INQUIRY REPORT

APPLICATION 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 *Food Standards Code* 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.

Executive Summary from the Full Assessment Report

- 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 were 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 United States Code of Federal Regulations (US CFR).

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

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

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

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

Executive Summary from the Inquiry Report

- Minor amendments to drafting prepared at Full Assessment are necessary to:

    - consistently name the resins;
    - update the specification for the SP resin to the current (2000) US CFR;
    - modify the specifications to the CM and DEAE resins, making them slightly more stringent; and
    - continue the existing permission for the SP resin to be used as a processing aid in packaged water and water used as and ingredient in other foods.

PREVIOUS ANZFA CONSIDERATION

ANZFA undertook a Full Assessment of the Application in October 1999, and the matter was subsequently advertised in accordance with section 24 of the *Australia New Zealand Food Authority Act 1991* on 10 November 1999, with a comment period of six weeks.

SUMMARY OF NEW SUBMISSIONS RECEIVED AT INQUIRY

At inquiry submissions were received from the **Food Technology Association of Victoria Inc (FTA Vic)** and **InforMed Systems Ltd**, both of which supported the draft variations to the *Food Standards Code*. The **FTA Vic** queried why there was no specific addendum-specification for sulphopropyl cellulose.

A submission from the **Queensland Health Department** sought assurances in relation to the toxicological evaluation of the resins. **Queensland Health Department** also suggested that the existing reference to one cellulose-based ion exchange resin listed in Table VI - Processing Aids used in Packaged Water and in Water Used as an Ingredient in Other Foods, of the processing aids standard should remain there, and all four resins be included in Table II Group VII – Ion Exchange Resins.

Additionally, the applicant requested amendments to the specifications proposed for two of the resins, the CM and DEAE resins.

ASSESSMENT OF ISSUES RAISED IN PUBLIC SUBMISSIONS AT INQUIRY

1. Specification for the SP resin

The **FTA Vic** queried why there was no specific addendum-specification for sulphopropyl cellulose.

As stated at Full Assessment, the Schedule to Standard A11 – Specifications for the Identity and Purity of Food Additives, Processing Aids, Vitamins, Minerals and Other Added Nutrients, currently cites the specification for the SP resin as the US Code of Federal Regulation (CFR), Title 21, part 173.25 (a)(20), in force as at 1 April 1994.

This differs slightly from the current CFR, in force as at 1 April 2000. As a part of this application the specification cited in Standard A11 is proposed to be updated to the current CFR.

One other resin, the QAE resin, has been listed in the inventory of effective premarket notifications for food contact substances, with specifications cited referring to CFR 173.25. The remaining two cellulose-based resins, CM and DEAE, have not yet been approved in the US.

The applicant has provided interim specifications for the QAE, CM, and DEAE resins for approval, based on specifications provided to the US FDA. The supplied specifications 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 in the addendum to Standard A11 will be deleted and the appropriate reference included in the schedule.

2. Specifications for the CM and DEAE resins

Subsequent to the preparation of the draft variations to the Code, in relation to this application, the applicant has provided further information and slightly amended the proposed specifications for the CM and DEAE resins. This is in line with the specifications currently proposed to be included in the US CFR. The changes to the proposed drafting are as follows:

Resin	Proposed at Full Assessment	Proposed at Inquiry
CM	… whereby the amount of epichlorohydrin plus propylene oxide does not exceed **250%** by weight…	… whereby the amount of epichlorohydrin plus propylene oxide does not exceed **70%** by weight…
DEAE (High Capacity)	… whereby the amount of epichlorohydrin plus propylene oxide does not exceed **250%** by weight…	… whereby the amount of epichlorohydrin plus propylene oxide does not exceed **70%** by weight…

Drafting proposed for insertion into Standard A16 – Processing Aids, should be similarly amended.

3. Toxicological Evaluation

Queensland Health Department sought assurances from ANZFA that the manufacturing processes used to produce the resins are such that potentially toxic reaction products and unreacted compounds such as amines are removed to the greatest possible extent. **Queensland Health Department** was also concerned that the purity tests described in CFR Part 21, 173.25 and in the proposed addenda to the standard adequately reflect the severity of the conditions of use of all of the resins.

From the data that was presented to ANZFA the following was concluded in the toxicological report:

"Considering the underlying toxicological concerns for propylene oxide and epichlorohydrin the levels of these compounds in foods should be nil or 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. In summary, 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.
>
> In conclusion, provided that there were no residues of the reagents epichlorohydrin and propylene oxide in the ion-exchange resins there would be no significant toxicological concerns."

The applicant also supplied ANZFA with data that was submitted to the USFDA for toxicological and environmental safety assessment. The level of epichlorohydrin reaction products left at the end of resin production is very low. Propylene oxide is either incorporated into the final product or converted to by products such as propylene glycol (a non-toxic compound used as an emulsifier in foods). Other chemicals used in the production of the resins are of limited toxicological significance as they are either incorporated into the final product, converted to non-toxic bi-products or washed out of the product unchanged. Many of the reagents already have approval for use in the *Food Standards Code*.

Furthermore, ANZFA notes that the USFDA previously approved the sulphopropyl resin (SP) under regulation US CFR 21, 173.25 and recently granted pre-market approval for the QAE resins in June 2000. Additionally, the applicant will shortly submit data on carboxymethyl and diethylamino resins for approval by the USFDA and has informed ANZFA that the main safety issues have already been dealt with for the SP and QAE resins.

The purity tests described in CFR Part 21, 173.25 and in the proposed addenda to the standard, limit use of the resins to aqueous process streams for the isolation and purification of protein concentrates and isolates, and state that "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". The US CFR specifications also state that under conditions of the highest temperature limit and using acid at pH2, the ion exchange resins result in no more than 25ppm of organic extractives.

The specifications limit the severity of the conditions of use of all of the resins. It is unlikely that these conditions of use would be exceeded as the extreme conditions of pH and temperature would adversely affect the functional properties of resulting protein isolates.

4. SP Resin as a water treatment agent

Queensland Health Department noted that ANZFA proposed to omit the reference to 'regenerated cellulose, cross-linked and alkylated with epichlorohydrin and propylene oxide' in Table VI - Processing Aids used in Packaged Water and in Water Used as an Ingredient in Other Foods, of Standard A16 and in the Schedule to A11. **Queensland Health Department** wondered whether the deletion of this substance is intentional, because it presumably still has a use in the processing of packaged water. The four products which are the subject of the application are chemical derivatives of this substance (and have different areas of application), and it would not seem that permission to use the former would logically extend to the latter. A reference to the 'parent' substance is therefore needed if it continues to have a use in the food industry.

Table VI - Processing Aids used in Packaged Water and in Water Used as an Ingredient in Other Foods, of Standard A16 – Processing Aids, currently permits the use of 'regenerated cellulose, cross-linked and alkylated with epichlorohydrin and propylene oxide'.
While the four products which are the subject of the application appear to be chemical derivatives of this substance, reference to the specification (CFR Part 21, 173.25) restricts use to only 'regenerated cellulose, cross-linked and alkylated with epichlorohydrin and propylene oxide *then sulphonated*'. Therefore the current permission in Table VI of Standard A16 is limited specifically to the SP resin.

However, in moving permission for the SP resin from Table VI to Group VII – Ion Exchange Resins, of Table II, it was not intended to remove permission to use the resin for water treatment. The listing of the SP resin should be retained in Table VI of Standard A16, to ensure that current permissions continue to apply.

ANZFA does not propose to omit the reference to 'regenerated cellulose, cross-linked and alkylated with epichlorohydrin and propylene oxide' from the schedule to Standard A11, but rather update the specification in the schedule to the current US CFR. In addition, specifications for the remaining three cellulose-based ion exchange resins which are the subject of this application will be included as addenda to Standard A11.

OTHER MATTERS

Approval of the resins in the US

The SP resin is approved for use in the US and cited, with specifications, in the US CFR. The QAE resin has recently (10 June 2000) been listed in the inventory of effective premarket notifications for food contact substances, as maintained by the US FDA Office of Premarket Approval, and is authorised for food contact use.

The remaining two resins, the DEAE and CM resins, are expected to be submitted in the near future for authorisation for food contact use and listing in the inventory of effective premarket notifications for food contact substances.

Naming of the resins

Minor amendments have been made to the drafting to ensure that naming of the resins is consistent with US FDA listings and consistent between Standards A11 and A16.

Inclusion in the Joint *Food Standards Code*

Permissions to use the four ion exchange resins should be included in the draft Joint Australia New Zealand *Food Standards Code*. ANZFA plans to prepare a proposal, pursuant to section 36 of the *Australia New Zealand Food Authority Act 1991*, to include the four ion exchange resins in the Table to Clause 8, Permitted Ion Exchange Resins, of Standard 1.3.3 – Processing Aids, and Standard 1.3.4 – Purity and Identity, of the Joint *Food Standards Code*.

CHANGES TO FULL ASSESSMENT/RIS RESULTING FROM INQUIRY

As a result of a submission received from the applicant at Inquiry, there have been minor amendments made to the drafting proposed at Full Assessment. However, the conclusions made in relation to the Full Assessment and Regulation Impact Statement remain unchanged.

CONCLUSIONS

As concluded at the Full Assessment:

- 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 US CFR.
- A consequential amendment should be made to draft Standard 1.3.4 – Identity and Purity, of the proposed joint Australia New Zealand *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.

ATTACHMENTS:

1. Proposed Draft Variations as amended
2. Statement of Reasons
3. Summary of Public Comment

ATTACHMENT 1

DRAFT VARIATION TO THE AUSTRALIAN FOOD STANDARDS CODE AS AMENDED

A367 – CELLULOSE-BASED ION EXCHANGE RESINS

To commence: On gazettal

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

omit

1 April 1994

substitute

1 April 2000

[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

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 70% by weight of the starting quantity of cellulose

immediately after

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 *in Column 1 of the Schedule*

and

Addendum 8 immediately opposite in Column 2 of the Schedule

insert

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

immediately after

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 70% by weight of the starting quantity of cellulose *in Column 1 of the Schedule*

and

Addendum 9 immediately opposite in Column 2 of the Schedule

insert

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 70% by weight of the starting quantity of cellulose

immediately after

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 *in Column 1 of the Schedule*

and

Addendum 10 immediately opposite in Column 2 of the Schedule

[4] *Standard A11, immediately after Addendum 7*

insert

ADDENDUM 8

(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 70% 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.

ADDENDUM 9

(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 10

(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 70% 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.

[5] Standard A16, Group VII of Table II of 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 70% by weight 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 70% by weight of the starting quantity of cellulose	NS
Sulphonated copolymer of styrene and divinylbenzene	NS

ATTACHMENT 2

STATEMENT OF REASONS

APPLICATION A367 – CELLULOSE BASED ION EXCHANGE RESINS

FOR RECOMMENDING A VARIATION TO STANDARD A16 – PROCESSING AIDS, AND STANDARD A11 – SPECIFICATIONS FOR IDENTITY AND PURITY OF FOOD ADDITIVES, PROCESSING AIDS, VITAMINS, MINERALS AND OTHER ADDED NUTIRENTS, TO PERMIT THE USE OF FOUR CELLULOSE-BASED ION EXCHANGE RESINS

The Australia New Zealand Food Authority (ANZFA) has before it an application received on 10 November 1998 from Life Technologies Limited to amend the *Food Standards Code* 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.

ANZFA recommends the adoption of the draft variation, as amended, for the following reasons:

- 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.

The drafting prepared after Full Assessment is amended for the following reasons:

- consistently name the resins;

- update the specification for the SP resin to the current (2000) United States Code of Federal Regulations;

- modify the specifications to the CM and DEAE resins, making them slightly more stringent; and

- continue the existing permission for the SP resin to be used as a processing aid in packaged water and water used as and ingredient in other foods.

The commencement date of the amended draft variation is from the date of gazettal.

REGULATION IMPACT

ANZFA has undertaken a regulation impact assessment process which also fulfils the requirement in New Zealand for an assessment of compliance costs.

That process concluded that the amendment to the Code is necessary, cost effective and of benefit to both producers and consumers.

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).

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 was not notified to the WTO.

DRAFT VARIATIONS TO THE *FOOD STANDARDS CODE*

(DRAFTING WILL BE INSERTED HERE)

ATTACHMENT 3

SUMMARY OF PUBLIC COMMENT

A367 – CELLULOSE-BASED ION EXCHANGE RESINS

Submittor	Comment
Food Technology Association of Victoria Inc	Support A question was raised as to why there is no specific addendum specification for Sulphopropyl cellulose.
Informed Systems Ltd	Support
Environmental Health Unit, Queensland Health	Sought assurances from ANZFA that the manufacturing processes used to produce the resins are such that potentially toxic reaction products and unreacted compounds such as amines are removed to the greatest possible extent. Also concerned that the purity tests described in CFR Part 21, 173.25 and in the proposed addenda to the Standard adequately reflect the severity of the conditions of use of all of the resins. It was noted that ANZFA proposes to omit the reference to 'regenerated cellulose, cross-linked and alkylated with epichlorohydrin and propylene oxide' in Table VI of Standard A16 and in the schedule to A11. Queensland Health wondered whether the deletion of this substance is intentional, because it presumably still has a use in the processing of packaged water. The four products which are the subject of the application are chemical derivatives of this substance (and have different areas of application), and it would not seem that permission to use the former would logically extend to the latter. A reference to the 'parent' substance is therefore needed if it continues to have a use in the food industry.