

**Supporting document 1**

Risk and technical assessment report – Application A1120

Agarose Ion Exchange Resin as a Processing Aid for Lactoferrin Production

# Executive summary

Application A1120 seeks approval to use an agarose ion exchange resin as a processing aid. The stated purpose of the resin, namely the production of high purity lactoferrin from bovine milk and milk-related products, is clearly described in the Application.

The resin has been approved by the United States Food and Drug Administration (USFDA) for use in the processing of milk and milk products, fruit and fruit juices, fruit drinks, beer and wine. A similar agarose ion exchange resin is already permitted in the Code as a processing aid for the removal of specific proteins and polyphenols from beer.

Lactoferrin, present in milk at low levels, has a range of physiological functions and the Application indicated that there is increasing interest in its use as a nutraceutical.

The information provided in the Application provides adequate assurance that use of the resin is technologically justified and is effective in achieving its stated purpose.

For each lactoferrin isolation cycle, the resin is subjected to cleaning/rinsing procedures that result in negligible impurity levels in the resin. This minimises the potential for resin impurities to be present in the isolated lactoferrin and in the flow-through milk/whey stream. Theoretical estimates of dietary exposure to resin impurities, calculated using conservative assumptions, provide confirmation that potential impurity levels are of no toxicological concern.

It is concluded that the proposed use of the agarose ion exchange resin as a processing aid for lactoferrin production is technologically justified and presents no identifiable public health and safety concerns.

**Table of contents**

[Executive summary i](#_Toc442967381)

[1 Introduction 2](#_Toc442967382)

[1.1 Objectives of the Assessment 2](#_Toc442967383)

[2 Food Technology Assessment 2](#_Toc442967384)

[2.1 Characterisation of the agarose ion exchange resin 2](#_Toc442967385)

[2.1.1 Identity of the agarose ion exchange resin 2](#_Toc442967386)

[2.1.2 Physical and chemical properties of the agarose ion exchange resin 3](#_Toc442967387)

[2.2 Production of the agarose ion exchange resin 4](#_Toc442967388)

[2.3 Specifications 4](#_Toc442967389)

[2.4 Technological function of the agarose ion exchange resin 4](#_Toc442967390)

[2.5 Food technology conclusion 5](#_Toc442967391)

[3 Hazard assessment 5](#_Toc442967392)

[3.1 Background 5](#_Toc442967393)

[3.2 Substances assessed by JECFA 6](#_Toc442967394)

[3.2.1 Food additives 6](#_Toc442967395)

[3.2.2 Contaminants 7](#_Toc442967396)

[3.2.3 Extraction solvents 7](#_Toc442967397)

[3.3 Other resin impurities 7](#_Toc442967398)

[Polyoxyethylene nonylphenyl phosphate ester, sodium salt 7](#_Toc442967399)

[Sodium borate 7](#_Toc442967400)

[Glyceryl allyl ether 7](#_Toc442967401)

[Allyl glycidyl ether 8](#_Toc442967402)

[Glycidol 8](#_Toc442967403)

[Epichlorohydrin 8](#_Toc442967404)

[3.4 Hazard assessment conclusion 8](#_Toc442967405)

[4 Dietary exposure assessment 8](#_Toc442967406)

[4.1 Estimated dietary exposure to resin impurities 8](#_Toc442967407)

[5 Risk characterisation 9](#_Toc442967408)

[6 References 10](#_Toc442967409)

# 1 Introduction

FSANZ received an Application from Fonterra Co-operative Group Limited seeking approval to use an agarose ion exchange resin as a processing aid. The Application states that this resin will be used for the production of high purity lactoferrin from bovine milk and milk-related products. The resin achieves this by binding and extracting lactoferrin from dairy streams such as skim milk and whey.

Lactoferrin, present in milk at low levels, has a range of physiological functions and the Application indicated that there is increasing interest in its use as a nutraceutical and as a potential pharmaceutical.

The agarose ion exchange resin is in the form of porous, spherical beads with a diameter of between 100−300 µm. It comprises an agarose backbone cross-linked with epichlorohydrin and reacted with allyl glycidyl ether (or propylene oxide), and then derivatised with sulphonate groups, to provide cation exchange functionality, which allows for effective binding and extraction of lactoferrin. Between 60−100% of the lactoferrin in the dairy stream passed through the resin is adsorbed.

Although other techniques for lactoferrin separation have been studied, the Application states that the agarose ion exchange resin is the only viable commercial method currently available for lactoferrin production.

## 1.1 Objectives of the Assessment

As there are no permissions for the use of this particular agarose ion exchange resin in the production of lactoferrin currently in the *Australia New Zealand Food Standards Code* (the Code), any application to amend the Code to permit the use of this resin as a food processing aid requires a pre-market assessment.

The objectives of this risk assessment are to:

* determine whether the proposed purpose is clearly stated and that the agarose ion exchange resin achieves its technological function in the form proposed to be used as a food processing aid
* evaluate any potential public health and safety concerns that may arise from the use of the agarose ion exchange resin as a processing aid.

# 2 Food Technology Assessment

## 2.1 Characterisation of the agarose ion exchange resin

### 2.1.1 Identity of the agarose ion exchange resin

Information regarding the identity of the agarose ion exchange resin that was taken from the Application has been verified using the USFDA Inventory of Effective Food Contact Substance (FCS) Notifications as a reference (USFDA 2004).

Generic common name: Agarose ion exchange resin

Chemical name: Agarose, polymer with (chloromethyl)oxirane, 2-hydroxy-3-(3-sulphopropoxy)propyl ethers, sodium salts

CAS number: 676618-71-6

Commercial name: SP Sepharose™ Big Beads Food Grade

### 2.1.2 Physical and chemical properties of the agarose ion exchange resin

The agarose ion exchange resin is a macroporous, strong cation exchanger, in the form of spherical beads with a diameter of between 100-300 µm. The resin comprises an agarose backbone highly cross-linked (6%) using epichlorohydrin and then reacted with allyl glycidyl ether (or propylene oxide). Sulphonate ion exchange groups are coupled through chemically stable ether bonds to the cross-linked agarose backbone. The Application indicated that the particle size and stability of the cross-linked agarose matrix are important factors for the efficient isolation of lactoferrin from skim milk/whey.

The medium is supplied in a liquid and gel suspension of 0.2 M sodium acetate in 20% v/v ethanol. The solution is colourless; the gel suspension is white to yellowish.

Schedule 18 of the Code permits the use of a comparable agarose ion exchange resin for the removal of specific proteins and polyphenols from beer (subsection S18—9). The resin which is the subject of this Application is similar with respect to the agarose backbone, which is cross-linked using epichlorohydrin. However, the currently permitted resin is derivatised with tertiary amine groups to provide anion exchange functionality, rather than derivatised with sulphonate groups, which provides cation exchange functionality (FSANZ 2007).

Figure 1 gives a structural representation of a fragment of the agarose ion exchange resin SP Sepharose™ Big Beads. The representation of complex gel structures using a chemical formula is not possible because the detailed structure has not been elucidated. In addition, substitution can take place at many different hydroxyl groups.



*Figure 1: Structural representation of a fragment of the agarose ion exchange resin SP Sepharose™ Big Beads (Source: Application)*

## 2.2 Production of the agarose ion exchange resin

The Application states that the manufacturing process to produce the agarose ion exchange resin is proprietary information. As such, no detailed information regarding the manufacturing process has been provided. However, the Application includes a schematic overview of the production process, which is similar to that for the permitted resin used to treat beer.

The production steps can be summarised as follows. An aqueous solution of agarose is dispersed in toluene to form droplets of between 100-300 µm in diameter. The gel is cross-linked with epichlorohydrin. The product is then wet-sieved and reacted with allyl glycidyl ether (or propylene oxide) to form the intermediate, allyl sepharose. The final step involves reacting allyl sepharose with sodium disulphite. After each manufacturing step, the product is washed repeatedly with an appropriate solution.

## 2.3 Specifications

There are no relevant specifications for agarose ion exchange resin referenced in the primary and secondary sources in Schedule 3. The comparable resin, which is permitted for the removal of specific proteins and polyphenols from beer (subsection S18—9) has an individual specification referenced in Schedule 3 (subsection S3—6). Another individual specification will need to be written into Schedule 3 for the resin for the production of lactoferrin.

To clearly differentiate between the two resins, they will be listed according to their composition. That is, the currently permitted resin will be re-named as an *amine* agarose ion exchange resin, and the new resin will be listed as a *sulphonate* agarose ion exchange resin.

The Application proposed a draft specification, and this was used as the basis for the following specification to be included in Schedule 3:

(a) This specification relates to agarose, cross-linked with epichlorohydrin and reacted with allyl glycidyl ether or propylene oxide, then derivatised with sulphonate groups, whereby the amount of epichlorohydrin plus allyl glycidyl ether or propylene oxide does not exceed 250% by weight of the starting quantity of agarose.

(b) When subjected to the extraction regime listed in the 21 CFR § 173.25(c)(4), but using dilute hydrochloric acid at pH 2 in place of 5% acetic acid, the ion exchange resins shall result in no more than 25 ppm of organic extractives.

## 2.4 Technological function of the agarose ion exchange resin

The agarose ion exchange resin is a macroporous, strong cation exchanger with specific characteristics that enable it to fulfil its technological function. These characteristics are:

* strong cation exchange functionality (i.e. the resin retains its function over a wide pH range)
* large pore size to bind lactoferrin, which has a high molecular mass
* large bead size to bind lactoferrin (which is present at low concentrations only) at extremely fast flow rates
* capacity to process dairy streams such as whey and skim milk without blockages
* sufficient mechanical strength to allow loading at high flow rates.

No other ion exchange resins in Schedule 18 of the revised Code have all of the above characteristics that ensure the efficient production of lactoferrin.

As the separation process can be run on small or larger scales, the sizes of the columns and the amount of resin required may vary widely. However, the main steps typically include:

1. Column preparation – The resin is packed into a fixed-bed ion exchange column, washed, rinsed and equilibrated to a suitable pH (the agarose beads are sold, stored and transported in 20% ethanol).
2. Pre-treatment – The dairy stream (whey or skim milk) is pre-treated by filtration or centrifugation to remove suspended solids.
3. Adsorption – The pre-treated dairy stream (pH adjusted) is passed through the column. The target substance, lactoferrin, is adsorbed (bound) to the charged functional groups of the resin. Between 60-100% of the lactoferrin is adsorbed.
4. Rinsing – The resin is rinsed using buffer (weak brine solution) to remove other minor milk proteins that have also bound to the resin. Typical rinsing volumes are 5-10 column volumes.
5. Desorption (elution) – Lactoferrin is desorbed from the resin with buffer (concentrated brine solution), typically 1-5 column volumes.
6. Ultrafiltration – Ultrafiltration is used to concentrate and de-salt the lactoferrin. Filtration or heat treatment is then applied to reduce microbial count.
7. Drying – The lactoferrin is freeze dried or spray dried to produce the finished product powder.

After each cycle, the resin is rinsed and equilibrated. Every five cycles, the column and resin are cleaned using alkali. The Application states that the resin may be used for a thousand cycles or more before it is discarded.

## 2.5 Food technology conclusion

The stated purpose of this agarose ion exchange resin as a processing aid, namely for use in the production of high purity lactoferrin from bovine milk and milk-related products, is clearly articulated in the Application. The evidence presented to support the proposed use provides adequate assurance that the resin is technologically justified and has been demonstrated to be effective in achieving its stated purpose. If this Application is approved Schedule 18 will need to be varied to include this new resin, and a specification for the resin will need to be written into Schedule 3.

# 3 Hazard assessment

## 3.1 Background

The Application indicated that 16 impurities in the resin may be present at trace levels in lactoferrin and in the flow-through dairy stream due to processing with the ion exchange resin (Table 1). Ten of these substances have been assessed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

Conclusions from the JECFA assessments are provided in Section 3.2. For the remaining six resin impurities, hazard information is provided in Section 3.3.

## 3.2 Substances assessed by JECFA

### 3.2.1 Food additives

As summarised in Table 1, six of the resin impurities are also used as food additives and have been assessed by JECFA. Summary information on these substances, including links to JECFA reports and monographs, is available from the online JECFA database.[[1]](#footnote-2)

Four substances (ethylcellulose, glycerol, sodium acetate and sodium sulphate) were assigned an Acceptable Daily Intake (ADI) of “not specified” or “not limited”, which indicates that dietary exposure to the substance arising from its use at levels necessary to achieve the desired effect, and from acceptable background levels in food, does not represent a health risk. The establishment of an ADI in numerical form was therefore not deemed necessary by JECFA.

For two of the substances, sodium metabisulphite and sodium hydrogen sulphite, the group ADI of 0–0.7 mg/kg bw for sulphur dioxide and sulphite compounds established by JECFA is applicable.

**Table 1: Resin impurities that have been assessed as food additives by JECFA**

|  |  |  |  |
| --- | --- | --- | --- |
| **Chemical name** | **CAS no.** | **INS No.a** | **JECFA ADI** |
| Ethylcellulose | 9004-57-3 | 462 | Not specified b |
| Glycerol | 56-81-5 | 422 | Not specified b  |
| Sodium acetate | 127-09-3 | 262(i) | Not limited b |
| Sodium sulphate | 7757-82-6 | 514(i) | Not specified b |
| Sodium metabisulphite | 7681-57-4 | 223 | 0–0.7 mg/kg bw c |
| Sodium bisulphite (sodium hydrogen sulphite) | 7631-90-5 | 222 | 0–0.7 mg/kg bw c |

a International Numbering System for food additives.

b JECFA currently uses the term “ADI not specified” if the total daily intake of the substance arising from its use at levels necessary to achieve the desired effect, and from acceptable background levels in food, does not represent a hazard to health. The establishment of an ADI in numerical form is therefore not deemed necessary (FAO/WHO 2011). The equivalent term “ADI not limited” was previously used by JECFA.

c Group ADI, expressed as sulphur dioxide, for calcium hydrogen sulphite, calcium metabisulphite, calcium sulphite, potassium hydrogen sulphite, potassium metabisulphite, potassium sulphite, sodium hydrogen sulphite, sodium metabisulphite, sodium sulphite, sodium thiosulphate, and sulphur dioxide.

The Application also indicated that trace amounts of soluble agarose fragments could be present in food processed using the ion exchange resin. JECFA has assigned an ADI “not limited” for agar (INS no. 406), of which agarose is a major component.

###

### 3.2.2 Contaminants

3-Chloro-1,2-propanediol (CAS no. 96-24-2) is a resin impurity that has been assessed as a food contaminant by JECFA. JECFA established a Provisional Maximum Tolerable Daily Intake (PMTDI) for 3-chloro-1,2-propanediol of 2 µg/kg bw. The PMTDI was established based on a lowest observed effect level (LOEL) of 1.1 mg/kg bw/day from a carcinogenicity study in rats and application of a safety factor of 500 (WHO 2007).

### 3.2.3 Extraction solvents

Two resin impurities, ethanol and toluene, have been assessed by JECFA for use as solvents in food processing applications. JECFA concluded that residues of toluene and ethanol occurring in food when these solvents are used in accordance with good manufacturing practice (GMP) would not pose any safety concerns (WHO 1971; WHO 1981).

## 3.3 Other resin impurities

The Application provided hazard information on six additional resin impurities that may be present in food processed using the ion exchange resin (Table 2).

**Table 2: Resin impurities that have not been assessed by JECFA**

|  |  |
| --- | --- |
| **Chemical name** | **CAS no.** |
| Polyoxyethylene nonylphenyl phosphate ester, sodium salt | 68954-84-7 |
| Sodium borate | 1303-96-4 |
| Glyceryl allyl ether | 123-34-2 |
| Allyl glycidyl ether | 106-92-3 |
| Glycidol | 556-52-5 |
| Epichlorohydrin | 106-89-8 |

### Polyoxyethylene nonylphenyl phosphate ester, sodium salt

No hazard information on this substance was located, however being a polymeric substance it would be expected to be poorly absorbed by the oral route and therefore of low toxicity. The substance is approved by the US Environmental Protection Agency (USEPA) as an inert ingredient in pesticide formulations.[[2]](#footnote-3)

### Sodium borate

Extensive toxicity data on sodium borate/boric acid were cited in the Application and the lowest no observed effect level (NOEL) in laboratory animal studies of up to 2 years duration was reported to be 20 mg/kg bw/day (Weir and Fisher 1972). Sodium borate/boric acid showed no potential for genotoxicity or carcinogenicity (Weir and Fisher 1972; NTP 1987).

### Glyceryl allyl ether

There is very limited toxicity information available for glyceryl allyl ether. An acute oral toxicity study in mice resulted in an LD50 of 4200 mg/kg bw indicating low acute oral toxicity.[[3]](#footnote-4)

Allyl glycerol ether was tested for its ability to cause gene mutations in bacteria, gene conversion in yeast and chromosomal aberrations in rat liver cells *in vitro*. No evidence of genotoxicity was observed (Dean et al 1985). No other toxicity data have been identified.

### Allyl glycidyl ether

Oral LD50 values have been reported as 390 mg/kg bw in mice and 1600 mg/kg bw in rats (Hine et al 1956). Allyl glycidyl ether is genotoxic in *in vitro* tests, where it has induced gene mutations in bacteria and chromosomal aberrations in Chinese hamster ovary cells. Because it contains an epoxide group, allyl glycidyl ether may also be clastogenic *in vivo*, but the limited data available are not sufficient to determine this (NTP 1990a). Allyl glycidyl ether is a volatile liquid and has shown carcinogenic activity in 2-year inhalation studies in mice and rats (NTP 1990a). Its potential for carcinogenicity via the oral route has not been investigated.

### Glycidol

The toxicity of glycidol is well characterised. It is genotoxic in a range of *in vitro* and *in vivo* assays and has shown carcinogenic activity in oral studies in mice and rats (NTP 1990b). The International Agency for Research on Cancer (IARC) concluded that glycidol is probably carcinogenic to humans (IARC 2000).

### Epichlorohydrin

Epichlorohydrin is genotoxic in a range of *in vitro* and *in vivo* assays and has shown carcinogenic activity in oral studies in rats (WHO 1984; NTP 2004). The IARC concluded that epichlorohydrin is probably carcinogenic to humans (IARC 1999).

## 3.4 Hazard assessment conclusion

The Application cites 16 resin impurities that may be present at trace levels in extracted lactoferrin and in the flow-through dairy stream following processing with the ion exchange resin. The hazard profiles of these substances range from those of low toxicity (e.g. ethylcellulose, glycerol, sodium acetate and sodium sulphate) to those that are genotoxic and potentially carcinogenic (e.g. glycidol and epichlorohydrin).

# 4 Dietary exposure assessment

## 4.1 Estimated dietary exposure to resin impurities

The Application provided information on estimated dietary exposure to resin impurities that could be present in food processed using the resin. This information was originally submitted by the Applicant to the USFDA as part of a food contact notification (FCN) for use of the resin in the processing of milk and milk products, fruit and fruit juices, fruit drinks, beer and wine (USFDA 2004).

In order to obtain upper estimates of dietary exposure to resin impurities, the Applicant made a conservative assumption that all consumed milk and milk products, fruit and fruit juices, fruit drinks, beer and wine are treated with the resin. Food consumption information was taken from US Department of Agriculture (USDA) food intake survey data collected in 1994-96.

Resin impurity concentrations in foods were estimated using conservative assumptions to calculate theoretical migration levels of substances from the resin into foods. The resulting estimated dietary exposures to resin impurities are extremely low. The highest estimated dietary exposure was for soluble agarose fragments (3.3 µg/kg bw/day), while estimated dietary exposure to the remaining individual resin impurities does not exceed 10 nanograms/kg bw/day. Estimated dietary exposure to genotoxic and potentially carcinogenic substances ranged from 0.01 to 0.05 nanograms/kg bw/day (Table 3).

**Table 3: Estimated dietary exposure to resin impurities**

| **Chemical name** | **CAS no.** | **Estimated dietary exposure (µg/kg bw/day)** |
| --- | --- | --- |
| Soluble agarose fragments | 9012-36-6 | 3.3 |
| Ethylcellulose | 9004-57-3 | 0.01 |
| Polyoxyethylene nonylphenyl phosphate ester, sodium salt | 68954-84-7 | 0.002 |
| Glycerol | 56-81-5 | 0.01 |
| Sodium acetate | 127-09-3 | 0.02 |
| Sodium sulphate | 7757-82-6 | 0.01 |
| Sodium metabisulphite | 7681-57-4 | 0.007 |
| Sodium bisulphite | 7631-90-5 | 0.008 |
| Ethanol | 64-17-5 | 0.01 |
| Toluene | 108-88-3 | 0.006 |
| Sodium borate | 1303-96-4 | 0.004 |
| Glycidol | 556-52-5 | 0.0001 |
| Glyceryl allyl ether | 123-34-2 | 0.00005 |
| Allyl glycidyl ether | 106-92-3 | 0.00001 |
| 3-Chloropropane-1,2-diol | 96-24-2 | 0.00005 |
| Epichlorohydrin | 106-89-8 | 0.00001 |

Any differences between US and Australia/New Zealand consumption of foods included in the submitted dietary exposure estimates (namely milk and milk products, fruit and fruit juices, fruit drinks, beer and wine) would be expected to have a relatively small impact on the outcome of the dietary exposure assessment which indicated that estimated dietary exposure to all of the impurities is exceedingly low. Therefore, FSANZ did not consider it necessary to conduct its own dietary exposure assessment.

# 5 Risk characterisation

Theoretical estimates of dietary exposure to resin impurities, calculated using conservative assumptions, are exceedingly low. For example, estimated dietary exposure to 3-chloro-1,2-propanediol is only 0.0025% of the JECFA PMTDI of 2 µg/kg bw. Estimated dietary exposure to genotoxic and potentially carcinogenic substances was calculated to range from 0.01 to 0.05 nanograms/kg bw/day. These dietary exposure values are 50 to 250–times lower than the threshold of toxicological concern derived from toxicity data on known carcinogenic substances (0.0025 µg/kg bw/day = 2.5 nanograms/kg bw/day; Kroes et al 2004). It is concluded that theoretical estimates of dietary exposure to resin impurities, calculated using conservative assumptions, provide confirmation that potential impurity levels are of no toxicological concern.

There are no identifiable public health and safety concerns with the proposed use of the ion exchange resin as a processing aid for the isolation of lactoferrin from bovine milk/whey.

# 6 References

Dean BJ, Brooks TM, Hodson-Walker G and Hutson DH (1985) Genetic toxicology testing of 41

industrial chemicals. Mutation Research 153:57-77.

FAO/WHO (2011) Environmental Health Criteria 240. Principles and methods for the risk assessment of chemicals in food. International Programme on Chemical Safety. Food and Agriculture

Organization of the United Nations, and World Health Organization.

FSANZ (2007) Final Assessment Report. Application A600 – Agarose ion exchange resin as a

processing aid for beer.

Hine CH, Kodama JK, Wellington JS, Dunlap MK, Anderson, HH (1956) The toxicology of glycidol and some glycidyl ethers. Arch. Ind. Health 14:250-264.

IARC (1999) Epichlorohydrin. In *Re-evaluation of Some Organic Chemicals, Hydrazine, and Hydrogen Peroxide.* IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 71, pp. 603-628. International Agency for Research on Cancer. Lyon, France.

IARC (2000) Glycidol. In *Some Industrial Chemicals.* IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 77. pp. 469-486. International Agency for Research on Cancer. Lyon, France.

Kroes R, Renwick AG, Cheeseman M, Kleiner J, Mangelsdorf I, Piersma A, Schilter B, Schlatter J, van Schothorst F, Vos JG, Würtzen G (2004) Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. Food Chem Toxicol. 42(1):65-83.

NTP (1987). Toxicology and carcinogenesis studies of boric Acid (CAS No. 10043-35-3) in B6C3F1 mice. National Toxicology Program, Technical Report Series No. 324. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health.

NTP (1990a) Toxicology and carcinogenesis studies of allyl glycidyl ether (CAS no. 106-92-3) in Osborne-Mendel rats and B6C3F1 mice (inhalation studies). National Toxicology Program, Technical Report Series No. 376. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health.

NTP (1990b) Toxicology and carcinogenesis studies of glycidol (CAS no. 556-52-5) in F344/N rats and B6C3F1 mice (gavage studies). National Toxicology Program, Technical Report Series No. 374. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health.

NTP (2004) Epichlorohydrin. Report on Carcinogens, 11:113-4.

USFDA (2004) Inventory of Effective Food Contact Substance (FCS) Notifications. Food Contact Notification No. 443. Amersham Biosciences. Food Contact Substance: Agarose, polymer with (chloromethyl)oxirane, 2-hydroxy-3(3-sulfopropoxy)propyl ethers, sodium salts (CAS Reg. No. 676618-71-6).

Weir RJ, Fisher RS (1972) Toxicologic studies on borax and boric acid. Toxicol Appl Pharmacol 23:351-364.

WHO (1971) Evaluation of Food Additives. Fourteenth report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series 462. World Health Organization, Geneva, Switzerland.

WHO (1981) Evaluation of Certain Food Additives. Twenty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series 669. World Health Organization, Geneva, Switzerland.

WHO (1984) Environmental Health Criteria No. 33. Epichlorohydrin. International Programme on Chemical Safety. World Health Organization, Geneva, Switzerland.

WHO (2007) Evaluation of Certain Food Additives and Contaminants. Sixty-seventh report of the

Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series 940. World Health Organization, Geneva, Switzerland.

1. JECFA database of food additives and contaminants: <http://apps.who.int/food-additives-contaminants-jecfa-database/search.aspx> [↑](#footnote-ref-2)
2. <http://actor.epa.gov/actor/GenericChemical?casrn=68954-84-7> [↑](#footnote-ref-3)
3. Information from the TOXNET database: <http://chem.sis.nlm.nih.gov/chemidplus/rn/123-34-2> [↑](#footnote-ref-4)