29 NOVEMBER 2000
10/01

FULL ASSESSMENT REPORT

MRL FOR ETHYLENE OXIDE IN HERBS AND SPICES

APPLICATION A412

OBJECTIVE OF THE APPLICATION

The Australia New Zealand Food Authority has before it application **A412** (received on 27 April 2000), from the National Registration Authority for Agricultural and Veterinary Chemicals (NRA) to amend the Australian *Food Standards Code* to establish a maximum residue limit (MRL) of 20 mg/kg for ethylene oxide (EtO) in herbs and spices.

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.

BACKGROUND

The need to use ethylene oxide on herbs and spices

Selected herbs and spices imported into Australia are treated with ethylene oxide (EtO) to control microbial contamination. Currently, three spices, namely paprika, pepper and cinnamon are routinely tested by AQIS for *Salmonella*. If the spices fail to meet the required standard, the importer must re-export or decontaminate the shipment – most chose to decontaminate the shipment with ethylene oxide. AQIS then test the spices for ethylene oxide residues according to the provisions of the Food Standards Code.

Ethylene oxide is volatile and dissipates quickly during the first few days after treatment. Cooking further reduces the level of EtO. Residues of EtO, itself, therefore, would be expected to be low and the data available in Australia and New Zealand supports this position. EtO, however, is also reactive and is readily forms the less toxic metabolites ethylene chlorohydrin and ethylene bromohydrin upon reaction with available chlorine and bromide, and higher levels of these residues are readily found in herbs and spices.

There seems to be no effective alternative to the use of EtO at this time in Australia. While irradiation is an effective alternative, there is currently no application before ANZFA to approve the use of irradiation on herbs and spices. Representatives from Steritech Pty Ltd will be visiting ANZFA very soon to discuss such an application.

AQIS sought advice from ANZFA recently about the status of EtO in relation to the Food Standards Code and was informed that there was no MRL for EtO and that therefore no residues of EtO were permitted in foods imported into or produced in Australia.
As a result, key herb and spice industry bodies have indicated that they are not prepared to continue importing herbs and spices or to continue supplying them from their current stocks for fear of prosecution and public criticism for breaching the Food Standards Code. Some food manufacturers are now anticipating serious problems of supply for herbs and spices and have indicated an intention to cease manufacture in the near future.

Legality of the use of ethylene oxide on domestic and imported foods

Registration for use through the National Registration Authority (NRA)

Until very recently, there was no registered agricultural use of ethylene oxide in Australia. The then NFA wrote to the NRA on 21 June 1993 seeking clarification of the status of EtO under the Agricultural and Veterinary Chemicals Act 1988. In a reply dated 9 July 1993, the NRA confirmed EtO is an agricultural chemical but at that time registration was still the responsibility of individual State and Territories and that national registration would not be in place until early 1994. The NRA suggested in their letter that EtO might be approved for use in individual States under permit to accommodate quarantine uses.

Recently, an import company applied to the NRA for an emergency use permit for ethylene oxide on herbs and spices (Application No. 3589). This permit was granted on 20 April 2000 until 30 September 2001. The NRA has subsequently made an application to ANZFA to have a maximum residue limit of 20 ppm for ethylene oxide in herbs and spices. The residue definition is ethylene oxide and does not include any metabolites.

Food Standard

There is currently no MRL for ethylene oxide in Standard A14 – Maximum Residue Limits - in the current *Food Standards Code*. It is therefore not lawful for residues to be present in food. The current wording in the Standard is: "If an MRL for an agricultural or veterinary chemical in a food is not listed in this Standard, there must be no detectable residue of that agricultural chemical in that food."

Prior to 1996, the then *Food Standards Code* did not give direction on chemicals that were not included in the Schedule to Standard A14. In effect, this permitted the risk associated with residues of chemicals not listed in Standard A14 to be managed within the general provisions of State *Food Acts* relating to food being suitable for human consumption. Amendment 30 (June 1996) to A14 inserted a clause that stated that if the chemical was not in the schedule to A14, there was no MRL and residues were defaulted to zero.

In this context, the advice given to AQIS in 1993 (see below) was correct, but this position is no longer valid, and an MRL for EtO residues is necessary for continued use.

Previous ANZFA consideration of EtO

The issue of EtO was raised with the then NFA Board in March 1993 as a result of a New Zealand initiative to review the use of EtO on herbs and spices with a view to phasing out the use of EtO. It was noted by the Board at the time that EtO was used in Australia on imported herbs and spices and that this use may be inconsistent with the Food Acts. However, it was also noted that the use of EtO was necessary to reduce the microbial contamination of some herbs and spices and that the alternative to EtO use, namely, irradiation, was not available. NFA agreed to review the continued use of EtO in co-operation with the NZ Department of Health and the Spice Industry.

At this time, NFA staff also has discussions with the Spice Association of Australasia and with AQIS. It was recognized that there was little data on the extent and level of residues of EtO on herbs and spices.

To address this matter, AQIS was directed to place EtO 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 is 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 re-enforced 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 EtO. While some data has been provided, only limited information was obtained from the ASTA.

The issue of establishing an MRL for EtO has not been pursued because:

(i) it was always assumed that the approval of irradiation would make the use of EtO obsolete;
(ii) the lack of adequate residue data on herbs and spices would make registration by the NRA unlikely:
(iii) residues of EtO were considered by State and Territory Health Authorities to be an issue of less public health concern than the potential for health problems caused by the microbial contamination.

Safety of EtO and its residues

Ethylene oxide is regarded as a highly toxic chemical. It has been shown to cause cancer in experimental animals and has strong mutagenic activity in both bacterial and mammalian assays. It is currently in Schedule 7 of the Uniform Schedule of Drugs and Poisons and thus requires special precautions in manufacture, handling, storage and use. There is a significant potential risk to workers handling this chemical.

EtO reacts with available chlorine and bromide to form detectable residues of ethylene chlorohydrin and ethylene bromohydrin in treated food. The residues of EtO itself decrease rapidly (usually <20 ppm) but residues of chlorohydrin may persist for much longer periods (up to 1500 ppm). The available data indicates that ethylene chlorohydrin is significantly less mutagenic than EtO and, as such, presents a significantly reduced public health and safety risk. There is no mutagenicity data available on ethylene bromohydrin.

Consideration of EtO in New Zealand

In New Zealand, until recently, EtO has been permitted for use on herbs and spices under a food notice that permits residues of EtO of 50 ppm. There has been on-going concern regarding the use of EtO 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 EtO residues in spices. This regulation came in force on 23 April 2000. This MRL does not include ethylene chlorohydrin.

WORLD TRADE ORGANIZATION (WTO) NOTIFICATION

Australia and New Zealand are members of the WTO and are bound as parties to WTO agreements. In Australia, an agreement developed by the Council of Australian Governments (COAG) requires States and Territories to be bound as parties to those WTO agreements to which the Commonwealth is a signatory. Under the agreement between the Governments of Australia and New Zealand on Uniform Food Standards, ANZFA is required to ensure that food standards are consistent with the obligations of both countries as members of the WTO.

In certain circumstances Australia and New Zealand have an obligation to notify the WTO of changes to food standards to enable other member countries of the WTO to make comment. Notification is required in the case of any new or changed standards which may have a significant trade effect and which depart from the relevant international standard (or where no international standard exists).

Matters relating to public health and safety are notified as a Sanitary or Phytosanitary (SPS) notification, and other matters as a Technical Barrier to Trade (TBT) notification.

As the preferred regulatory option involves the development of a new food standard and one for which there is no international regulation, a World Trade Organization (WTO) notification would be required on the basis of constituting a Technical Barrier to Trade (TBT).

FOOD STANDARDS SETTING IN AUSTRALIA AND NEW ZEALAND

The Governments of Australia and New Zealand entered an Agreement in December 1995 establishing a system for the development of joint food standards. The Australia New Zealand Food Authority is now developing a joint *Australia New Zealand Food Standards Code* which will provide compositional and labelling standards for food in both Australia and New Zealand.

Until the joint *Australia New Zealand Food Standards Code* is finalised the following arrangements for the two countries apply:

- **Food imported into New Zealand other than from Australia** must comply with either the Australian *Food Standards Code*, as gazetted in New Zealand, or the New Zealand *Food Regulations 1984*, but not a combination of both. However, in all cases maximum residue limits for agricultural and veterinary chemicals must comply solely with those limits specified in the New Zealand *Food Regulations 1984*.
- **Food imported into New Zealand from Australia** must comply with either the Australian *Food Standards Code* or the New Zealand *Food Regulations 1984*, but not a combination of both. However, in all cases maximum residue limits for agricultural and veterinary chemicals must comply solely with those limits specified in the New Zealand (Maximum Residue Limits of Agricultural Compounds) Mandatory Food Standard 1999
- **Food imported into New Zealand from Australia** must comply with either the Australian *Food Standards Code* or the New Zealand *Food Regulations 1984*, but not a combination of both.
- **Food imported into Australia from New Zealand** must comply with the Australian *Food Standards Code*. However, under the provisions of the Trans-Tasman Mutual Recognition Arrangement, food may be imported into Australia from New Zealand if it

complies with the New Zealand *Food Regulations 1984* or *Dietary Supplements Regulations 1985.*

- **Food manufactured in Australia and sold in Australia** must comply solely with the Australian *Food Standards Code*, except for exemptions granted in Standard T1.

In addition to the above, all food sold in New Zealand must comply with the New Zealand *Fair Trading Act 1986* and all food sold in Australia must comply with the Australian *Trade Practices Act 1974,* and the respective Australian State and Territory *Fair Trading Acts.*

Any person or organisation may apply to ANZFA to have the *Food Standards Code* amended. In addition, ANZFA may develop proposals to amend the Australian *Food Standards Code* or to develop joint Australia New Zealand food standards. ANZFA can provide advice on the requirements for applications to amend the *Food Standards Code.*

INVITATION FOR PUBLIC SUBMISSIONS

The Authority has completed a full assessment of the application and amended the Australian *Food Standards Code* ANZFA, pursuant to section 37 of the *Australia New Zealand Food Authority Act 1991,* to avoid compromising the objective set out in subsection 10(1)(a) of the Act, namely the protection of public health and safety. The Authority is now conducting an inquiry as required under the *Australia New Zealand Food Authority Act 1991*.

Written submissions containing technical or other relevant information which will assist the Authority in undertaking a full assessment on matters relevant to the application, including consideration of its regulatory impact, are invited from interested individuals and organisations. Technical information presented should be in sufficient detail to allow independent scientific assessment.

Submissions providing more general comment and opinion are also invited. The Authority's policy on the management of submissions is available from the Standards Liaison Officer upon request.

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 confidential information contained in a submission to remain confidential to the Authority, you should clearly identify the sensitive information and provide justification for treating it 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.

All correspondence and submissions on this matter should be addressed to the **Project Manager - Application A412** at one of the following addresses:

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NEW ZEALAND
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Submissions should be received by the Authority by **10 January 2001.**

General queries on this matter and other Authority business can be directed to the Standards Liaison Officer at the above address or by Email on <slo@anzfa.gov.au>. Submissions should not be sent by Email as the Authority cannot guarantee receipt.
Requests for more general information on the Authority can be directed to the Information Officer at the above address or by Email <info@anzfa.gov.au>.

PUBLIC CONSULTATION

Under section 37, ANZFA is required as soon as practicable to hold an inquiry into the standard as adopted.

SCIENTIFIC ASSESSMENT

The basis for the recommended MRL is a 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) and commissioned by the New Zealand Ministry of Health (see Attachment 3).

The report provides an estimate for the potential cancer risk associated with the presence of EtO residues and its breakdown products in dry spices in New Zealand.

The report concludes that:

1. On the basis of the current monitoring data and the risk assessment undertaken, there is negligible cancer risk to consumers from EtO residues in spices.

2. There are no known significant cancer risks associated with consumption of ethylene chlorohydrin and ethylene bromohydrin at the levels found in spices. It is acknowledged, however, that the toxicological database on these compounds is limited.

3. An MRL of 20 ppm for 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.

CONCLUSIONS

On the basis of the data available, an MRL of 20 ppm for ethylene oxide in herbs and spices is justified and does not pose any additional public health and safety risk.

ATTACHMENTS

1. Draft variation to the Australian *Food Standards Code*
2. Statement of Reasons
3. Report prepared by the New Zealand Institute of Environmental and Scientific Research (ESR) entitled: *Cancer Risk Assessment Of Ethylene Oxide Residues In New Zealand Spices*

Attachment 1

DRAFT VARIATION TO THE AUSTRALIAN FOOD STANDARDS CODE

A412 - MAXIMUM RESIDUE LIMIT FOR ETHYLENE OXIDE IN HERBS AND SPICES

Explanatory Note: This is a new MRL for an agricultural chemical not previously listed in Standard A14.

To commence: On gazettal

Standard A14 is varied by inserting in column 1of Schedule 1 the chemical (shown in bold type) and inserting in column 1 and 2 respectively of Schedule1 the food and maximum residue limit for that food, listed below-

Chemical	
Food	MRL
Ethylene oxide	
Herbs	20
Spices	20
The MRLs for ethylene oxide cease to have effect on 30 September 2001	

Attachment 2

STATEMENT OF REASONS – DRAFT

APPLICATION A412

MAXIMUM RESIDUE LIMIT FOR ETHYLENE OXIDE IN HERBS AND SPICES

The Australia New Zealand Food Authority has before it application **A412** (received on 27 April 2000), from the National Registration Authority for Agricultural and Veterinary Chemicals (NRA) to amend the Australian *Food Standards Code* to establish a maximum residue limit (MRL) of 20 mg/kg for ethylene oxide (EtO) in herbs and spices.

ANZFA has completed a full assessment of the application, 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.

The Australia New Zealand Food Authority recommends the adoption of the draft variation to Standard A14 for the following reasons:

- The MRL for EtO has been recommended by the NRA after the granting of an Emergency Use Permit for fumigant use of EtO on herbs and spices on 20 April 2000.

- The use of EtO of herbs and spices is required to reduce microbial contamination. The alternative decontamination method, namely irradiation, is not yet available for herbs and spices.

- The MRL of 20 mg/kg is set at a level consistent with good agricultural practice.

- On the basis of the 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), there is negligible cancer risk to consumers from EtO residues in spices.

- The MRL will expire on 30 September 2001, which is the date of expiration of the Emergency Use Permit.

- The MRL for EtO is predicated on A timely industry application to vary Standard A17 – Irradiated Food – to permit irradiation of herbs and spices.

The commencement date of the draft variation is to be from the date of gazettal.

Attachment 3

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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GroupClient Report
FW9980

Cancer Risk Assessment of Ethylene Oxide Residues in New Zealand Spices

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

by

Jefferson Fowles, Ph.D.

December 1999

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Jim Mitchell (ESR)
Jim Wilson (Project Manager, Ministry of Health)
Rob Smith (Food Standards, Ministry of Health)
Marion Riordan (Team Leader-Food Standards, Ministry of Health)
Tom McDonald, Ph.D (California Environmental Protection Agency)
Peter Abbott, Ph.D (Australia New Zealand Food Authority)

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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 3.4×10^{-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 $(mg/kg/d)^{-1}$ 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 $(mg/kg/d)^{-1}$ 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 1×10^{-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 1×10^{-5} (10 in a million), but would be much lower for the average consumer. Cancer risks to ETO fumigators are not addressed in this report.

The estimated upper-end of the range of consumption of ECH and EBH from the monitoring results is 7.4×10^{-4} and 5.8×10^{-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 3.0×10^{-2} $(mg/kg/d)^{-1}$, 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	Leukaemia incidence Reported by:		
(ppm)	(mg/kg/day) [a]	(mg/kg/day)[b]	USEPA (1985)	WHO (1985)	Snellings *et al*. (1984)
0	0	0	22/186[c]	22/235[d]	11/115[e]
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

[a] 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

[b] Equivalent human lifetime doses were calculated using the surface area adjustment:
dose (human) = dose (animal)/$[wt(h)/wt(a)]^{1/3}$, using 70 kg for average human weight and 0.22 kg for an adult female rat. Doses using body weight to the ¾ power are shown in parentheses.

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

[d] Data reported by WHO include all observations, interim and final - including consideration of all negative findings at interim sacrifice as negative findings.

[e] 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)[a]	**Incidence of rat stomach tumours**	**Systemic tumours**
0	0	0/100	40/100
7.5	0.51	8/50[b]	28/50[b]
30	2.03	31/50 [b]	29/50 [b]

[a] Equivalent human lifetime doses were calculated using the surface area adjustment:
dose (human) = dose (animal)/[wt(h)/wt(a)]$^{1/4}$, 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.

[b] 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[a]	Cal/EPA[b]
0	0/100	0	0
15	2/50	0.44	0.63
60	19/50	1.76	2.51

[a] USEPA calculated equivalent human lifetime doses using the surface area adjustment:
dose (human) = dose (animal)/[wt(h)/wt(a)]$^{1/3}$, 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.
[b] 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 adenosarcoma (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.

Linearised multistage model: $P(d) = 1- e^{-(q_0 + q_1 d + q_2 d^2 + \ldots + q_k d^k)}$

$P(0) = 1-e^{-q_0}$

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 $(mg/kg/d)^{-1}$. The data used in their calculations came from the Snellings et al., (1981) study. Later, the Cal/EPA revised the CPF to 0.31 $(mg/kg/d)^{-1}$. Recently, a review of interspecies scaling methodologies by USEPA and Cal/EPA have indicated that body weight should be raised to the ¾ power rather than the 2/3 power used previously. Although the 0.29 $(mg/kg/d)^{-1}$ value was based on the 2/3 power scaling, it is not clear if this is also the case for the 0.31 $(mg/kg/d)^{-1}$ 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 ¾ 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 (q1 and q1*) in $(mg/kg/d)^{-1}$ and other multistage model parameters derived from the tumour incidence data in Tables 1a, 1b, and 1c.

	Mononuclear cell leukaemia (inhalation)			Forestomach tumours (oral) - ETO	Forestomach tumours (oral) - PO
Parameter	**CARB (1987)**	**WHO (1985)**	**Snellings *et al*. (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)	**0.29[a] (0.18)**	**0.17**	**0.51**	0.73 [b] **0.55 [c]** 0.36 [d]	**0.17**
p-value, chi-square goodness of fit test	0.16	0.005[e]	0.64	1.0	1.0

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

[a] 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 $(mg/kg/d)^{-1}$ 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 ¾ power for interspecies scaling, which is the currently accepted default.

[b] Cancer potency including carcinomas, fibrosarcomas, and in-situ carcinomas of the forestomach and stomach.

[c] 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.

[d] Cancer potency from all systemic tumours distal to the stomach.

[e] 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" (1.6×10^{-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[a,b]	ETO levels mg/kg (ESR 1999)	Proportion with ECH residues	Upper-end ETO intake[c] (µg/person/day)
Black pepper	0.076	0.225 (0.42)[d]	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
Total	**0.366**		**31/200 (15.5 %)**	**0.21**

[a] NZ population estimated at 3,797,100 (Statistics New Zealand, November 1998).

[b] Spice import data from NZ Customs (October 1997-September 1998).

[c] "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.

[d] 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) [a]	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[b]
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)

[a] Values are expressed as means. Standard deviations are given in parentheses.

[b] 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.

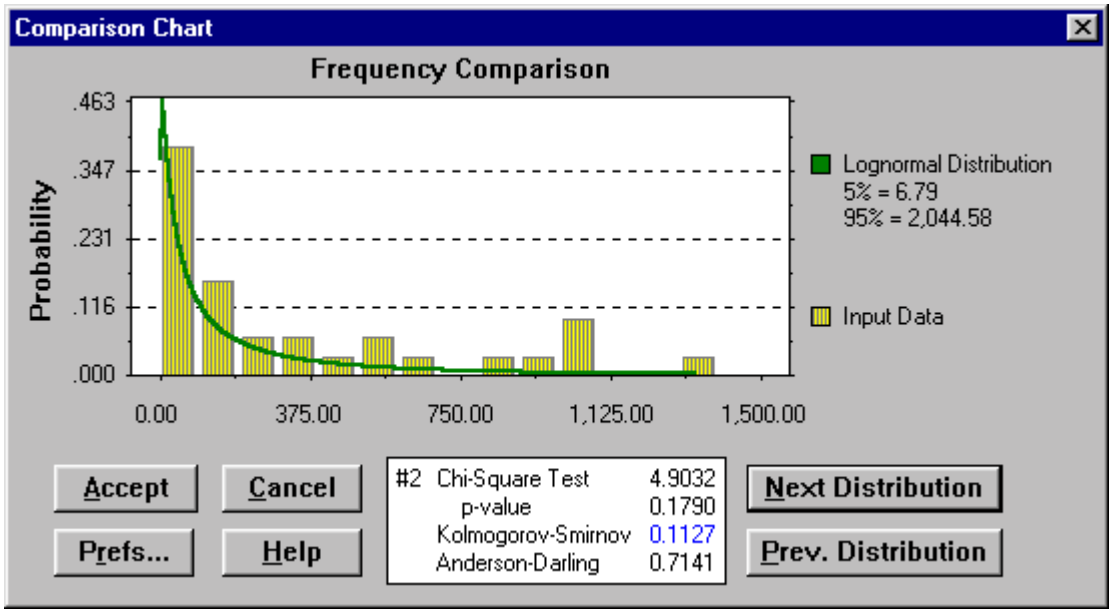
The USEPA data are from analytical monitoring of fumigation trials (USEPA, 1988), and from data collected by the United States Spice Trade Association, supplied to the USEPA (USEPA, 1996). These data gave an indication of the decay rate of ethylene oxide residues following fumigation. Significant levels 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 ½ 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

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

[1] 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 $(mg/kg/d)^{-1}$, or the value derived in this report from an oral exposure study, 0.55 $(mg/kg/d)^{-1}$. 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 $(mg/kg/d)^{-1}$, 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

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

[a] assumes a 70 kg person.

[b] 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 $(mg/kg/day)^{-1}$. A CPF for EBH was derived as 0.03 $(mg/kg/day)^{-1}$.

[c] 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.

7 References

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