OOS
OCTOBER 1999

FULL ASSESSMENT REPORT AND REGULATION IMPACT ASSESSMENT

SUBJECT: A367 – CELLULOSE-BASED ION EXCHANGE RESINS

EXECUTIVE SUMMARY

- An application was received by the Australia New Zealand Food Authority (ANZFA) from Life Technologies Limited, on 10 November 1998, requesting an amendment to the Australian *Food Standards Code* (AFSC) to permit the use of four cellulose-based ion exchange resins, namely:
  Sulphopropyl cellulose (SP) resin;
  Carboxymethyl cellulose (CM) resin;
  Diethyl aminoethyl cellulose (DEAE) resin; and
  Quaternary amine cellulose (QAE) resin.

- The matter was advertised for public comment for a period of six weeks on 3 March 1999. Four submissions were received in response to the call for public comment, all of which supported or had no objection to the application.

- There are no significant toxicological concerns in relation to the application.

- Use of the resins is technologically justified for isolating specific proteins from production liquors or waste streams, which can then be used as food ingredients with highly specific functional characteristics.

- Permission to use the four resins should be included in Group VII of Table II in Standard A16 – Processing Aids, and should not be restricted to specific applications.

- Specifications for the CM, DEAE and QAE resins should be included as an addendum to Standard A11 – Specifications for Identity and Purity of Food Additives, Processing Aids, Vitamins, Minerals, and Other Added Nutrients, until such time as specifications are included in the source specification document, the US Code of Federal Regulations(US CFR).

- The specification for the SP resin in Standard A11 should be updated to the current (1999) US CFR.

- A consequential amendment should be made to draft Standard 1.3.4 – Identity and Purity, of the proposed joint Food Standards Code, to include the US CFR as a secondary source of specifications.

- The Regulatory Impact Statement supports the inclusion of the four ion exchange resins in Standard A16 of the Food Standards Code.

- It is not necessary to notify this application to the WTO as an SPS or TBT notification.

BACKGROUND AND ISSUE

An application was received by ANZFA from a New Zealand company, Life Technologies Limited, on 10 November 1998, requesting an amendment to the AFSC to permit the use of four cellulose-based ion exchange resins.

Currently, in Australia, the AFSC lists ion exchange resins in Group VII - Ion Exchange Resins, of Table II - Processing Aids Restricted by Function and Residue Level, in the schedule to Standard A16 - Processing Aids.

Group VII of Standard A16 lists specific substances, which may be used as ion exchange resins in the manufacture of food or food ingredients. Cellulose-based ion exchange resins are currently not listed in this table. However, 'regenerated cellulose, cross-linked and alkylated with epichlorohydrin and propylene oxide' is currently listed in Table VI - Processing Aids Used In Packaged Water and In Water Used As An Ingredient In Other Foods, of Standard A16.

The cellulose-based ion exchange resins which are the subject of this application could be regarded as derivatives of the regenerated cellulose currently permitted by Table VI of Standard A16. However, the resins in question are sufficiently different so as to warrant separate safety assessment and approval.

The applicant states that cellulose-based ion exchange resins are used for isolating proteins from production liquors or waste streams. Exactly which ion exchange resin is used depends on the properties of the target proteins and the liquid stream from which it is to be isolated.

Other separation technologies (for example, membrane filtration technology) may be used for the separation of proteins. However, the applicant claims that the use of ion exchange resins for protein separation results in proteins with a higher degree of purity, which significantly improves their functional properties.

OBJECTIVE

The objective is to provide for the use of four cellulose-based ion exchange resins in the production of proteins for use as food ingredients, namely:

Sulphopropyl cellulose (SP resin);
Carboxymethyl cellulose (CM resin);
Diethyl aminoethyl cellulose (DEAE resin); and
Quaternary amine cellulose (QAE resin).

The base matrix is crosslinked hydroxypropylated regenerated cellulose.

RELEVANT PROVISIONS

Relevant provisions contained in the AFSC are Standard A16 - Processing Aids, and Standard A11 - Specifications for Identity and Purity of Food Additives, Processing Aids, Vitamins, Minerals and Other Added Nutrients.

There is no comparable standard for processing aids in the *New Zealand Food Regulations* 1984. Processing aids are either regulated as food additives or are not specifically regulated in New Zealand.

Codex does not provide a separate standard for processing aids.

PUBLIC CONSULTATION

This application underwent preliminary assessment in February 1999, and was subsequently advertised for public comment for a period of six weeks, in accordance with section 14 of the *Australia New Zealand Food Authority Act 1991*, on 3 March 1999.

Submissions were received from the Food Technology Association of Victoria Inc (FTAV), the Victorian Food Safety Council Food Standards Sub-Committee, the Western Australian Food Advisory Committee and the New Zealand Dairy Board.

Three submissions supported or had no objection to the application.

The FTAV supported the application provided approval was accompanied by an assessment of health and safety issues and supported by full data. The FTAV considered that only specific applications for use should be permitted for this processing aid.

OPTIONS including alternatives to regulation

1. Amend the AFSC to permit the use of the four cellulose-based ion exchange resins as processing aids.

2. Maintain the *status quo* and do not permit the use of the four cellulose-based ion exchange resins as processing aids.

Alternatives to a standard are not considered appropriate to regulate the use of ion exchange resins. Processing aids used in Australia are currently listed in Standard A16. New entries in the schedule to Standard A16 are required to undergo an evaluation to ensure there are no health and safety concerns with permitting their use. The standard is intended to reflect current use and prohibit inappropriate use of processing aids.

ASSESSMENT

Conclusions from the Toxicology Report

In consideration of the toxicological concerns regarding exposure to propylene oxide and epichlorohydrin, the levels of these compounds in foods should be as low as can be achieved by good manufacturing processes.

The applicant supplied data on extraction tests carried out on resin samples to check specifically for residues of propylene oxide and epichlorohydrin. These chemicals were at or below limits of detection, which were 5-20 ppb for all four resin types.

The US FDA had accepted that there are negligible residues and did not require specific toxicological testing of the resins.

Provided that there were no detectable residues of the reagents epichlorohydrin and propylene oxide in the ion-exchange resins, there would be no significant toxicological concerns.

Conclusions from the Food Technology Report

- Ion exchange resins are currently permitted in the Food Standards Code as processing aids.

- Cellulose-based ion exchange resins may be used to isolate protein from production liquors or waste streams and is technologically justified.

- When used under specific conditions of pH and temperature, cellulose-based ion exchange resins are able to isolate selected proteins in a more purified form than other methods of protein separation technology, which greatly increases the functional properties of the protein.

Issues Raised By Public Submissions

The FTAV considered that the use of these processing aids should be limited to specific applications.

ANZFA proposes not to list specific applications for the use of cellulose-based ion exchange resins. As the resins have been evaluated as having no significant toxicological concerns there is no reason to limit their potential use to specific applications. This approach would also be consistent with the current regulation of other ion exchange resins in Standard A16.

Regulation Impact Analysis

Option 1 Amend the AFSC to permit the extended use of cellulose-based ion exchange resins as processing aids.

Advantages/benefits

Food manufacturers will benefit from the availability of a greater range of food ingredients with more precise functional properties.

Consumers may benefit from the availability of a greater range of food products in the market place.

Disadvantages/costs

There may be some cost to government agencies due to the need to become familiar with and enforce new requirements.

Option 2 Maintain the *status quo* and do not permit the extended use of cellulose-based ion exchange resins as processing aids.

Advantages/benefits

Enforcement agencies would not be required to regulate or enforce further requirements.

Disadvantages/costs

Food manufactures will be disadvantaged by a continued limited range of functional food ingredients.

Consumers may be disadvantaged by not having access to a greater range of foods in the market place.

Evaluation

Consideration of the Regulatory Impact for this proposal concludes that the benefits to industry and consumers of providing permission for the extended use of cellulose based ion exchange resins outweighs any slight costs to enforcement agencies.

Implementation and review

Implementation of this application should be at the time of gazettal of the draft variation to the Food Standards Code.

Specific review of the proposed draft variation would not be required. Applications to amend food standards may be made at any time, or alternatively, the Authority may raise a proposal to amend food standards should the need arise.

ANZFA Section 10 Objectives

(a) The protection of public health and safety.

This application raises no significant issues in relation to public health and safety.

(b) The provision of adequate information relating to food to enable consumers to make informed choices and to prevent fraud and deception.

Ion exchange resins are regulated as processing aids, and are therefore not required to be declared on the label of a food product. As ion exchange resins are used to remove components from foods or to separate foods, they are not usually present in the final food and therefore declaration of their presence is not useful.

(c) The promotion of fair trading in food

All food or food ingredient manufacturers will be equally affected by providing a permission in the Food Standards Code for the use of cellulose-based ion exchange resins.

(d) The promotion of trade and commerce in the food industry.

Permitting the use of cellulose-based ion exchange resins may promote trade and commerce in the food industry by enabling the production of a range of proteins with specific functional characteristics. This in turn may promote innovation in food manufacture.

(e) The promotion of consistency between domestic and international food standards.

The *New Zealand Food Regulations* and Codex do not contain equivalent standards regulating the use of processing aids.

The US CFR permits the use of some cellulose-based ion exchange resins, including one of those requested in this application. The US Food and Drug Administration is also currently considering approval of the other ion exchange resins which are the subject of this application.

OTHER RELEVANT MATTERS

Specifications

The SP resin is currently permitted by the FSC in Standard A16, specifically as an ion exchange resin for water treatment. The specification cited in Standard A11 – Specifications for Identity and Purity of Food Additives, Processing Aids, Vitamins, Minerals and Other Added Nutrients, is the US CFR, Title 21, part 173.25 (a)(20), in force as at 1 April **1994**, which states:

regenerated cellulose, cross-linked and alkylated with epichlorohydrin and propylene oxide, then sulfonated whereby the amount of epichlorohydrin plus propylene oxide employed does not exceed **60 percent** by weight of the starting quantity of cellulose.

This differs from the current CFR, in force as at 1 April **1999**, which states that "the amount of epichlorohydrin plus propylene oxide employed does not exceed **250 percent** by weight of the starting quantity of cellulose". Additionally, the 1999 CFR provides for a greater range of pH and temperature of operation.

As a part of this application, permission to use SP resins has been included in the general list of ion exchange resins in Standard A16, and the specification cited in Standard A11 updated to the current (1999) CFR.

The other three cellulose-based resins, CM, DEAE and QEA, have not yet been approved in the US. The applicant has provided interim specifications, based on specifications provided to the US FDA for approval, which will be included as an addendum to Standard A11. If the resins are approved in the US and appropriate specifications included in the CFR, the specifications will be updated.

Review of the Food Standards Code

A review of Standard A16 (Proposal P188 – Review of Processing Aids – Standard A16) is currently at Inquiry. The specific ion exchange resins under consideration in this application were not included in the review of A16 as they had not previously undergone a safety evaluation or approval process.

At Full Assessment Proposal P188 considered that as the US regulations for ion exchange resins were more comprehensive than those listed in Standard A16 and proposed to refer to the list of US approved ion exchange resins. P188 also proposed to review the regulation of ion exchange resins if and when the European model of regulation is adopted.

Proposal P189 – Review of Standard A11, is recommending a joint Australia New Zealand Standard 1.3.4 – Identity and Purity, be developed and that a hierarchy of sources be used to supply specifications for substances used in food, as follows:

2 Substances with specifications in primary sources

A substance must comply with a relevant monograph (if any) in one of:

(a) Food and Nutrition Paper 52 Compendium of Food Additive Specifications Volumes 1 and 2, including addenda 1 to 6, published by the Food and Agriculture Organisation of the United Nations in Rome (1992);

(b) the fourth edition of the Food Chemicals Codex published by the National Academy of Sciences and the National Research Council of the United States of America in Washington, DC. (1996); or

(c) the Schedule to this Standard.

3 Substances with specifications in secondary sources

If there is no monograph applying to a substance under clause 2, the substance must comply with a relevant monograph (if any) published in one of:

(a) the *British Pharmacopoeia* Volumes 1 and 2 1993, HMSO, London, 16th Edition (1998);
(b) *The United States Pharmacopeia,* 23rd Revision and *The National Formulary*, 18th Edition. Official from January 1, 1995. United States Pharmacopeial Convention Inc. Rockville, Md. (1994);
(c) *The Pharmaceutical Codex*, 12th Edition, Council of the Pharmaceutical Society of Great Britain. The Pharmaceutical Press, London (1994);
(d) *Martindale The Extra Pharmacopoeia,* 31st Edition, JEF Reynolds (Ed), The Pharmaceutical Press London (1996);
(e) the *European Pharmacopoeia* 3rd Edition, Council of Europe, Strasbourg (1996);
(f) the *International Pharmacopoeia* 3rd Edition, Volumes 1, 2, 3 and 4, World Health Organisation, Geneva (1994);
(g) *The Merck Index*, 12th Edition, Merck and Co. Ltd. Whitehouse Station, N.J. (1996);
(h) Regulatory Aspects of Enzymes, the Association of Manufacturers of Fermentation Enzyme Products, 5th Edition (1997).

P189 proposed not to include a reference to the US CFR. However, discussions with the P189 review team concluded that the US CFR should be included in draft Standard 1.3.4 in order to supply specifications for ion exchange resins in the joint Food Standards Code, as recommended in Proposal P188. Furthermore, inclusion of the US CFR in draft Standard 1.3.4 will automatically provide specifications for the four cellulose-based resins currently under consideration, as the CFR is updated.

CONCLUSIONS

- There are no significant toxicological concerns raised in relation to the application.

- Use of the four cellulose-based ion exchange resins is technologically justified for isolating specific proteins from production liquors or waste streams, which can then be used as food ingredients with highly specific functional characteristics.

- Permission to use the four cellulose-based ion exchange resins should be included in Group VII of Table II in Standard A16 – Processing Aids, and should not be restricted to specific applications.

- Specifications for the CM, DEAE and QAE resins should be included as an addendum to Standard A11– Specifications for Identity and Purity of Food Additives, Processing Aids, Vitamins, Minerals, and Other Added Nutrients, until

such time as specifications are included in the source specification document, the US CFR.

- The specification for the SP resin in Standard A11 should be updated to the current (1999) US CFR.

- A consequential amendment should be made to draft Standard 1.3.4 – Identity and Purity, of the proposed joint Food Standards Code, to include the US CFR as a secondary source of specifications.

- The Regulatory Impact Statement in relation to this application supports the approval of the ion exchange resins as processing aids.

- Implementation of this amendment should be at the time of gazettal.

WORLD TRADE ORGANISATION (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).

This application may be a potential SPS matter. However, while there is no international standard for the regulation of processing aids, or specifically ion exchange resins, the matter is not expected to have a significant trade effect and therefore should <u>not</u> be notified to the WTO.

<u>Attachments to the Report:</u>

1. Draft Variation to the Australian *Food Standards Code*
2. Draft Explanatory Notes
3. Toxicological Report
4. Food Technology Report

ATTACHEMENT 1
OOS
OCTOBER 1999

DRAFT VARIATION TO THE AUSTRALIAN FOOD STANDARDS CODE

LES HAS ALL THE BITS IN RED IN ANOTHER DOC – PLEASE LET HIM KNOW IF YOU CHANGE ANYTHING HERE !!!!!

A367 – CELLULOSE-BASED ION EXCHANGE RESINS

To commence: On gazettal

[1] Standard A11, subclause (1)(k)

omit

"1 April 1994"

substitute

"1 April 1999"

[2] Standard A11, column 1 of the Schedule

omit

"Regenerated cellulose, cross-linked and alkylated with epichlorohydrin and propylene oxide"

substitute

"Regenerated cellulose, crosslinked and alkylated with epichlorohydrin and propylene oxide, then sulphonated whereby the amount of epichlorohydrin plus propylene oxide does not exceed 250% by weight of the starting quantity of cellulose"

[3] Standard A11, Schedule

insert

"Quaternary amine cellulose" immediately after "Pyridoxine hydrochloride" in Column 1 of the Schedule and "Addendum 7" immediately opposite in Column 2 of the Schedule

insert

"Diethyl aminoethyl cellulose" immediately before "Dimethyl dicarbonate" in Column 1 of the Schedule and "Addendum 8" immediately opposite in Column 2 of the Schedule

insert

"Carboxymethyl cellulose" immediately after "Carbon dioxide" in Column 1 of the Schedule and "Addendum 9" immediately opposite in Column 2 of the Schedule

[4] Standard A11, after Note 1 to Addendum 6 (Specification for Oxidised Polyethylene)

insert

ADDENDUM 7

SPECIFICATION FOR QUATERNARY AMINE CELLULOSE

(a) This specification relates to regenerated cellulose, crosslinked and alkylated with epichlorohydrin and propylene oxide, then derivatised with quaternary amine groups whereby the amount of epichlorohydrin plus propylene oxide does not exceed 250% by weight of the starting quantity of cellulose.

(b) The resins are limited to use in aqueous process streams for the isolation and purification of protein concentrates and isolates. The pH range for the resins shall be no less than 2 and no more than 10, and the temperatures of water and food passing through the resin bed shall not exceed 50°C.

(c) When subjected to the extraction regime listed in the CFR, part 21, 173.25(c)(4), but using dilute hydrochloric acid at pH2 in place of 5% acetic acid, the ion exchange resins result in no more than 25ppm of organic extractives.

ADDENDUM 8

SPECIFICATION FOR DIETHYL AMINOETHYL CELLULOSE

(a) This specification relates to:

(i) Regenerated cellulose, crosslinked and alkylated with epichlorohydrin and propylene oxide, then derivatised with tertiary amine groups whereby the amount of epichlorohydrin plus propylene oxide does not exceed 250% by weight of the starting quantity of cellulose; and

(ii) Regenerated cellulose, crosslinked and alkylated with epichlorohydrin then derivatised with tertiary amine groups whereby the amount of epichlorohydrin does not exceed 10% by weight of the starting quantity of cellulose.

(b) The resins are limited to use in aqueous process streams for the isolation and purification of protein concentrates and isolates. The pH range for the resins shall be no less than 2 and no more than 10, and the temperatures of water and food passing through the resin bed shall not exceed 50°C.

(c) When subjected to the extraction regime listed in the CFR part 21, 173.25(c)(4), but using dilute hydrochloric acid at pH2 in place of 5% acetic acid, the ion exchange resins shall result in no more than 25ppm of organic extractives.

ADDENDUM 9

SPECIFICATION FOR CARBOXYMETHYL CELLULOSE

(a) This specification relates to regenerated cellulose, crosslinked and alkylated with epichlorohydrin and propylene oxide, then derivatised with carboxymethyl groups whereby the amount of epichlorohydrin plus propylene oxide does not exceed 250% by weight of the starting quantity of cellulose.

(b) The resins are limited to use in aqueous process streams for the isolation and purification of protein concentrates and isolates. The pH range for the resins shall be no less than 2 and no more than 10, and the temperatures of water and food passing through the resin bed shall not exceed 40%C.

(c) When subjected to the extraction regime listed in the CFR part 21, 173.25(c)(4), but using dilute hydrochloric acid at pH2 in place of 5% acetic acid, the ion exchange resins shall result in no more than 25ppm of organic extractives.

[5] Standard A16

omit

Group VII (Ion-Exchange resins) in Table II (Processing Aids Restricted by Function and Residue Level) in the Schedule

substitute

Group VII - Ion-Exchange Resins

Column 1 **Substance**	**Column 2** **Maximum permitted residue (mg/kg)**
Cross-linked phenol-formaldehyde activated with one or both of the following: triethylene tetramine and tetraethylenepentamine	NS
Cross-linked polystyrene, chloromethylated, then aminated with trimethylamine, dimethylamine, diethylenetriamine, or dimethylethanolamine	NS
Divinylbenzene copolymer	NS
Epichlorohydrin cross-linked with ammonia and then quaternised with methyl chloride to contain not more than 18% strong base capacity by weight of total exchange capacity	NS
Hydrolysed copolymer of methyl acrylate and divinylbenzene	NS

Methyl acrylate-divinylbenzene-diethylene glycol divinyl ether terpolymer containing not less than 7% divinylbenzene and not more than 2.3% diethylene glycol divinyl ether, aminolysed with dimethaminopropylamine and quaternised with methyl chloride	NS
Regenerated cellulose, crosslinked and alkylated with epichlorohydrin and propylene oxide, then derivatised with carboxymethyl groups whereby the amount of epichlorohydrin plus propylene oxide does not exceed 250% by eight of the starting quantity of cellulose	NS
Regenerated cellulose, crosslinked and alkylated with epichlorohydrin and propylene oxide, then derivatised with quaternary amine groups whereby the amount of epichlorohydrin plus propylene oxide does not exceed 250% by weight of the starting quantity of cellulose	NS
Regenerated cellulose, crosslinked and alkylated with epichlorohydrin and propylene oxide, then sulphonated whereby the amount of epichlorohydrin plus propylene oxide does not exceed 250% by weight of the starting quantity of cellulose	NS
Regenerated cellulose, crosslinked and alkylated with epichlorohydrin and propylene oxide, then derivatised with tertiary amine groups whereby the amount of epichlorohydrin plus propylene oxide does not exceed 250% by eight of the starting quantity of cellulose	NS
Sulphonated copolymer of styrene and divinylbenzene	NS

[6] Standard A16, Table VI

omit

"Regenerated cellulose, cross-linked and alkylated with epichlorohydrin and propylene oxide" in Column 1 of the Table and "NS" immediately opposite in Column 2 of the Table

ATTACHEMENT 2
OOS
OCTOBER 1999

EXPLANATORY NOTES - DRAFT

APPLICATION A367 – CELLULOSE-BASED ION EXCHANGE RESIN

The Australia New Zealand Food Authority has before it an application received on 10 November 1998 from Life Technologies Limited to amend the Australian *Food Standards Code* to permit the use of four cellulose-based ion exchange resin.

Approval was requested for four main variations of ion exchange resin using a common base matrix:

Sulphopropyl cellulose (SP resin);
Carboxymethyl cellulose (CM resin);
Diethyl aminoethyl cellulose (DEAE resin); and
Quaternary amine cellulose (QAE resin).

The base matrix is crosslinked hydroxypropylated regenerated cellulose.

- There are no significant toxicological concerns raised in relation to the application.

- Use of the four cellulose-based ion exchange resins is technologically justified for isolating specific proteins from production liquors or waste streams, which can then be used as food ingredients with highly specific functional characteristics.

- Permission to use the resins should be included in Group VII of Table II in Standard A16 – Processing Aids, and should not be restricted to specific applications.

- Specifications for the resins should be included as an addendum to Standard A11– Specifications for Identity and Purity of Food Additives, Processing Aids, Vitamins, Minerals, and Other Added Nutrients, until such time as specifications are included in the source specification document, the US Code of Federal Regulations (US CFR).

- A consequential amendment should be made to draft Standard 1.3.4 – Identity and Purity, of the proposed joint Food Standards Code, to include the US CFR as a secondary source of specifications.

PROPOSED DRAFT VARIATION TO THE AUSTRALIAN FOOD STANDARDS CODE

Secretariat to action

REGULATION IMPACT ANALYSIS

The Authority develops food regulation suitable for adoption in Australia and New Zealand. It is required to consider the impact, including compliance costs to business, of various regulatory (and non-regulatory) options on all sectors of the community which includes the consumers, food industry and governments in both countries. The regulation impact assessment will identify and evaluate, though not be limited to, the costs and benefits of the regulation, and its health, economic and social impacts. In the course of assessing the regulatory impact, the Authority is guided by the Australian *Guide to Regulation* (Commonwealth of Australia 1997) and *New Zealand Code of Good Regulatory Practice.*

Consideration of the Regulatory Impact for this proposal concludes that the benefits to industry and consumers of providing permission for the use of cellulose-based ion exchange resins outweighs any slight costs to enforcement agencies as a result of implementing and administering new requirements.

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.

This matter does not need to be notified to the WTO as a SPS notification or a TBT notification because, while there is no international standard for the regulation of processing aids, or specifically ion exchange resins, the matter is not expected to have a 'significant' trade effect.

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 Australia other than from New Zealand** must comply solely with the Australian *Food Standards Code.*

- **Food imported into New Zealand 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.

- **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 **also** be imported into Australia from New Zealand provided it complies with the New Zealand *Food Regulations 1984.*

- **Food manufactured in Australia and sold in Australia** must for most products comply solely with the Australian *Food Standards Code.*

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, prepared draft variations to the Australian *Food Standards Code* and will now conduct an inquiry to consider the draft variations and its regulatory impact.

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 A367** at one of the following addresses:

Australia New Zealand Food Authority
PO Box 7186
Canberra Mail Centre ACT 2610
AUSTRALIA
Tel (02) 6271 2222 Fax (02) 6271 2278

Australia New Zealand Food Authority
PO Box 10559
The Terrace WELLINGTON 6036
NEW ZEALAND
Tel (04) 473 9942 Fax (04) 473 9855

Submissions should be received by the Authority by **..... 1999.**

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>.

ATTACHEMENT 3
OOS
OCTOBER 1999

TOXICOLOGICAL REPORT

A367 – CELLULOSE-BASED ION EXCHANGE RESINS

The applicant has applied for permission for approval of four cellulose-based ion exchange resins which are derivatives of regenerated cellulose, namely, sulphopropyl cellulose, carboxymethyl cellulose, diethyl aminoethyl cellulose and quaternary amine cellulose. A list of reagents used in each resin was supplied.

The applicant stated in the application that no formal toxicological studies have been carried out on the resins and suggested, that considering that their structure is very similar to native cellulose and is readily biodegradable, that they would pose a very low toxicological concern. Furthermore, an application for approval of these resins has been submitted to the USFDA and the result is pending.

Regulation of ion-exchange resins

Limited literature is available on the previous regulation of ion exchange resins for food use.

Australian Food Science and Technology Committee 1991

The NHMRC Working Party on Processing Aids drew to the attention of the FST that as there was limited data on the safety of ion exchange resins that only resins that had FDA or NHMRC approval would be included in the 'Guidelines for the Use of Processing Aids'.

Council of Europe

Adopted a resolution on ion exchange resins 13 September 1989:

> "ion exchange resins used to process food may, by reason of the migration of their components, pose under certain conditions a risk to human health".

The most recent resolution 30 September 1997 listed substances that were used in the manufacture of ion exchange and adsorbent resins for food processing. However, they did not include cellulosic ion exchangers.

Review of Standard A16

At Preliminary Assessment, ANZFA proposed that the US regulations for ion exchange resins were more comprehensive than those listed in Standard A16, and

that this posed a potential barrier to trade for importers, as well as potentially restricting innovation within Australia and New Zealand.

The *AFGC* supported the inclusion of US approved ion exchange resins in the joint processing aids standard. *Frucor Processing* suggested that alignment with the "European Model" was more desirable than alignment with the US regulations. *Frucor Processing* claim that alignment with US regulations would mean that they could not continue to use some particular resins, that they are currently using, as they were not recognised by the US regulations. Furthermore, they contended that the US regulations did not reflect the more recent innovations in resin technology.

Frucor Processing state in their submission that the European Model is currently before the Council of Europe, and as it is still under development, it contains all the recent data on current resin manufacturing processes, as well as maximum residues expected in foods. They also state that the primary advantage of the European Model is that it attempts to accommodate the adoption of future innovations in resin manufacture, without requiring continual changes to the legislation.

There are limitations in adopting a list of US approved ion exchange resins for use in Australia and New Zealand, for the reasons outlined in the submission received from *Frucor Processing*. However the European Model is still in a draft stage, so ANZFA cannot adopt its recommendations until it has been adopted by the EU in its final form.

ANZFA proposes to list the US approved ion exchange resins in the interim, and proposes to review the regulation of ion exchange resins, if and when the European Model is adopted. ANZFA recognises that this has the potential to limit practices in the New Zealand industry. However, with sufficient lead-in time for the introduction of the proposed processing aids standard, industry and consumers are unlikely to be adversely affected in the longer term if the European Model progresses in the next year or two.

Propylene oxide and epichlorohydrin

From analysis of the reagents used in construction of the resins supplied by the applicant, two principle components may raise toxicological concerns, propylene oxide and epichlorohydrin. These are discussed below.

The *Australian Food Standards Code* does not prescribe levels for either chemicals in any food. The EU legislation has set a maximum limit of 1 mg/kg for epichlorohydrin and propylene oxide in materials or articles in contact with food (EC 1990).

Propylene oxide and epichlorohydrin have been previously evaluated for any toxicological concerns. Relevant toxicological data on both epichlorohydrin and propylene oxide have been evaluated by the USA EPA. The USEPA have failed to establish a reference dose for chronic oral exposure for both compounds, and as

such, due to the evidence of carcinogenicity in animals (albeit insufficient evidence in humans) that there has not been established a safe level of consumption for humans. Available toxicological data on the two chemicals have been summarised below.

Epichlorohydrin

An extensive review and summary of the animal and human toxicity data has been performed (IPCS, 1984). In laboratory animals epichlorohydrin is rapidly absorbed after ingestion and is distributed to the liver, kidneys and pancreas.

A long-term study in male rats administered epichlorohydrin in the drinking water for 81 weeks reported a decrease in leucocytes and an increase in incidence of forestomach hyperplasia at 18mg/kg bw/day and tumours of the forestomach at a dose of 39mg/kg bw/day.

A 2-year gavage study in rats, using doses of 2 or 10 mg/kg bw/day, also reported induction of forestomach carcinomas. Epichlorohydrin has been shown to be genotoxic both in *vitro* and in *vivo*. It is an alkylating agent and a direct acting mutagen.

The International Agency for Research on Cancer has concluded that epichlorohydrin is probably carcinogenic to humans (Group 2A, insufficient evidence in humans, sufficient evidence in animals) (IARC, 1987).

Based on these health considerations, it has been established that the concentration of epichlorohydrin in drinking water should not exceed 0.0005 mg/L (NHMRC, 1996).

Propylene oxide

Toxicological data on propylene oxide has been reviewed in a document from the USEPA Integrated Risk Information System internet site.

Animal data consisted of oral, inhalation and subcutaneous studies in three strains of rats and two strains of mice. Propylene oxide caused tumours at or near the site of administration in rodents, causing forestomach tumours following oral administration and nasal tumours after inhalation exposure.

Groups of 50 female Sprague-Dawley rats were administered propylene oxide by gavage (twice weekly in salad oil) at 0, 15 or 60 mg/kg bw for 150 weeks. Forestomach tumours developed in high dose treated animals during week 79 (Dunkelberg, 1982).

It was suggested that it was a probable human carcinogen as there was evidence for mutagenicity in a variety of test systems and the fact that propylene oxide is

structurally similar to other chemicals that demonstrate carcinogenic activity in animals.

The Chemical Assessments Unit of the TGA evaluated propylene oxide in October 1986.

Propylene oxide is clearly mutagenic in a wide range of *in-vitro* studies, however, the in-vivo results are generally negative with the exception of a single micronucleus assay. Repeat assays were negative when propylene oxide was administered orally or when administered IP in a different vehicle.

Propylene oxide generally produces cancers at the portal of entry. Hence, squamous cell carcinomas of the forestomach were observed after oral administration in rats at 15 mg/kg bw, local sarcomas in mice after subcutaneous injection and respiratory epithelial tumours following inhalational exposure in rats and mice.

There should be no residues in food.

Migration testing

The applicant supplied extensive data on the migration of epichlorohydrin and propylene oxide from the resins.

Diethylaminoethylcellulose resins

Water, 15% ethanol in water, pH 3.5 water and n-heptane extractions of Diethylaminoethylcellulose resins contain less than 0.005mg/L epichlorohydrin and 0.02mg/L propylene oxide. It was concluded that no epichlorohydrin or propylene oxide was able to be extracted from these resins.

Carboxymethylcellulose resins

The data showed that in resins washed according to the manufacturer's instructions no chloroacetic acid was detected in the resins nor in the solvents used to extract the resins (LOD 5 ppb).

Extraction data was not submitted by the applicant for epichlorohydrin and propylene oxide. ANZFA contacted the applicant for an explanation. The applicant responded by claiming that the production reactions for this resin are more vigorous and of longer time course than the other resins and the likelihood of finding residues is extremely low.

Quaternary Amine Cellulose-QAE resins

Water, 15% ethanol in water, pH 3.5 water and n-heptane extractions of quaternary amine cellulose-QAE resins contain less than 0.005mg/L

epichlorohydrin and 0.02mg/L propylene oxide. It was concluded that no epichlorohydrin or propylene oxide was able to be extracted from these resins.

Cross-Linked Sulphopropylcellulose-SP2 Resins

Water, 15% ethanol in water, pH 3.5 water and n-heptane extractions of sulphopropylcellulose-SP2 resins contain less than 0.01mg/L of epichlorohydrin and propylene oxide.

Conclusions

In consideration of the toxicological concerns regarding exposure to propylene oxide and epichlorohydrin, the levels of these compounds in foods should be as low as can be achieved by good manufacturing processes.

The applicant supplied data on extraction tests carried out on resin samples to check specifically for residues of propylene oxide and epichlorohydrin. These chemicals were at or below limits of detection, which were 5-20 ppb for all four resin types.

The USFDA had accepted that there are negligible residues and did not require specific toxicological testing of the resins.

Provided that there were no detectable residues of the reagents epichlorohydrin and propylene oxide in the ion-exchange resins, there would be no significant toxicological concerns.

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ATTACHEMENT 4
OOS
OCTOBER 1999

FOOD TECHNOLOGY REPORT

A367 – CELLULOSE-BASED ION EXCHANGE RESINS

Introduction

An application was received by ANZFA requesting approval of four cellulose based ion exchange resins as processing aids for the isolation of proteins from production liquors or waste streams. These proteins may then be used as food ingredients, providing particular nutritional or functional properties to a food product.

The applicant claims that purification of proteins using ion exchange resins results in a higher degree of protein purity than other separation technologies. The higher degree of purity of the proteins enhances their functional properties.

One of the main uses of these processing aids would be for the treatment of whey to recover and refine whey proteins, although other uses may be possible, for example isolation of protein from abattoir waste (1).

There are four main variations of ion exchange resin using a common base matrix:

Sulphopropyl cellulose (SP resin);
Carboxymethyl cellulose (CM resin);
Diethyl aminoethyl cellulose (DEAE resin); and
Quaternary amine cellulose (QAE resin).

The base matrix is crosslinked hydroxypropylated regenerated cellulose.

Existing Regulation

The use of ion exchange resins as processing aids in many food manufacturing processes is already established. This is reflected in Standard A16 – Processing Aids, of the Food Standards Code, which lists a number of ion exchange resins in Group VII of Table II, Processing Aids Restricted by Function and Residue Level. There are also a number of ion exchange resins listed in Table VI – Processing Aids Used in Packaged Water and in Water Used as an Ingredient in Other Foods, including 'regenerated cellulose, cross-linked and alkylated with epichlorohydrin and propylene oxide'.

This application represents an extension of use of the existing cellulose-based resin from water treatment to all foods, and approval of three new cellulose-based resins for use in food.

Approval of this application will result in the four cellulose based resins being listed in Group VII of Table II.

The New Zealand Food Regulations and Codex do not provide separate standards for the regulation of processing aids.

The four cellulose based ion exchange resins which are the subject of this application are currently undergoing assessment and approval by the US Food and Drug Administration for inclusion in the United States Code of Federal Regulations (US CFR)

Ion Exchange (adsorption) technology

An ion exchange resin consists of large molecules (polymers) that have many ionic sites (2). Cationic resins carry positive ions (eg H+, NH3+, etc) to which negative ions (anions) are attracted. Anionic resins are the reverse, carrying negative ions (eg OH-, COO-, etc) and exchanging positive ions (cations) (3). Various resins will adsorb ions under one set of conditions and release them under other conditions (4).

As the process stream is passed through the ion exchange resin the potential for exchange diminishes as the charged sites become occupied with cations or anions. The resins can be regenerated by flushing with acids (eg HCl for cationic resins) and bases (eg NaOH for anionic resins) to strip off the adsorbed ions to be replaced with the original exchangeable ions (3).

Ion exchange technology is currently used for such purposes as water softening, metal recovery, purification of chemicals and chemical analysis (4).

Ion exchange processing of whey is most often carried out with synthetic ion exchange resins which consist of co-polymer beads to which ionic groups have been attached, eg co-polymerisedstyrene and divinyl benzene with the styrene group carrying the exchangeable ion (3).

The resins are usually packed into two columns and clarified defatted whey is passed first through the cationic resin and then through the anionic resin. The salts in whey are dissociated as Ca2+ and Cl- and also Na+ and Cl-. The ions are removed by exchange with H+ and OH- ions, yielding a whey with a much lower salt content and more useful in a wider range of applications (3).

It is usual for a level of 90-98% demineralisation to be achieved and demineralisation normally takes place at low temperatures (ie 8-10°C) to reduce the possibility of microbial growth in the ion exchange columns (3).

Methods of Whey Protein Fractionation

Whey solids contain about 11% protein. Many of the most popular methods of whey treatment aim at increasing this level, with end-products containing between 35% and virtually 100% protein (5).

Ultrafiltration is the most commonly used method to produce a range of whey products with increased protein content, known as whey protein concentrates (WPCs). WPCs are produced from a wide range of wheys, generally to protein contents of 35% (often used as a less expensive skim milk powder replacer), 50% (not often manufactured and generally used for specific applications only) and 75%. WPCs of 75% protein content can have very desirable functional properties, and these can be readily manipulated by modification of the manufacturing process. Such products often have excellent water binding, gelation and emulsifying properties (5).

Generally, the functionality of WPCs manufactured by ultrafiltration is often poor and/or highly variable and well below what can be expected from their protein composition. This may be due to mechanical or heat damage to the proteins during manufacture, or to the presence of other compounds in whey which inhibit the development of full functionality (5).

Precipitation of whey proteins, such as Lactalbumin, can be carried out by heat treatment under appropriate conditions of pH and ionic strength. Whey is heated to denature, coagulate and precipitate the whey proteins, the sediment is recovered (settling and decantation or centrifugation), washed to remove excess salt and the product recovered. The heat treatment used in this process results in extensive denaturation of the whey proteins, resulting in a product of poor functionality. The product may be used where protein fortification is necessary but is not required to provide any functional properties (5).

Whereas WPCs contain the whey proteins in about the same proportions as that in whey (for example those products produced by ultrafiltration), protein isolates or protein fractions are high protein products with a higher ratio of a particular protein than that present in whey. Such protein isolates may be manufactured by the use of a non-specific absorbent to bind the proteins in whey. Absorbents which have been commercially used include carboxy-methylcellulose and a range of mineral oxides. Although these absorbents are comparatively non-specific, they can show preference for binding particular proteins under set conditions of pH, temperature and ionic strength and therefore can be used to produce protein isolates (5).

Evaluation Using the Codex General Principles for the Use of Food Additives

(i) To preserve the nutritional qualities of the food; an intentional reduction of the nutritional quality of the food would be justified in the circumstances set in sub-paragraph (ii), and also in other cases where the food does not constitute a major item of the normal diet;

As the cellulose-based ion exchange resins are used in the manufacture protein based food ingredients with specific nutritional or functional characteristics, the food ingredients may be used to enhance the nutritional qualities of food.

(ii) To provide the ingredients or constituents necessary for food products manufactured for consumer groups with specific dietary needs;

Not relevant to this application.

(iii) To enhance the keeping quality or stability of a food or to improve its organoleptic properties, provided that this does not so change the nature, substance or quality of the food as to deceive the consumer;

Not relevant to this application.

(iv) To aid in the manufacture, processing, preparation, treatment, packaging, transport or storage of food; provided that the additive is not used for the purpose of masking the effects of the use of defective raw materials or of undesirable (including unhygienic) methods or techniques during the course of any of these activities;

The four cellulose-based ion exchange resins are considered as processing aids. They are used in the manufacture protein based food ingredients with specific nutritional or functional characteristics. The resins perform no function (and there is likely to be no detectable residues present) in the food ingredient or the final food.

(v) To maintain the safety of foods by inhibiting the growth of bacteria or other organisms that may cause disease.

Not relevant to this application.

Conclusion

- Ion exchange resins are currently permitted in the Food Standards Code as processing aids in the processing of foods or food ingredients.
- The use of cellulose based ion exchange resins is technologically justified.
- Cellulose-based ion exchange resins may be used to isolate protein from production liquors or waste streams.
- When used under specific conditions of pH and temperature, cellulose-based ion exchange resins are able to isolate selected proteins in a more purified form than other methods of protein separation technology, which greatly increases the functional properties of the protein.

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