be more effective than ethylene oxide at reducing microbial populations on herbs and spices (ANZFA, 2001).

Other decontamination methods include hot ethanol vapour, however, this is not suitable for treating ground or leafy spices. Another chemical method of treatment is hydrochloric acid. This reduces the viable cell count by acidifying the product, which is then followed by neutralisation. However, such a procedure is only applicable over a very limited range of conditions and for few commodities. Microwave treatment has had little practical utility as heating is seriously hampered in the presence of low moisture content (ICMSF, 1998).

Steam sterilisation, utilising superheated steam, can be used for spice seeds, but is less useful for leafy herbs which lose flavour and colour, and ground products such as onion and garlic which cake and must be re-milled (ICMSF, 1998).

In general, treatments that result in large reductions to viable cell counts also result in serious losses to the sensory or functional properties of products. Therefore, the modern heat processing methods are only suitable for treating herbs and spices when there is slight to moderate degrees of contamination with micro-organisms.(ICMSF, 1998). The problem of highly contaminated natural spices cannot be addressed simply through end-product decontamination processes. A combination of preventative hygiene control measures at the production level, and end-product treatments is needed.

## **5. Risk characterisation**

- *Microbiological*

While levels of *Salmonella* naturally contaminating plant foods may be low, the infectious dose of some strains may be only a few bacteria, particularly when incorporated into a high fat food that may allow survival of the pathogen. Conditions may also exist prior to consumption of the food that allow resuscitation of bacteria which may lead to significant increases in bacterial numbers. The latter may also occur with *Bacillus* spores, but in this case bacterial numbers will need to increase to much higher numbers, in the order of  $10^6$ . In most circumstances toxin production will also need to occur before these microbes present a hazard.

Some spices have been linked to food poisoning as a result of contamination with *Bacillus* sp.. However these reports are infrequent and have often been associated with time and/or temperature abuse following incorporation of the spices into a meal being freshly prepared in the home or by the food service industry. No major outbreaks associated with a processed food have been identified. Although *Cl. perfringens* has been documented as a contaminant of spices, food poisoning as a result of this pathogen has not been associated with spices.

There thus appears to be only a low risk posed by *Cl. perfringens* and *Bacillus* sp. contamination of dried spices. The risk is most appropriately managed by food processors excluding materials with high spore counts from their processes through ingredient specifications and by management of post-processing cooling steps, which if too slow will allow any surviving spores to germinate.

There have been some *Salmonella* outbreaks associated with dried spices. The most hazardous spices appear to be pepper and paprika. Two major outbreaks of salmonellosis have been implicated with pepper (ICMSF, 1998). Pepper is commonly consumed raw as a condiment without further cooking and may also be added as a garnish to foods stored for longer periods.

There have been no major reported outbreaks of food borne disease linked to herbs. However, due to the similar growing conditions and processing of herbs and spices, the risk of contamination could be similar, although the evidence is not apparent.

## **CONCLUSIONS AND PROPOSED RECOMMENDATIONS**

The risks to human health and safety resulting from the possible association of pathogens with herbs and spices falls into several classes. Firstly, the assessment demonstrates that spices can sometimes have a high incidence of microbial contamination. It is likely that herbs will sometimes also be contaminated with microorganisms, because of the similarity of growing and processing conditions for herbs and spices. However, there is limited evidence to verify this assumption.

If the herbs and spices are included in a food product prior to a cooking or other high heat processing step, then even contaminated herbs and spices do not pose a risk to public health and safety. This type of heat treatment kills potential pathogens.

However, the risk associated with herbs and spices is potentially higher in those cases of addition to food that does not undergo further processing and/or are consumed without cooking or high heat treatment. In these cases, the microorganisms associated with the herbs and spices may proliferate, and then may pose a risk to public health and safety. However, the risks vary significantly between foods that provide different environments for growth of various microorganisms and because of the different impacts of various processing steps adopted. Therefore, not all foods in this category can be considered to be 'at risk' because of the addition of herbs and spices. However, there will be some 'at risk' foods that, in the absence of a suitable treatment for herbs and spices should either; be withdrawn from the food supply; require changes in processing procedures to incorporate a suitable 'kill' step; or require changes in reformulation.

The risks posed by different pathogens also vary. There is evidence to demonstrate that for two potential spore forming pathogens (*Clostridium* and *Bacillus* spp), the public health risk is relatively low. The risk posed by these pathogens is best managed by food processors excluding significantly contaminated material through ingredient specification and by the appropriate management of post processing cooling steps. A third pathogen (*Salmonella*) has been mostly associated with specific dried spices (eg pepper and paprika). These spices, and particularly pepper, are often consumed raw as a condiment without a heat treatment. This group of spices pose the highest risk, if used without a heat treatment.

A number of factors reduce the risk posed by untreated, but potentially contaminated herbs and spices. First, the current microbiological requirements and the high frequency testing requirements for imported products for *Salmonella* in pepper, paprika and cinnamon ensure that the risk to public health and safety from this organism is kept to a minimum. However, it is recognised that end product testing can be an insensitive tool for the detection of low level contamination.

Second, the use of HACCP in the production, transport and handling of herbs and spices plays a major role in reducing levels of contamination. It is recognised internationally that appropriate procedures should be in place to protect raw herbs and spices from contamination by human, animal and other waste. The international standard setting body, the Codex Alimentarius Commission, has developed guidance for the production, harvesting and handling of herbs and spices under hygienic conditions. Further reduction in contamination can be achieved through good manufacturing practice.

Third, herbs and spices are used in very small quantities in individual products. It is notable that the levels are so small that they are not recorded in ANZFA's database of food recipes, limiting ANZFA's ability to estimate dietary intake and more accurately estimate the risk posed by potential contaminants. The dose required to cause disease in most cases will be high, therefore, although herbs and spices may be contaminated with a particular microorganism, this may not occur at a sufficient level, nor have the appropriate virulence factors to cause disease.

Finally, it is noted that chemical decontamination processes have been banned in some countries, including the European Union and Japan, for many years. There is no documented evidence to suggest that this has led to an increase in food borne illness from herbs and spices in these countries.

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## PATHOGEN DESCRIPTIONS

### *B. cereus*

*B. cereus* is widely distributed in nature, being readily isolated from soil, dust, cereal crops, vegetation, animal hair, fresh water and sediments. It forms spores and can therefore survive most stages of food processing except severe heat treatment. When present in foods, *B. cereus* is usually at concentrations of  $<10^3/g$ . However, the minimum infective dose has been found to be  $>10^5/g$  and cell density only reaches these numbers under time/temperature abuse. Most documented reports of *B. cereus* intoxication have involved a cereal, or cereal- or spice-containing product as the food vehicle.

There are two types of *B. cereus*-mediated intoxication. The first is characterised by diarrhoea after the ingestion of large numbers of cells or toxin. The diarrhoea is not severe and recovery typically occurs within 24 h. The second type of infection is characterised by emesis (vomiting) after ingestion of toxin and again is not serious and recovery occurs within 12 - 24 h. Neither form of illness is threatening to normal healthy patients. The two disease forms are caused by two significantly different enterotoxins the diarrhoeagenic toxin and the emetic toxin.

Different strains of *B. cereus* vary in their growth and survival characteristics, with some being psychrotrophic and some being mesophilic. In general, growth does not occur below pH 4.8 (HCl as acidulant) or pH 5.6 (lactic acid as acidulant), or below an  $a_w$  of 0.92 - 0.93 (NaCl as humectant). The heat resistance of *B. cereus* spores is similar to that of most mesophilic spore-forming bacteria.

### *Clostridium perfringens*

*C. perfringens* is widely distributed in soil, vegetation and raw, dehydrated and cooked food and is part of the normal intestinal flora of humans and animals.

Food poisoning from *C. perfringens* leads to symptoms of abdominal pain, nausea and acute diarrhoea up to 24 h after ingestion of large numbers of the organism. The illness is usually of short duration and it is normal for full recovery to occur within 24 - 48 h. *C. perfringens* is grouped into five types (A - E) according to the exotoxins (soluble antigens) produced. Types A, C, and D are human pathogens, while types B, C, D and possibly A are pathogens in animals. Types A and C also produce an enterotoxin which is the cause of the acute diarrhoea that is the main symptom of *C. perfringens* food poisoning. Type A strains are responsible for gas gangrene, while type C strains are responsible for the disease enteritis necroticans jejunitis ('pig-bel').

This organism produces spores which vary in their heat resistance. Those spores which are highly heat resistant will be more likely to cause food poisoning due to survival and outgrowth during and after cooking. The food vehicles are usually cooked meat and poultry dishes stored after cooking for long periods of time at ambient temperature.

Outgrowth of spores commonly occurs after the heat shock encountered during cooking and is favoured in anaerobic microenvironments within the food. Vegetative cells will not grow below 12°C, below pH 5.5 or below an  $a_w$  of 0.93.

### **EHEC *eg. E. coli* O157:H7**

The reservoir for *E. coli* O157:H7 has not been definitively identified, but major outbreaks in the US, UK and Canada have occurred as a result of consumption of undercooked ground beef and to a lesser extent, drinking raw milk. Other outbreaks have been linked to foods as diverse as potatoes; ham, turkey and cheese sandwiches; drinking water and acidic foods such as apple cider and mayonnaise. Surveys of food in the US have found very low incidences of *E. coli* O157:H7 in retail ground beef (3%) and pork and poultry (1 - 2%).

All clinical isolates produce one or two verotoxins which are thought to be important virulent factors in mediation of disease. EHEC colonise the intestinal tract and then elaborate verotoxin(s) which are active in the colon. The disease-defining symptom of EHEC is haemorrhagic colitis (HC) (bloody diarrhoea). Several severe life-threatening complications of HC can occur, of which haemolytic uraemic syndrome (HUS) is the most common. Occurring most often in children under the age of 10, this complication arises approximately a week after the onset of gastrointestinal symptoms and is characterised by microangiopathic haemolytic anaemia (intravascular destruction of red blood cells), thrombocytopenia (lowered platelet counts), oligo-anuria (lack of urine formation), oedema (swelling) and acute renal failure. Over half of HUS patients require dialysis and the mortality rate is 3-5%.

*E. coli* O157:H7 grows in the temperature range 8 - 45°C and survives well at refrigeration temperatures. It will grow at pH 4.5 in a medium adjusted with HCl but not in fermented cheeses at pH  $\leq$  5.4. It will grow in broth containing 6.5% NaCl ( $a_w = 0.957$ ) but not 8.5% NaCl ( $a_w = 0.943$ ).

### **Salmonellae**

Salmonellae are found worldwide and are considered to be zoonotic organisms. Several animal reservoirs have been identified and many foods, mostly of animal origin or those subject to sewage pollution, have been responsible for transmission of salmonellae to humans. Food, feeds and water are the primary vehicles, but salmonellae can also become established and multiply in the environment and equipment of food-processing plants.

A few serovars (*eg. S. typhi*, *S. paratyphi* A and C) are host-adapted to humans and cause a septicaemia-typhoidal syndrome. The other serovars (*eg. S. typhimurium*, *S. enteritidis*, *S. heidelberg*, *S. infantis*) cause gastroenteritis in humans, mostly through the ingestion of contaminated foods. Typhoid fever is quite common in developing countries, whereas *Salmonella*-caused gastroenteritis is among the leading causes of food-borne morbidity in developed countries. Salmonellae cause disease by invading regions of the intestine, leading to an inflammatory reaction. Invasive strains (*eg. S. typhi*) invade individual cells which can lead to septicaemia. The infective dose is usually relatively high at  $>10^5$ , but can be lower ( $<100/g$ ) when the food vehicle is a fatty or buffered product allowing passage through the acidic environment of the stomach.



The temperature range for growth is 5.2 - 46.2°C (however, most serotypes fail to grow below 7°C), the pH range is approximately 3.8 - 9.5 and growth occurs at an  $a_w$  as low as 0.94. Freezing is detrimental to salmonellae but does not guarantee destruction of cells in food. Salmonellae survive particularly well in very dry foods over a wide range of temperatures and on surfaces such as ceramic, glass and stainless steel and on human skin.

### ***Staphylococcus aureus*/SET**

*S. aureus* is ubiquitous and occurs in the mucous membranes and skin of most warm-blooded animals, including all food animals. At any one time, up to 50% of humans will be carriers of this organism. It is resistant to drying and can colonise moist areas on food-processing equipment and dust in ventilation systems. Staphylococcal food poisoning occurs most frequently when a cooked food is contaminated by a colonised person and then the food is kept warm for several hours. Examples of foods implicated in food poisoning are cream-filled bakery products, cooked meats (*eg.* ham) and shellfish. If cheeses and salamis do not ferment correctly they can allow *S. aureus* to proliferate and form toxins during maturation.

*S. aureus* is an opportunistic pathogen and causes infection via open wounds or when the host's physiology is altered (*eg.* hormone imbalance). *S. aureus* forms a wide range of substances associated with infectivity and disease, including the enter toxins that cause food poisoning. Seven antigenic types of staphylococcal enterotoxins are currently recognised, with types A and D being involved in most food poisoning outbreaks. The toxins are thought to stimulate neuroreceptors in the intestinal tract which trigger the vomiting centre of the brain. It is generally agreed that enterotoxin in the range 0.1 - 1.0 µg/kg will cause illness in a human.

The temperature range for growth is 7 - 48°C, the minimum  $a_w$  for growth is as low as 0.85 and the pH range for growth is 4 - 10. The temperature range for toxin production is 10 - 48°C, the pH range is 4.5 - 9.6 and toxin production occurs at an  $a_w$  as low as 0.87. The organism is readily destroyed by cooking or pasteurisation of food, but the toxins are very heat resistant and may survive the heat treatment used to sterilise low-acid canned foods.

## APPENDIX 2

### Average daily consumption of herbs and spices by sex and age (National Nutrition Survey, 1995)

Sex	Age (years)	No. consumers surveyed	No. consuming herbs and spices (% of no. surveyed)	Average amount of herbs and spices eaten per day (g)
Male	2-3	170	1 (0.6)	1.0
Male	4-7	416	3 (0.7)	11.3
Male	8-11	385	-	-
Male	12-15	349	-	-
Male	16-18	215	2 (0.9)	9.7
Male	19-24	485	3 (0.6)	5.4
Male	25-44	2140	19 (0.9)	12.7
Male	45-64	1554	23 (1.5)	15.6
Male	65+	902	18 (2.0)	6.5
Female	2-3	213	2 (0.9)	0.26
Female	4-7	383	1 (0.3)	0.24
Female	8-11	354	-	-
Female	12-15	304	-	-
Female	16-18	218	-	-
Female	19-24	575	2 (0.3)	5.9
Female	25-44	2385	34 (1.4)	12.4
Female	45-64	1752	38 (2.2)	11.2
Female	65+	1058	17 (1.6)	10.2

# **Cancer Risk Assessment of Ethylene Oxide Residues in New Zealand Spices**

A Report Produced for the New Zealand Ministry of Health

December 1999

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Prepared as part of a Ministry of Health  
contract for scientific services

by

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December 1999

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## Executive Summary

This report provides an estimate for the potential cancer risk associated with the presence of ethylene oxide (ETO) residues and its breakdown products in dry spices in New Zealand. The cancer risks were calculated using reported analytical measurements of ETO, ethylene chlorohydrin (ECH) and ethylene bromohydrin (EBH) in retail samples of various spices in New Zealand. Spice consumption estimates were derived using New Zealand Customs annual importation data for black pepper, cinnamon/cassia, paprika, nutmeg, and chilli powder as a conservative measure of per capita intake of these spices. These spices were chosen as they are often not cooked before being consumed. Using this information, a conservative upper-end intake of ETO is estimated to be  $3.4 \times 10^{-6}$  mg/kg/d. This estimate would be expected to decrease as the proportion of these spices that are cooked increases. An oral cancer potency factor of  $0.55 \text{ (mg/kg/d)}^{-1}$  for ETO was derived using the linearised multistage model from a chronic oral cancer study on ETO in rats. A published potency factor of  $0.29 \text{ (mg/kg/d)}^{-1}$  based on an inhalation study was also used. The use of these potency factors with estimated ETO intakes gave upper-end lifetime cancer risk estimates for a consumer beginning at  $1 \times 10^{-6}$  (1 in a million). High intake estimates for spices in NZ were not found, but the 97.5% intake for spice consumption in the U.S. is reported to be about 6.3-fold higher than the estimated average NZ spice consumption. This could mean that the worst-case estimate of lifetime cancer risk from ETO in spices is about  $1 \times 10^{-5}$  (10 in a million), but would be much lower for the average consumer. Cancer risks to ETO fumigants are not addressed in this report.

The estimated upper-end of the range of consumption of ECH and EBH from the monitoring results is  $7.4 \times 10^{-4}$  and  $5.8 \times 10^{-5}$  mg/kg/d, respectively. Exposure to these compounds is considerably higher (200-300 fold on average) than to ETO itself. It is apparent that ECH and EBH occur in significant quantities in spices and persist long after fumigation. However, the contribution to any potential cancer risk from EBH and ECH is unknown due to a lack of adequate toxicity data on these compounds. The evidence for carcinogenicity and *in vivo* mutagenicity of ECH is conflicting or negative. For EBH, one animal study showed a significant increase in stomach tumours following oral exposure. However, even if this result were sufficient evidence of carcinogenicity in animals, the potency factor from the study is  $3.0 \times 10^{-2} \text{ (mg/kg/d)}^{-1}$ , which would yield a cancer risk less than that posed by ETO given the current monitoring results.

The spices currently surveyed were all compliant with the current regulatory limit (MRL) for ETO in the NZ Food Notice of 1999 of 50 ppm. Only two samples of cinnamon out of 22 sampled were detectable at the limit of detection of 2 ppm. The highest value encountered was 15 ppm in one sample. The exposures and cancer risks to average consumers from ETO are extremely small and are unlikely to be significant even using the conservative assumptions in this report. On the other hand, it appears that if an MRL for ETO is to be retained, it may be unnecessary to keep the MRL at the current 50 ppm level as it is evident that the MRL could be reduced without any impact to the spice industry. Additionally, ETO is a known human carcinogen, and any exposures, no matter how slight, should be reduced in the food supply by using Good Manufacturing Practices. These points support a reduction in the MRL for ETO.

As with ETO, it does not appear that the breakdown products, ECH and EBH, pose significant cancer risks, given the current toxicological data. However, it should be emphasised that there are large data gaps, including the absence of a 2-year cancer bioassay by the oral route of exposure for ECH, and further studies should also be done on EBH to ascertain the nature and degree of hazards posed by these chemicals at chronic low level exposures.

### **Recommendations**

It is recommended the New Zealand Ministry of Health:

1. Acknowledge that the current monitoring and risk assessment has indicated that there is negligible cancer risk to both upper-end and worst-case scenario consumers associated with ETO residues in spices.
2. Acknowledge that there are no known significant cancer risks associated with consumption of ECH or EBH at the levels found in retail spices. Neither compound is a known carcinogen. However there is a significant degree of scientific uncertainty in this advice as some key toxicological studies have not been done for these compounds.
3. Consider lowering the current temporary MRL for ETO in spices from 50 ppm to 20 ppm, as it appears this level is unnecessarily high, and because ETO residues should be kept at current levels or lower if practically achievable.
4. Maintain a watching brief on chronic oral toxicity studies or international toxicological assessments on ECH and EBH, particularly those relating to mutagenicity or carcinogenicity.

## 1 Background

Ethylene oxide (ETO) is considered by the International Agency for Research on Cancer (IARC) to be a human carcinogen (IARC, 1994). As a fumigant, ETO gas is currently used as a way to disinfect spices potentially contaminated with pathogenic bacteria, such as salmonella, in New Zealand, the United States, and Canada. However, in Europe, ETO is banned as a food fumigant due to concerns of the potential toxicological risks to workers and consumers. Many countries permit irradiation as an alternative treatment to ETO fumigation of spices.

On the 21 April 1998, the New Zealand Government put in place a Food Notice allowing the presence of ETO residues in spices up to a maximum residue limit (MRL) of 50 ppm for a period of 12 months. As part of the condition of the Food Notice, the Minister of Health agreed to allow the Ministry of Health to undertake an assessment of the potential risks from ETO residues in spices. The purpose of the Food Notice was to legalise the practise of ETO fumigation until sufficient data on exposures could be collected and assessed. These data were critical in determining if current residual levels of ETO present a significant risk to public health, and to allow a scientific assessment to form a basis for the determination of any MRL in the event of a future food standard for ETO. Delays in obtaining the analytical data resulted in a second Food Notice in 1999.

The US has an MRL for ETO of 50 ppm (40 CFR 180, 1997), however the scientific basis for this MRL was not found. Communications with staff at the US Environmental Protection Agency (USEPA) have indicated that the permission for ETO is unlikely to undergo further assessment for several years under the U.S. Food Quality Protection Act due to the volume of evaluations being currently undertaken (Dr Lisa Niesensen, OPTS; personal communication, 1999). Canadian legislation contains a permission for the breakdown product, ECH (or 2-chloroethanol) of 1500 ppm in spices. The basis for this MRL is unknown, however, both MRLs from the US and Canada correspond to residual levels of these compounds in spices following fumigation studies done by the American Spice Trade Association (ASTA) for the USEPA (USEPA 1988; 1996). There are no regulatory limits internationally for ethylene bromohydrin (EBH) in foods.

The prevailing view among the USEPA and the World Health Organisation (WHO) has been that the contribution of any cancer risk from the consumption of low levels of ETO residues in spices is unlikely to be significant due to the relatively small exposures involved (WHO 1985; USEPA 1996).

A report conducted by ESR in 1994 found that a significant proportion of spices entering New Zealand was treated with ETO. A more recent report in 1999 indicates that the proportion of spices treated with ETO has decreased since 1994, but chemical residues of ethylene chlorohydrin (ECH) and ethylene bromohydrin (EBH) can still be found in a considerable proportion of some retail spices, and these levels can be quite high (e.g. over 1300 ppm for ECH and up to 55 ppm for EBH).

## 2 Hazard Assessment of ETO, ECH, and EBH

The status of ETO was upgraded by the IARC from Group 2A to Group 1 (*carcinogenic in humans*) in 1994 due to increasing epidemiological and occupational evidence of carcinogenicity and laboratory genetic toxicity studies showing that ETO was a genotoxic carcinogen capable of causing tumours in both animals and humans. The evidence of carcinogenicity in laboratory animals comes largely from inhalation studies (Snellings *et al.*, 1984; NTP 1985), but the designation by IARC is not qualified by the route of exposure. Furthermore, oral exposure data in laboratory animals have yielded stomach and systemic tumours (Dunkelberg, 1982). It is therefore assumed, for the purposes of this risk assessment, that ETO is a human carcinogen by ingestion. Structurally similar chemicals such as formaldehyde and propylene oxide (PO) are also probable human carcinogens. When comparing the potency of ETO in laboratory animals and human epidemiological studies, the State of California and the USEPA concluded that the potency of ETO was comparable in animals and humans (California Air Resources Board (CARB), 1987). The USEPA and the State of California have designated ETO a carcinogen and ETO air emissions by facilities are subject to tight regulatory controls.

Chemically similar compounds have also been shown to be carcinogens. Propylene oxide is structurally similar to ETO and is considered a B2 carcinogen (*probably carcinogenic in humans*) by the USEPA. The USEPA have calculated both inhalation and oral cancer potency factors from animal studies on PO (USEPA IRIS database, 1999). The oral cancer potency factor for PO is derived from the study in rats by Dunkelberg (1982), and is based on a dose-dependent increased incidence of forestomach tumours. Formaldehyde is also a probable human carcinogen.

Laboratory bioassays have shown lymphoid, mesothelial, subcutaneous, pituitary, and brain tumours to occur in rats exposed to ETO by inhalation (Snellings *et al.*, 1981, 1984; Lynch *et al.*, 1984), and forestomach squamous cell carcinomas and fibrosarcomas upon oral exposure in rats (Dunkelberg, 1982). Inhalation studies in mice have shown a significantly elevated incidence of lung tumours in males and females as well as an increase in uterine and mammary tumours in females (NTP, 1986). Laboratory studies have shown that ETO is absorbed efficiently by animals upon inhalation (WHO, 1985). Studies on the oral absorption of ETO are not available and the kinetics of breakdown of ETO in the gastrointestinal tract are not known. It is reasonable to assume that the stomach lining, as a point of first contact would be a tissue at risk for developing cancer from ETO exposure.

In a review of the toxicological literature on ETO, all but one of the animal studies involved an inhalation exposure. However, the tumours observed were frequently systemic in nature. Therefore, ETO is likely to be well absorbed, resulting in target tissue effects beyond the portal of entry.

A wide range of *in vitro* studies have demonstrated that ETO is a powerful mutagen in mammalian cells, as well as in bacteria, plants, and fungi (WHO, 1985; IARC, 1994).

Ethylene oxide also has a wide variety of non-cancer health effects in animals when inhaled in high concentrations, including reproductive and developmental toxicity and toxicity to various parts of the lung (CARB, 1987). These effects occur at levels many orders of magnitude higher than would be encountered from residues typically found in foods.

## 2.1 *Epidemiological data*

Epidemiological studies have shown positive associations between ETO exposures and lymphatic and haematopoietic cancer incidence in hospital workers that sterilised hospital equipment with ETO (Hogstedt *et al.*, 1986; Bisenti *et al.*, 1993). Similar elevations in rates of these types of cancers are seen in chemical workers in manufacturing or otherwise using ETO (IARC, 1994).

## 2.2 *Breakdown products*

Most of the ETO residues react with available chloride or bromide to form 2-chloroethanol (ethylene chlorohydrin; ECH) or 2-bromoethanol (ethylene bromohydrin; EBH), the toxicity of which are not well characterised in terms of long term studies of cancer risk. Other breakdown products include ethylene glycol, chloroacetaldehyde, and chloroacetic acid.

One long term animal study on EBH was located. Male and female B6C3F1 mice (29 each) were exposed to 75 mg/kg/day in distilled drinking water for 1.5 years (Van Duuren *et al.*, 1985). Squamous papillomas of the stomach were found in 10 females and 9 males. Two stomach papillomas were reported in the 95 control animals. No significant incidence of tumours were reported at any other site. A single long term animal study on ECH was carried out by the National Toxicology Program (NTP) in 1985. This study exposed rats and mice for 2 years by the dermal route and found no evidence of carcinogenicity. However, the only study on carcinogenicity of ECH by the oral route was the study by Johnson (1967) in which 4 groups of 6 rats were given 0, 4, 8, or 16 mg/kg ECH in drinking water for 2 years without any apparent gross or histological effects. This study would not be considered adequate for the purposes of measuring carcinogenicity of ECH.

A comparison of the mutagenicity of ECH and ETO shows that, as an *in vitro* mutagen, ECH is approximately 20-fold less mutagenic than ETO at the same dose levels in bacteria (Pfeiffer and Dunkelberg, 1980). The NTP (1985) reviewed the literature on the mutagenicity of ECH and concluded there was evidence of mutagenicity in bacterial and non-mammalian eukaryotes. The evidence for mutagenicity of ECH in mammalian systems is less clear. Storer and Connolly (1985) found no evidence of DNA damage in livers of mice injected *i.p.* with high doses of ECH. In *in vitro* mammalian cell test systems, ECH tested positive for inducing unscheduled DNA synthesis in human fibroblasts (Stich *et al.*, 1976) and caused chromosomal aberrations in rat bone marrow cells (Isakova *et al.*, 1971). Similarly, reverse mutations and chromosome aberrations were reported in mammalian cells in the presence of the metabolising S9 fraction of liver homogenate (McGregor *et al.*, 1988; Ivett *et al.*, 1989). However, three studies of different aspects of mammalian cell mutagenicity were negative (Epstein *et al.*, 1972; Conan *et al.*, 1979; Sheu *et al.*, 1983). Under aqueous conditions or in the presence of liver metabolising enzymes, ECH is oxidised to 2-chloroacetaldehyde and ultimately to 2-chloroacetic acid. The NTP (1985) have concluded that ECH is a weak mutagen but that its oxidised metabolic product, 2-chloroacetaldehyde, is a strong mutagen.

There is evidence from oral gavage studies that ECH and EBH react with fatty acids to form fatty acid conjugates that can be measured in the liver several days after treatment (Kaphalia and Ansari, 1989).

There is some evidence that chlorohydrin exposure in occupational settings is carcinogenic. Benson and Teta (1993) found significant increases in pancreatic, lymphopoietic and haematopoietic cancers in 278 workers assigned to ethylene and propylene chlorohydrin production units for a mean duration of 5.9 years, with a mean follow up of 36.5 years. A subsequent study (Olsen *et al.*, 1997) found no significant increases in cancers in 1361 workers in a similar work setting, but the duration of exposure in this latter study included people with just 30 days or more workplace experience.

### **3 Dose Response Assessment**

There were three studies available for calculation of a cancer potency factor (CPF) for ETO (Dunkelberg 1982; Snellings *et al.*, 1984; NTP 1985). The 2-year inhalation study in rats by Snellings *et al.* (1981; 1984) was used by the United States Environmental Protection Agency (USEPA) and the State of California (CARB, 1987) to derive inhalation and oral CPFs for ETO. The 2-year gavage study in rats by Dunkelberg (1982) is the only study to assess effects of oral exposure to ETO. The calculations of CPFs from the Snellings *et al.* (1984) and Dunkelberg (1982) studies are provided in this risk assessment. For both studies the dosages, tumour type, and tumour incidence are presented in Tables 1a, 1b, and 1c. The results of the Snellings *et al.* (1981; 1984) studies have been reported by several sources and have been critically analysed by various agencies. Table 1a shows the mononuclear cell leukaemia incidence in experimental rats reported by the USEPA (1985) and later by the State of California (CARB, 1987), the incidence reported by the World Health Organization (1985), and the incidence reported in a paper by Snellings *et al.* (1984). The Snellings *et al.* (1981) study examined the “time to tumour” occurrence in rats through use of interim sacrifices. The number of rats used in the cancer potency analyses varied depending on the assumptions made about the contribution of negative findings at the interim sacrifice. The USEPA and CARB chose not to include negative findings at interim sacrifice as indicating true negative results as these rats could have been at risk for developing tumours later in the study, whereas WHO included all rats throughout the study in the denominator. Snellings *et al.* published part of their studies in a 1984 paper, which is also publicly available. All sources were in agreement that mononuclear cell leukaemia in female rats was the most sensitive cancer endpoint with ETO inhalation.

**Table 1a Mononuclear cell leukaemia in female Fischer-344 rats exposed to ETO by inhalation 5 days/week for 25 months (Snellings *et al.*, 1981, 1984)**

Exposure Dose (rat)		Equivalent human lifetime dose (mg/kg/day) <sup>b</sup>	Leukaemia incidence Reported by:		
(ppm)	(mg/kg/day) <sup>a</sup>		USEPA (1985)	WHO (1985)	Snellings <i>et al.</i> (1984)
0	0	0	22/186 <sup>c</sup>	22/235 <sup>d</sup>	11/115 <sup>e</sup>
10	2.7	0.28 (0.46)	14/71	14/77	11/54
33	5.12	0.75 (0.86)	24/72	24/79	14/48
100	20.24	2.11 (3.42)	28/73	28/113	15/26

<sup>a</sup> Toxicokinetic studies indicated approximate dosages from inhaled concentrations of ETO. A time adjustment of 5/7 was applied to account for the 5 days/week exposure in the rat study

<sup>b</sup> Equivalent human lifetime doses were calculated using the surface area adjustment: dose (human) = dose (animal)/[wt(h)/wt(a)]<sup>1/3</sup>, using 70 kg for average human weight and 0.22 kg for an adult female rat. Doses using body weight to the 3/4 power are shown in parentheses.

<sup>c</sup> Data analysed by United States Environmental Protection Agency - negative tumour results at interim sacrifice (18 months) were not included in the analysis.

<sup>d</sup> Data reported by WHO include all observations, interim and final - including consideration of all negative findings at interim sacrifice as negative findings.

<sup>e</sup> The data in Snellings *et al.* (1984) contains only part of the total Bushy Run study.

**Table 1b Forestomach tumours in rats exposed to ETO by oral gavage (Dunkelberg *et al.*, 1984)**

Exposure (mg/kg)	Equivalent human lifetime dose (mg/kg/day) <sup>a</sup>	Incidence of rat stomach tumours	Systemic tumours
0	0	0/100	40/100
7.5	0.51	8/50 <sup>b</sup>	28/50 <sup>b</sup>
30	2.03	31/50 <sup>b</sup>	29/50 <sup>b</sup>

<sup>a</sup> Equivalent human lifetime doses were calculated using the surface area adjustment: dose (human) = dose (animal)/[wt(h)/wt(a)]<sup>1/4</sup>, using 70 kg for average human weight and 0.22 kg for an adult female rat. A time adjustment of 2/7 was applied to account for the 2 days/week exposure in the rat study.

<sup>b</sup> Significantly greater incidence than controls (p < 0.05, Fisher's Exact Test).

**Table 1c Forestomach tumours in rats exposed to PO by oral gavage (Dunkelberg *et al.*, 1984; cited by USEPA 1999)**

Exposure (mg/kg)	Incidence of rat stomach tumours	Equivalent human lifetime dose (mg/kg/day)	
		USEPA <sup>a</sup>	Cal/EPA <sup>b</sup>
0	0/100	0	0
15	2/50	0.44	0.63
60	19/50	1.76	2.51

<sup>a</sup> USEPA calculated equivalent human lifetime doses using the surface area adjustment: dose (human) = dose (animal)/[wt(h)/wt(a)]<sup>1/3</sup>, using 70 kg for average human weight and 0.35 kg for an adult female rat. A time adjustment of 2/7 was applied to account for the 2 days/week exposure in the rat study.

<sup>b</sup> Using the Cal/EPA default for rat body weight of 0.22 kg rather than the USEPA default of 0.35 kg, which results in a potency estimate of 0.17 vs. that of 0.24.

The inhalation study in mice by NTP (1986) found a significant incidence of lung tumours, malignant lymphoma, uterine adenoma (females), and mammary gland adenocarcinoma (females), but the sample groups were small in comparison to the studies in rats, and only 2 dose groups were studied in addition to controls. For these reasons, the inhalation data from the NTP study are not discussed further in detail.

The oral gavage studies in rats by Dunkelberg are the only long-term oral carcinogenicity studies for ethylene oxide and propylene oxide. The USEPA used the Dunkelberg study in their derivation of an oral potency value for PO, and the data on PO is shown for comparison with the data for ETO in Table 1c. Both compounds induced squamous cell carcinomas in rats at the doses used. Female rats (50 per group, plus 50 vehicle controls and 50 untreated rats) were gavaged twice per week for 150 weeks with ethylene oxide or propylene oxide in salad oil. Doses of ethylene oxide were 0, 7.5, or 30 mg/kg and for propylene oxide, the treatments were 0, 15, or 60 mg/kg. Treatments were temporarily suspended due to a pneumonia outbreak in the test animals. All animals were treated with antibiotics during the interruption period.

There was a similar rate of mortality between treated and control groups at 104 weeks (30%). The tumours observed were primarily squamous cell carcinomas of the forestomach with both chemicals.

### 3.1 Derivation of Cancer Potency Factors (CPFs)

Cancer potencies were calculated using the linearised multistage model originally described by Crump (1984) and Mstage software (Cambridge Environmental, Inc. 1992) for the PC.

$$\text{Linearised multistage model: } P(d) = 1 - e^{-(q_0 + q_1d + q_2d^2 + \dots + q_kd^k)}$$
$$P(0) = 1 - e^{-q_0}$$

where  $P(d)$  is the probability of developing a tumour at a given dose rate and  $P(0)$  is the estimated background incidence. The  $q$  parameters are derived from the model.

Model fit was tested using a chi-square goodness of fit test with  $n-1$  degrees of freedom (where  $n$  is the number of dose groups), and  $p < 0.05$  as the criterion for rejection.

The results of fitting the linear multistage model to these various data sets are shown in Table 2. The State of California (CARB, 1987) extensively reviewed the available literature in their derivation of the oral cancer potency value of  $0.29 \text{ (mg/kg/d)}^{-1}$ . The data used in their calculations came from the Snellings et al., (1981) study. Later, the Cal/EPA revised the CPF to  $0.31 \text{ (mg/kg/d)}^{-1}$ . Recently, a review of interspecies scaling methodologies by USEPA and Cal/EPA have indicated that body weight should be raised to the  $3/4$  power rather than the  $2/3$  power used previously. Although the  $0.29 \text{ (mg/kg/d)}^{-1}$  value was based on the  $2/3$  power scaling, it is not clear if this is also the case for the  $0.31 \text{ (mg/kg/d)}^{-1}$  value.



A reassessment of the 0.29 value using this new scaling factor is provided in Table 2, but is not used in the risk assessment. The derived potency values in this report use the  $\frac{3}{4}$  power scaling factor.

Although the Snellings et al. study involved an inhalation exposure, the tumours observed were systemic in nature. Therefore, the outcome is likely to be relevant to other exposure routes, but would not reflect the potency toward portal of entry tumours for the oral route of exposure.

The data presented by WHO did not meet the Chi-square test for goodness-of-fit criteria and were not used in the current assessment. As indicated in Table 2, the WHO compared the number of animals with tumours to the total number of animals in the study. A more statistically appropriate and health protective assumption used by USEPA is to ignore negative cases at interim sacrifice times. This is because there is no guarantee these animals would not have had some incidence of tumours if they had been allowed to live out their lifespan or to the end of the 25 month study. For these reasons, the data shown in the WHO report are not the most appropriate for determining a cancer potency value.

The results of the Dunkelberg oral study in rats show that ETO has a greater potency than PO for induction of tumours in rats (Table 2). The range of risks from ETO exposure was calculated using the published CPF from USEPA/CARB and also the oral CPF calculated in this assessment from the Dunkelberg study.

**Table 2 Cancer potency values ( $q_1$  and  $q_1^*$ ) in  $(\text{mg/kg/d})^{-1}$  and other multistage model parameters derived from the tumour incidence data in Tables 1a, 1b, and 1c.**

Parameter	Mononuclear cell leukaemia (inhalation)			Forestomach tumours (oral) - ETO	Forestomach tumours (oral) - PO
	CARB (1987)	WHO (1985)	Snellings <i>et al.</i> (1984)	Dunkelberg (1982)	Dunkelberg (1982)
$q_0$	0.14	0.13	0.10	0	0
$q_1$	0.20	0.11	0.35	0.30	0.023
$q_1^*$ (95% UCL)	<b>0.29<sup>a</sup></b> <b>(0.18)</b>	<b>0.17</b>	<b>0.51</b>	0.73 <sup>b</sup> <b>0.55<sup>c</sup></b> 0.36 <sup>d</sup>	<b>0.17</b>
p-value, chi-square goodness of fit test	0.16	0.005 <sup>e</sup>	0.64	1.0	1.0

$q_1^*$  values represent 95% upper confidence limits (UCL) of cancer potency factors in  $(\text{mg/kg/d})^{-1}$

<sup>a</sup> this cancer potency value was derived by the California Air Resources Board in 1987 based on an earlier USEPA (1985) assessment. A revised value of  $0.31 (\text{mg/kg/d})^{-1}$  is currently found on the Cal/EPA OEHHA website at: <http://www.oehha.org>. The 0.18 value represents the same data using the body weight raised to the  $\frac{3}{4}$  power for interspecies scaling, which is the currently accepted default.

<sup>b</sup> Cancer potency including carcinomas, fibrosarcomas, and in-situ carcinomas of the forestomach and stomach.

<sup>c</sup> Cancer potency including carcinomas and fibrosarcomas of the stomach and forestomach. This is the value used as the oral cancer potency estimate for ETO in this risk assessment.

<sup>d</sup> Cancer potency from all systemic tumours distal to the stomach.

<sup>e</sup> the data presented in the WHO monograph do not meet goodness-of-fit requirements for the multistage model. This cancer potency factor was therefore not used in the risk assessment.

## 4 Exposure Assessment

### 4.1 *ETO fumigation prevalence*

A report published by ESR in June 1999 analysed ETO, ECH, and EBH residues in 200 samples of spices purchased off the shelf in stores in New Zealand. Although only 2 samples tested positive (above 2 ppm) for the presence of ETO, ECH residues, which are much more stable than ETO were detected in 31 samples. ECH or EBH residues above 5 ppm were detected in 18 of 80 black pepper samples (23%), 5 of 22 cinnamon/cassia samples (23%), 2 of 13 paprika samples (13%), 1 of 15 curry samples (7%), 0 of 12 chilli powder and 0 of 7 coriander samples, 1 of 1 sample of nutmeg, 1 of 32 (3%) miscellaneous spices including cloves, anise, cardamom and ginger, and 4 of 18 (22%) of various spice mixtures. These figures contrast sharply with a similar survey of NZ spices conducted by ESR in 1994 in which 18/25 (72%) pepper samples, 7/12 (56%) chilli samples, and 3 of 4 (75%) paprika samples contained ECH residues. The use of ETO as a fumigant for spices coming in to NZ has clearly decreased since 1994.

### 4.2 *ETO residues in spices*

Ethylene oxide is a volatile gas and most of the residue dissipates from spices after fumigation. Data from the USEPA (1988; 1996, see Appendix 1) have shown that ETO levels decrease rapidly over the first few days and then more slowly become non-detectable (at 0.1 ppm) by a period of about 2 months. The study by ESR (1999; Table 3b) indicated the levels fell below 5 ppm in fumigated black peppercorns or ground pepper within 14 days. In the survey of retail samples in NZ, 2 of 31 (6.5%) samples known to be treated with ETO still had measurable levels of ETO (above 2 ppm) after an unknown length of time on the shelf (ESR, 1999).

Internationally, the issue of ETO exposures from food have been considered in a qualitative sense, but no risk assessments have been published. The WHO concluded that significant oral exposure of humans to ETO residues from fumigations is unlikely, due to the rapid disappearance of the residues through evaporation and the rapid formation of stable breakdown products (WHO, 1985). Statements have also been made by prominent researchers in toxicology, such as Dr. John Doull, on behalf of the American Spice Trade Association, that it is not valid to conclude there is a cancer risk from minute quantities of ETO in spices, since the exposures to people are more than a million times lower than that used in animal studies (FCN, 1995). However, no published reports were found to substantiate these claims. The NTP (1998) cited a report by the Agency for Toxic Substance and Disease Registry (1990) that found there was no information indicating ETO is a common contaminant in food, but no studies were cited to support this conclusion.

The California Air Resources Board staff report on ethylene oxide (CARB, 1987) contains cited estimates of ETO intake through foods. The National Toxicology Program (NTP, 1985) cited an FDA communication that the "...potential daily intake [of ETO] per person in the United States is estimated to be 10 micrograms" ( $1.6 \times 10^{-4}$  mg/kg/d) (Modderman, 1986; cited in CARB, 1987). This estimate apparently included dietary intakes from all other sources, such as packaging materials (ethylene oxide polymers) and food additives (polysorbate emulsifiers). The proportion of this intake coming from spices was not given. The worst case exposure estimate given was as high as 19 micrograms per person, which is about 1000-fold below the daily dose causing 16% added incidence of tumours in rats.

Data from the USEPA and ESR indicate that the vast majority of the stable residues found in fumigated spices are in the form of ECH or EBH (USEPA, 1996; ESR, 1999). In the current assessment, the available data on ETO residues in retail spices was used to estimate the daily dietary exposure associated with consuming spices fumigated with ETO (Table 3). The USEPA residue data are provided for comparison (Table 4).

#### 4.3 Assumptions used with limit of detection (LOD)

In reports of residual levels of contaminants in foods, such as in the New Zealand Total Diet Survey, a conventional assumption is that analytical results that are below the LOD are assigned a value of zero in the case of contaminants that are not reasonably anticipated to occur in the sample. Alternatively, results are assigned a value of ½ LOD in the case of contaminants that are either ubiquitous in the environment or are reasonably anticipated to occur in that sample. For the purposes of the current risk assessment, the presence of residual levels of ECH was taken to be an indicator of an ETO fumigation event. Therefore, samples that had measurable levels of ECH but less than detectable levels of ETO were assigned a value of ½ LOD for ETO residues, or 1 ppm. If no ECH was detected, the non-detected ETO samples were assigned a value of zero. A similar set of assumptions was used to estimate EBH residue levels. For ECH residues, a non-detected result was assumed to indicate zero ECH in the sample.

**Table 3a Per Capita Consumption of Selected Spices and ETO**

Spice	Spice Consumption kg/person/year <sup>a,b</sup>	ETO levels mg/kg (ESR 1999)	Proportion with ECH residues	Upper-end ETO intake <sup>c</sup> (µg/person/day)
Black pepper	0.076	0.225 (0.42) <sup>d</sup>	18/80 (22.5%)	4.7E-2
Cinnamon/ cassia	0.032	1.0 (3.25)	5/22 (22.7%)	9.0E-2
Paprika	0.013	0.15 (0.38)	2/13 (15.4%)	5.3E-3
Chilli powder	0.013	0	0/12 (0 %)	0
Nutmeg	0.006	1	1/1 (100 %)	1.6E-2
Other spices	0.226	0.08 (0.29)	5/72 (6.9 %)	5.0E-2
<b>Total</b>	<b>0.366</b>		<b>31/200 (15.5 %)</b>	<b>0.21</b>

<sup>a</sup> NZ population estimated at 3,797,100 (Statistics New Zealand, November 1998).

<sup>b</sup> Spice import data from NZ Customs (October 1997-September 1998).

<sup>c</sup> “Upper-end” estimates contain several conservative assumptions: 1) there is no loss of ETO from food preparation/cooking before consumption, 2) there is no waste of spices, 3) that ‘non-detects’ are at ½ the limit of detection when ECH/EBH residues are present.

<sup>d</sup> Mean and standard deviations.

**Table 3b ETO Fumigation Trial Data (ESR, 1999)**

	Concentration at time since fumigation (ppm)		
	1-2 hours	7 days	14 days
Black peppercorns			
ETO	82.5	12	ND
ECH	547	388	365
EBH	37	37.6	29.4
Ground pepper			
ETO	90.2	6.3	ND
ECH	702	446	456
EBH	29.6	38.2	36.4

Data represent mean values from top, middle, and bottom of bag

ND Not detected at a detection limit of 5 ppm

**Table 4 Ethylene oxide levels reported in fumigated spices (USEPA 1988, 1996)**

Spice	Concentration at time since fumigation (ppm)		
	4-7 days	14 days	30 days
Black pepper	51.1 (50.9) <sup>a</sup>	49.4 (42.7)	27.9 (59.3)
Cinnamon/cassia	122.9 (139.1)	23.5 (21.9)	0.43 (0.31)
Paprika	23.5 (22.3)	183.5 (123, 244)	354 <sup>b</sup>
Chilli powder	80.2 (106.0)	33.0 (15.9)	3.2 (5.3)
Nutmeg	61.9 (37.5)	25.8 (32.4)	14.1 (30.1)

<sup>a</sup> Values are expressed as means. Standard deviations are given in parentheses.

<sup>b</sup> Only 2 values were available for paprika at 14 days, the 2 values are given in parentheses. Only one sample was reported for paprika at 30 days. This single paprika sample was treated as an outlier. The limit of detection for ETO was 0.1 ppm - 0.5 ppm.

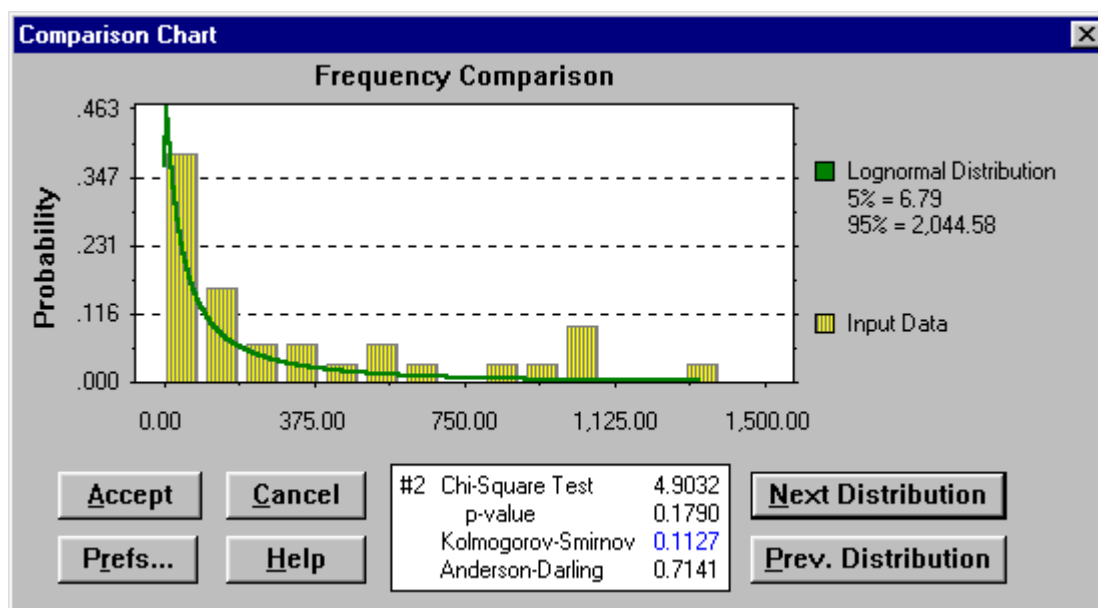
The USEPA data are from analytical monitoring of fumigation trials (USEPA, 1988), and from data collected by the United States Spice Trade Association, supplied to the USEPA (USEPA, 1996). These data gave an indication of the decay rate of ethylene oxide residues following fumigation. Significant levels of ETO forming a large range (0.1 to 354 ppm) were detected in the five spices 30 days after fumigation. By contrast, the ESR fumigation trials showed a much more rapid decay of ETO residues in pepper, decreasing to below 5 ppm at 14 days. The USEPA data have a mean value of about 50 ppm in pepper at 14 days. The reason for the discrepancy in decay rate results is unknown but may be due to differences in sampling or ETO fumigation methods. The ESR study included samples from the top, mid section, and bottom of the container. There were no large differences in ETO content found between different parts of the container of spices.

An analysis of the USEPA data show that, in general, residues decreased with time but were still detectable by 30 to 60 days. The few paprika samples available exhibited increasing residues with time for unknown reasons, but the 30-day time point represents only one sample and this could be an outlier. The greatest reduction in average ETO levels by 30 days was with cinnamon, and the slowest rate of reduction was for black pepper.

#### 4.4 ECH and EBH residues

Thirty-one samples of spices had detectable levels of ECH above 5 ppm. A statistical analysis of these residue levels shows a log-normal distribution for the entire group (Chi squared test = 4.9,  $p < 0.18$ , 1 degree of freedom; see Figure 1). The average value for ECH in this group was 342 ppm, the median was 140 ppm, and the 95% value was 2044 ppm. There were 8 samples positive for EBH. It was assumed that EBH was present at  $\frac{1}{2}$  LOD (i.e. 2.5 ppm) for 23 samples, and zero for those in which no ECH was detected.

**Figure 1** Log-normal distribution of ethylene chlorohydrin residues (in ppm) in retail spices in NZ (Crystal Ball software for Microsoft Excel).



#### 4.5 Spice consumption

*Five spices: black pepper, paprika, nutmeg, cinnamon, and chilli powder (including red chilli pepper) were identified as routine targets for ethylene oxide fumigation due to concerns of microbiological contamination and likelihood that they may not undergo cooking before being consumed. These spices, with the exception of chilli, are not grown in New Zealand. However, as no residues of ECH were found in chilli powder, it does not factor into the ETO intake equation. Per capita consumption of the five spices of concern was determined by using importation data from NZ Customs for the time period October, 1997 - September, 1998 (Table 3a). The data on importation of the 5 spices of concern indicate that black pepper was the spice consumed in the greatest quantity, followed by cinnamon/cassia, paprika, chilli powder (including chilli powder, dried ground chillies, dried ground capsicum, and red pepper flakes), and nutmeg. The total amount imported was assumed to be equivalent to the amount consumed during the year (i.e. no information on amounts wasted, or imported/exported in processed food was available).*

*The sum total of these spices amounted to 0.14 kg/person/year. Adding available Customs data for all other spices gives a per capita figure of 0.364 kg/person/year, or about 1 gram per day. The average spice consumption value is used for the purposes of an estimation of cancer risk due to the chronic lifetime nature of the exposures required for cancer to develop. Data on high intake consumers of spices in NZ are not available. As a surrogate, the U.S. 97.5% adult intake of all spices is 2.3 kg/person/year (Codex, 1999), or about 6.3-fold higher than the estimated NZ mean value for all spices of 0.364 kg/person/year.*

#### 4.6 Cooking and fumigation incidence

Cooking reduces ETO residues in spices substantially. The USEPA reports that at least 90% of ETO residues are converted to the non-carcinogenic ethylene glycol or 1,2-ethanediol upon cooking (USEPA, 1996). The proportion of spices cooked on average is not known and would be very difficult to estimate with any accuracy. The estimates in this report assume there is no cooking involved and therefore provide a conservative upper estimate of the true cancer risk. The spices other than the 5 examined in this report had no detectable ETO residues and most of them, such as curried mixes, would be expected to undergo cooking before consumption.

**Table 5 Summary of ETO, ECH and EBH Intakes**

<b>Residue</b>	<b>Estimated upper-end consumption<sup>1</sup> (µg/person/day)</b>	<b>Estimated worst-case intake using ratio US97.5%/NZ average (µg/person/day)</b>
ETO	0.21	1.3
ECH	48	300
EBH	0.5	3.2

<sup>1</sup> both average and high intake figures assume no loss of ETO due to cooking

## 5 Risk Characterisation

There are actually three individual, but related risk assessments in this report, corresponding to the three compounds (ETO, ECH and EBH) found following ETO fumigation. For ETO, the estimate of cancer risk is straightforward as it is clear this chemical is a human carcinogen and potency factors have been derived by international authorities. The cancer risk estimate from ETO residues in spices is a function of point estimates for average consumption of individual spices (taken as the worst case scenario of no loss due to cooking) combined with one of two possible cancer potencies: the published value from USEPA of 0.29 (mg/kg/d)<sup>-1</sup>, or the value derived in this report from an oral exposure study, 0.55 (mg/kg/d)<sup>-1</sup>. The range of cancer risks from ETO, ECH, and EBH in spices is shown in Table 6.

The potential for carcinogenicity of ECH and EBH is not known. There is some evidence that both compounds may be mutagenic and/or carcinogenic. Levels of ECH in spices are comparatively high and remain so for a considerable duration. However, the only animal toxicology data on ECH have been negative for carcinogenicity and mutagenicity. However, an oral cancer study is needed to ascertain if ECH is a potential carcinogen when eaten. From the animal data available, it appears that residues of this compound do not pose a cancer risk.

Human epidemiological reports of chlorohydrin carcinogenicity are conflicting and may not be identifying chlorohydrins specifically, but rather the occupational setting and composite exposures of the workers there.

The potential risks of EBH are formulated on different grounds. Although the estimated intakes of EBH are less than those for ECH, there is evidence that EBH may be a carcinogen. The only *in vivo* chronic study for EBH showed a highly significant increase in stomach papillomas in mice treated orally at the only dose tested. A cancer potency factor for EBH from this limited study is 0.03 (mg/kg/d)<sup>-1</sup>, which shows it is much less potent than ETO itself, and would be expected to yield significantly lower cancer risks at similar doses. Further animal studies, especially those lasting a full 2 years, would be necessary to precisely estimate a CPF for EBH.

**Table 6 Summary of Cancer Risk Estimates**

<b>Residue</b>	<b>lifetime cancer risk for the upper-end consumer<sup>a</sup></b>	<b>cancer risk - worst-case intake consumer<sup>b</sup></b>
<b>ETO</b>	8.0E-7 or 1.7E-6 <sup>c</sup>	5.0E-6 or 1.1E-5
<b>ECH</b>	none or very low	none or very low
<b>EBH</b>	< 1E-6	1E-6
<b>Combined</b>	8.0E-7 or 1.7E-6	6.0E-6 or 1.2E-5

<sup>a</sup> assumes a 70 kg person.

<sup>b</sup> assumes the worst-case consumer has a 6.3-fold higher spice consumption level than average, based on US consumption data for all spices, compared with per capita NZ levels. Both estimates assume worst case exposures of no loss due to cooking. The two values represent the use of 2 different CPFs for ETO: 0.29 and 0.55 (mg/kg/day)<sup>-1</sup>. A CPF for EBH was derived as 0.03 (mg/kg/day)<sup>-1</sup>.

<sup>c</sup> 1.0E-6 means there is a probability of 1 in 1,000,000 lifetime risk of getting cancer.

## 6 Summary of findings and uncertainties

Ethylene oxide is a human carcinogen that is present as residual contamination in spices following fumigation. Although it occurs as a gas, it does leave residual contamination in foods following fumigation. However, a survey of retail spices by ESR showed that only 2 out of 31 fumigated samples contained ETO levels above 2 ppm. However, it is apparent that up to 23% of some important spices that can be consumed without further cooking, such as pepper, are subjected to ETO fumigation. The residues of ETO in spices in the ESR survey are all below the temporary Food Notice MRL of 50 ppm, and are typically below the detectable limit of 2 ppm (ESR, 1999). The highest residue encountered was 15 ppm.

The exposure estimate in this report assumes there is no loss of ETO through cooking, which is an overestimate of actual exposure, probably by several fold.

Following fumigation, both the USEPA and NZ fumigation trial data show that the breakdown products, ECH and EBH, remain at considerable concentrations in spices for a long time. Whether or not these breakdown products contribute to any potential cancer risk is unknown, as there have been no definitive assessments of their potential for carcinogenicity by the oral route. However, the information available suggests that any cancer risk posed by these breakdown products is negligible at current intake estimates.

The cancer risk assessment indicates that in this worst-case scenario, cancer risk is about 1 in 1,000,000 for an upper-end consumer and about 1 in 100,000 for a worst-case intake consumer. The risk to the average person would be less than these estimates due to the conservative assumptions used regarding loss of ETO levels during cooking. These levels of risk would probably not be considered significant by overseas regulatory authorities considering the degree of uncertainty in the estimates.

The potential health risks from ECH and EBH residues are less clear. Although the potential cancer risks from these compounds appears to be negligible, considerable data gaps exist in their toxicological assessment. It has been shown that ECH and EBH are residues that will be persistent in retail samples at high levels, and it is suggested that consideration be given to forming food standards for these compounds.



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**Toxicology Evaluation on Ethylene Oxide From Chemicals and Non-Prescription Medicines Branch of the Therapeutic Goods Administration**

**Ethylene Oxide**

**Company:** HJ Langdon and Co. Pty Ltd.

**CPAS submission No:**12040

**June 2001**

**Introduction**

HJ Langdon Co. Pty. Ltd has applied to renew the permit for the use of ethylene oxide to fumigate imported herbs and spices for the purpose of controlling microbial contaminants. The current permit expires on 21 August 2001. Ethylene oxide does not currently have an ADI and is currently in schedule 7 of the SUSDP.

**Discussion**

No toxicology data were provided to support the permit application. The toxicology of ethylene oxide has been reviewed by ECETOC in 1982, WHO (IPCS) and USEPA in 1985 and on several occasions by IARC, most recently in 1994.

After parenteral administration, ethylene oxide is rapidly and extensively distributed throughout the body, and metabolised by conjugation with glutathione or by hydrolysis to give ethylene glycol and cysteine adducts which are excreted mainly in the urine. No data is available on the toxicokinetics of ethylene oxide after oral administration. It is of high acute oral ( $LD_{50}$  280-365 mg/kg bw) in rats and mice and moderate to high acute inhalation toxicity ( $LC_{50}$  1500-2630 mg/m<sup>3</sup>) in rats, mice and dogs. It is a skin and eye irritant in laboratory animals and in humans. In humans, accidental acute inhalation exposures resulted in nausea, vomiting, headache, diarrhoea, eye, skin and upper respiratory tract irritation, pruritus and, in some cases, reversible peripheral neuropathy. Some cases of sensitisation and apparent allergic reactions have been reported after occupational exposures.

In short term inhalation studies the main effects observed in a variety of species were respiratory tract irritation with lung hyperaemia, oedema and local alveolar collapse, haematological effects including reduced haemoglobin levels and anaemia and changes in hepatic enzyme activities including decreased glutathione reductase and peroxidase activities. Gastric irritation was the main effect observed after short term oral exposure of rats. In long term inhalation studies in rodents, non-neoplastic effects included decreased body weights, increased organ weights (liver, lung, brain and spleen), haematological changes (increased leukocyte count and reduced RBC and Hb), vacuolation and/or hyperplasia or hypertrophy in the adrenals, respiratory tract inflammation, muscular atrophy and cataracts.

Neurotoxic effects of ethylene oxide exposure have been observed in mice, rats, rabbits, monkeys and humans and included impaired sensory and locomotor functions, hind/lower limb paralysis or weakness and axonal degeneration with demyelination.

In male rats and guinea pigs ethylene oxide exposure caused some degeneration of the seminiferous tubules and reduced sperm counts and sperm motility. Fewer implantations, increased post-implantation losses and a tendency to longer gestation times were observed in a rat reproduction study. There was no evidence of a teratogenic effect in rats and rabbits. However, a teratogenic effect was observed in mice after inhalation exposure to high concentrations of ethylene oxide at or around the time of fertilisation. This effect was shown to be a result of a direct action on the zygote. Ethylene oxide was associated with an increase in spontaneous abortions in two epidemiological studies of pregnancy outcomes in sterilizing staff working in hospitals and in an epidemiological study of pregnancy outcomes in dental workers exposed to ethylene oxide, there was an increased risk of spontaneous abortions, and pre- and post term delivery (Rowland et al 1996).

Ethylene oxide is an electrophilic alkylating agent that will react with nucleophilic centres in proteins and nucleic acids. It will form protein (haemoglobin) and DNA adducts. It was genotoxic in a variety of *in vitro* and *in vivo* genotoxicity studies in bacteria, animals and plant systems and it induced heritable translocations in germ cells of mice. Following occupational exposures to ethylene oxide, increased frequencies of sister chromatid exchange, chromosomal aberrations and micronuclei were observed in peripheral blood lymphocytes. Ethylene oxide has been demonstrated to be carcinogenic in laboratory animals when exposed by oral and inhalation routes. After oral gavage administration to rats, an increased incidence of squamous cell carcinomas was observed in the forestomach and after inhalation exposures of rats and mice increased incidences of several tumours were observed, including leukaemia, brain tumours, pulmonary tumours and tumours of the Harderian gland. Subcutaneous exposure of rats to ethylene oxide resulted in an increased incidence of local sarcomas. Several epidemiological studies in humans suggest that occupational exposures to ethylene oxide increase the risks of lymphatic and haematopoietic cancers and possibly stomach cancer. It is a known genotoxic carcinogen and is classified by IARC as being carcinogenic to humans (group 1) and is listed in the NTP Ninth Report on Carcinogens as "known to be a human carcinogen".

After fumigation of food products, residues of ethylene oxide, ethylene chlorohydrin (2-chloroethanol) and ethylene bromohydrin (2-bromoethanol) and ethylene glycol (1,2 ethandiol) can be found (WHO, 1985). Certain aspects of the toxicology of ethylene chlorohydrin have been previously evaluated by CPAS. It is of high acute oral ( $LD_{50}=71$  mg/kg) toxicity in mice and high acute inhalation ( $LC_{50}=290$ mg/m<sup>3</sup>) and dermal ( $LD_{50}=18$  mg/kg) toxicity in rats and is a skin and eye irritant in rabbits. Short term studies in rats and mice after dermal administration were largely unremarkable apart from pancreatic acinar cell vacuolation and necrosis. Ethylene chlorohydrin was not teratogenic in mice and no reproduction studies are available. It was genotoxic in some bacterial and non-mammalian eukaryotic assays and it induced DNA repair in human fibroblasts and chromosomal aberrations in an *in vivo* rat bone marrow assay. However, it did not induce chromosomal aberrations, micronuclei, heritable translocations or dominant lethal mutations in mouse assays *in vivo*. It is regarded as a weak genotoxin, but may be metabolised to 2-chloroacetaldehyde which is a strong mutagen. However, 2-chloroacetaldehyde may be further metabolised to give 2-chloroacetic acid which is not mutagenic (NTP, 1985). After dermal application to mice, no treatment related carcinogenicity was observed and after dermal application to rats, there was an increased incidence of pituitary adenomas in females, but the incidence of pituitary carcinoma and combined adenoma and carcinoma were not significantly different from controls.

Two epidemiological studies suggest that occupational exposure to ethylene chlorohydrin may increase pancreatic and lymphopoietic cancers in humans, but others have found no such relationship.

Toxicology data on ethylene bromohydrin are quite limited. It was mutagenic in bacteria. After consuming ethylene bromohydrin in drinking water, an increased incidence of squamous cell papillomas were found in rats (Van Duuren et al., 1985)

Residue levels of ethylene oxide after fumigation will depend on a large number of variables including the concentration of ethylene oxide used, time and temperature during fumigation, the physical and chemical nature of the commodities fumigated and conditions of storage after fumigation. Residues of ethylene oxide can dissipate relatively rapidly, but residues of ethylene chlorohydrin and ethylene bromohydrin may persist in some fumigated commodities. After cooking residues will be lower. A Danish study, reported in the IARC Monograph, measured ethylene oxide residues at 14-580 mg/kg in herbs and spices, and studies cited in EHC 55 (WHO, 1985) were reported to show residues of ethylene chlorohydrin at concentrations up to several thousand ppm. In a New Zealand study of residues in retail samples of spices, residues of ethylene oxide (up to 15 ppm) were only detected in 2/200 samples of spices analysed, whereas ethylene chlorohydrin was present at up to 1350 ppm and residues of ethylene bromohydrin were present at up to 55 ppm (Fowles et. al, 2000 and in press). The New Zealand risk assessment estimated ethylene oxide intake from imported spices to be  $3.4 \times 10^{-6}$  mg/kg bw /day and the average lifetime excess cancer risk to be 0.8-1.7 in a million with an extreme upper estimate of 1.4 in 100 000 and concluded that these risks were practically negligible. However, similar quantitative cancer risk estimates for ethylene chlorohydrin and ethylene bromohydrin cannot be made since suitable carcinogenicity studies in which these compounds were administered via the oral route are not available.

The risk assessment conducted by Fowles et al (in press and 2000) included spice consumption only, whereas current permit application includes herbs and spices. If imported herbs and spices were fumigated with ethylene oxide exposure to ethylene oxide residues (including ethylene chloride and ethylene bromide) could be higher. There are currently no data available on ethylene oxide residues in imported herbs and spices treated with ethylene oxide under the conditions of use proposed in the permit application under consideration. However, the applicant has indicated that such data are currently being collated.

The USEPA has established a tolerance of 50 ppm (mg/kg) for residues of ethylene oxide. Australia and New Zealand currently have a temporary MRL for ethylene oxide of 20 ppm (mg/kg) and Canada has a tolerance of 1500 mg/kg for 2- chloroethanol (ethylene chlorohydrin). Under the current arrangements herbs and spices imported from New Zealand may be legally sold in Australia provided the residues of ethylene oxide are below the current temporary MRL set by New Zealand.

As outlined above there is evidence that occupational exposures to ethylene oxide may be carcinogenic. There may be potential for occupational exposures to ethylene oxide when imported herbs and spices are fumigated in Australia. Therefore, the advice of the NOHSC should be sought in relation to this matter.

Although ethylene oxide fumigation is useful in reducing the public health risks that may be associated with the contamination of herbs and spices with microbial pathogens, there may be some cancer risks associated with its use. The irradiation of imported herbs and spices may be an effective alternative means of controlling microbial pathogens. The Australia New Zealand Food Authority is currently considering an application to use irradiation for such purposes in herbs and spices. If irradiation of imported herbs and spices were permissible, it would have the potential to eliminate any excess cancer risk that may be associated with the use of ethylene oxide fumigation.

### **Recommendations**

- 1 Ethylene oxide is a potent genotoxic carcinogen. Furthermore, the breakdown products likely to be found as components of the residues are also genotoxic and potentially carcinogenic. The TGA considers that while quantitative estimates of cancer risk may be low, there is no threshold to the risk, and exposure to clearly genotoxic chemicals is to be avoided where suitable alternatives exist. Accordingly, the approval of a permit to use ethylene oxide to fumigate imported herbs and spices is not supported from a toxicological perspective.
- 2 The advice of NOHSC should be sought for any occupational health and safety implications of the use of ethylene oxide.
- 3 Current recommendations on poison scheduling are appropriate.
- 4 An ADI will not be established for ethylene oxide since it is considered to be a genotoxic carcinogen and therefore there is no acceptable threshold for exposure.
- 5 ADIs will not be established for either ethylene chlorohydrin or ethylene bromohydrin because of the absence of sufficient toxicological data. In addition, the available data raises some concerns with respect to the genotoxic and carcinogenic potential of these compounds.

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