Betaïne

Tweede beoordeling van de veiligheid voor de consument, volgens de Europese verordening 258/97 betreffende nieuwe voedingsmiddelen en nieuwe voedselingrediënten

Betaine

Second opinion regarding consumer safety, in accordance with European Regulation 258/97 concerning novel foods and novel ingredients

Gezondheidsraad:
Commissie Veiligheidsbeoordeling nieuwe voedingsmiddelen (VNV)

Health Council of the Netherlands
Committee on the Safety Assessment of Novel Foods

aan/to

de minister van Volksgezondheid, Welzijn en Sport/
the Minister of Health, Welfare and Sport

de minister van Landbouw, Natuur en Voedselkwaliteit/
the Minister of Agriculture, Nature and Food Quality

Nr 2003/03VNV, Den Haag, 23 oktober 2003
No. 2003/03VNV, The Hague, October 23, 2003

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Inhoud/Contents

Gezondheidsraad
Health Council of the Netherlands

Vice-voorzitter

Aan de Minister van Volksgezondheid,
Welzijn en Sport

Onderwerp : Tweede beoordeling veiligheid Betaïne
Uw kenmerk : VGB/VL 2407857
Ons kenmerk : 2003/03VNV, U-1520/MR/cv/622-CM
Datum : 23 oktober 2003

Mijnheer de minister,

Dit schrijven dient ter beantwoording van de adviesaanvraag over de veiligheid van nieuwe voedingsmiddelen en nieuwe voedselingrediënten, die door u mede namens de Minister van Landbouw, Natuur en Voedselkwaliteit aan de Gezondheidsraad is voorgelegd. Aan de orde is een zogenoemde tweede beoordeling, conform de Europese verordening 258/97, van betaïne. De chemische naam hiervan is trimethylglycine. De aanvrager die dit nieuwe voedselingrediënt op de markt wil brengen is de firma Finnfeeds Finland Ltd. Betaïne komt niet direct beschikbaar voor de consument, maar het zal worden verwerkt in verschillende categorieën levensmiddelen. De beoordeling is verricht door de Commissie 'Veiligheidsbeoordeling nieuwe voedingsmiddelen' van de Gezondheidsraad (Commissie VNV).

De eerste beoordeling van de aanvraag voor markttoelating is verricht in Finland door de *Novel Food Board* (NFB). De belangrijkste conclusie van de NFB is dat, alhoewel de aanvrager veel informatie heeft verstrekt over het effect van betaïne in bepaalde patiënten, informatie uit wetenschappelijk onderzoek bij gezonde vrijwilligers beperkt is. De NFB stelt dat een betrouwbare beoordeling van de veiligheid voor de consument daarom niet mogelijk is.

De Commissie VNV maakt bezwaar tegen toelating op de markt van betaïne als voedselingredient. Zij baseert haar oordeel op het rapport van de eerste beoordeling door de NFB (zie Bijlage E), de informatie in het dossier (voor een samenvatting zie Bijlage D) en de wetenschappelijke literatuur. De Commissie VNV stemt ten dele in met de Finse beoordeling en maakt zelf nog enkele kritische opmerkingen bij het dossier. Het is de Commissie VNV niet altijd duidelijk hoe zwaarwegend de kanttekeningen die de NFB heeft geplaatst, moeten worden opgevat. De belangrijkste kritiek van de Commissie VNV op het veiligheidsdossier is dat de veilige bovengrens van inneming onvoldoende wordt onderbouwd. Deze kritiek is gebaseerd op het feit dat adequaat onderzoek bij gezonde mensen ontbreekt en dat ongewenste metabole effecten zijn waargenomen bij

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Uw kenmerk : VGB/VL 2407857
Ons kenmerk : 2003/03VNV, U-1520/MR/cv/622-CM
Datum : 23 oktober 2003

proefdieren. Gezien voornoemde onzekerheden oordeelt de commissie ook negatief over het brede productassortiment dat de aanvrager voorstelt. In de tekst hieronder wordt het oordeel van de Commissie VNV verder uitgewerkt.

Algemene productinformatie

De drie producten, die de aanvrager op de markt wil brengen te weten Betafin BF20, AP en TMG20, bestaan uit bijna zuivere betaïne (minstens 99%) en bevatten geen ongewenste bestanddelen of microbiologische verontreinigingen. De Commissie VNV is het eens met de NFB dat de productinformatie in het dossier representatief is voor de op de markt te brengen voedselingrediënten betaïne. Deze informatie is voldoende om de veiligheidsbeoordeling te kunnen uitvoeren.

In verband met de stabiliteit van betaïne merkt de Commissie VNV op dat het nieuwe ingrediënt niet aan levensmiddelen mag worden toegevoegd die in de thuissituatie mogelijk boven de 200 °C verhit zullen worden (bijvoorbeeld in ovengerechten) in verband met de verhoogde kans op ongewenste pyrolytische esterificaties. Ook zou volgens de Commissie VNV betaïne niet geschikt zijn om te worden verwerkt in levensmiddelen die een mogelijke bron van *Lysteria* besmetting vormen (zoals zuivelproducten van rauwe melk), omdat bij osmotische of koude stress deze bacteriën in voedsel worden beschermd door de aanwezigheid van betaïne.

Betaïne wordt verkregen uit een extract van suikerbietmelasse waarbij voornamelijk standaardtechnieken worden gebruikt. De Commissie VNV stemt in met de NFB dat de kwaliteit van het industriële productieproces gewaarborgd is. Evenals de Finse beoordelaars accepteert de Commissie VNV dat producten uit niet-genetisch gemodificeerde suikerbiet een lange geschiedenis van gebruik kennen in de menselijke voeding. Suikerbietmelasse wordt beschouwd als een veilige grondstof voor levensmiddelen.

Veiligheid en werkzaamheid

De Commissie VNV beoordeelt alleen de veiligheid en niet de werkzaamheid van het bio-actieve ingrediënt betaïne. Volgens de aanvrager is een dagelijkse inneming van 4 gram betaïne ruim voldoende om de serumhomocysteïnespiegel effectief te verlagen hetgeen gunstig zou zijn ter voorkoming van hart en vaatziekten. Aangezien de aanvrager belang hecht aan de veronderstelde gezondheidsbevorderende werking van betaïne wijst de Commissie VNV op het definitieve voorstel van de Europese Commissie voor een Verordening inzake voedings- en gezondheidsclaims voor levensmiddelen (EC03).

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Onderwerp : Tweede beoordeling veiligheid Betaïne
Uw kenmerk : VGB/VL 2407857
Ons kenmerk : 2003/03VNV, U-1520/MR/cv/622-CM
Datum : 23 oktober 2003

Veilige bovengrens van inneming

De Commissie VNV stemt in met de beoordeling van de NFB dat het dossier voldoende voedingskundige informatie bevat over het nieuwe voedselingrediënt. De commissie wijst erop dat betaïne onderdeel is van de normale methyleringcyclus in het menselijk lichaam; het is een metaboliet van choline en fungeert als donor van een methylgroep. Blootstelling aan betaïne is niet nieuw. Het is van nature aanwezig in bepaalde plantaardige en dierlijke producten en wordt ook als technische hulpstof toegevoegd aan bepaalde levensmiddelen (voor details zie Bijlage D en E). De dagelijkse inneming die de aanvrager voorstelt is zo'n 2 à 4 maal meer dan de hoeveelheid die men via de gewone voeding binnenkrijgt. In de Verenigde Staten varieert dit van gemiddeld ongeveer 1 g tot 2,5 g bij een *seafood*-rijke voeding.

In de EU zijn sinds 1982 voedingsupplementen op de markt met betaïne in de vorm van het hydrochloride zout, met een dagelijks aanbevolen hoeveelheid variërend van 7 tot 324 mg. De NFB wijst erop dat gedocumenteerde gegevens over de gevolgen van het gebruik hiervan ontbreken. Het is ook niet bekend in hoeverre ongewenste effecten kunnen optreden, als de consumptie de dosering die de aanvrager voorstelt overschrijdt.

In 1996 is betaïne is als weesgeneesmiddel* ter behandeling van homocystinuria, een zeldzame stofwisselingziekte, toegelaten in Amerika door de *Food and Drug Administration* (handelsnaam 'Cystadane') en daarna is het ook in Canada en Australië geregistreerd. Als medicijn is de dagelijks dosering gewoonlijk 6 g, maar kan oplopen tot 20 g. De Commissie VNV ondersteunt de kritiek van de NFB dat het dossier geen informatie bevat over de veiligheidsbeoordelingen bij deze registraties. In aanvulling op het dossier en het beoordelingsrapport van de NFB meldt de Commissie VNV dat in de EU betaïne het predikaat 'weesgeneesmiddel' is toegekend in juli 2001, maar dat de autorisatieprocedure voor markttoelating nog niet is afgerond (EU01). Op basis van productinformatie (Can03) constateert de Commissie VNV dat de toxicologische gegevens die nodig waren voor de registraties als weesgeneesmiddel (buiten Europa) beperkt zijn, zo hoefde er bijvoorbeeld geen vruchtbaarheidsonderzoek en carcinogeniciteitsonderzoek bij proefdieren te worden uitgevoerd. Ook is er geen farmacokinetisch onderzoek bij mensen gedaan.
Mensgebonden onderzoek. De Commissie VNV stelt dat de conclusie van de aanvrager dat consumptie tot 30 g betaïne per dag extra geen gezondheidskundig of voedingskundig risico

* geneesmiddelen voor zeldzame aandoeningen (zie ook Linthorst GR, Hollak CEM. Europese verordening inzake weesgeneesmiddelen: kansen en bedreigingen. Ned Tijdschr Geneeskd 2003;147:143-145)

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Onderwerp : Tweede beoordeling veiligheid Betaïne
Uw kenmerk : VGB/VL 2407857
Ons kenmerk : 2003/03VNV, U-1520/MR/cv/622-CM
Datum : 23 oktober 2003

oplevert, onvoldoende is onderbouwd. De aanvrager heeft de resultaten besproken van 43 mensgebonden onderzoeken, waarvan er 36 bij verschillende typen patiënten zijn uitgevoerd. In 20 % hiervan is het effect van langdurige blootstelling (minstens één jaar) aan relatief hoge doseringen betaïne (6 – 20 g per dag) bestudeerd. Alhoewel er geen acute klachten zijn gerapporteerd, tekent de Commissie VNV aan dat ongewenste bijwerkingen niet systematisch in kaart zijn gebracht in deze patiëntenonderzoeken.

Van de zeven onderzoeken bij gezonde vrijwilligers is in de meeste gevallen het effect onderzocht van een eenmalige blootstelling aan betaïne (2- 6 g), terwijl in twee onderzoeken een blootstelling van 6 g per dag gedurende meerdere weken is geëvalueerd. De Commissie VNV merkt op dat, alhoewel deze onderzoeken waren opgezet om de werkzaamheid te bestuderen, de resultaten hiervan wel ondersteunende waarde hebben voor de veiligheidsbeoordeling van betaïne. Bijlage 14 van het dossier bevat de resultaten van een placebo-gecontroleerd onderzoek bij 48 gezonde vrijwilligers met overgewicht, dat gerandomiseerd en dubbelblind parallel is uitgevoerd (Sch02). Bij een blootstelling van 6 g per dag gedurende 12 weken traden er volgens de aanvrager geen bijwerkingen op. In een ander onderzoek met 15 gezonde vrijwilligers die gedurende drie weken dagelijks 6 g consumeerden werden eveneens geen ongewenste effecten waargenomen, maar dit onderzoek was niet placebo-gecontroleerd uitgevoerd en heeft daarmee minder bewijskracht.

Alhoewel de Commissie VNV op grond van het beperkt klinisch onderzoek geen aanwijzingen heeft dat er duidelijke klachten zullen optreden bij een dagelijkse inneming van ten hoogste 6 g betaïne extra, is zij het niet eens met de conclusie van de aanvrager dat er geen nadelige bijwerkingen zouden zijn. Onderzoekers hebben namelijk wel significante veranderingen in het cholesterolmetabolisme ten gevolge van betaïne inneming waargenomen. Dit is beschreven in verschillende onderzoeken die in het dossier zijn opgenomen, uitgevoerd met vrijwilligers (Sch02) of met patiënten (Abd01, McG02), als ook in ander ongepubliceerd onderzoek waarvan de commissie over de vertrouwelijke resultaten beschikt. De Commissie VNV concludeert dat de verhouding 'totaal /HDL cholesterol' in ongunstige zin verschuift, en beoordeelt dit als een ongewenste bijwerking. Ook wijst zij erop dat dit het door de aanvrager beoogde positieve effect van het nieuwe voedselingrediënt tegengaat. Om de veiligheid van betaïne voor de consument te kunnen beoordelen, eist de Commissie VNV dat er uitgebreider onderzoek wordt gedaan bij gezonde vrijwilligers met een zo hoog mogelijk verantwoorde dosis. Hierbij moeten, behalve de verschillende leverenzymen, ook alle gangbare cardiovasculaire risicofactoren worden bestudeerd.

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Onderwerp : Tweede beoordeling veiligheid Betaïne
Uw kenmerk : VGB/VL 2407857
Ons kenmerk : 2003/03VNV, U-1520/MR/cv/622-CM
Datum : 23 oktober 2003

Proefdieronderzoek. Uit het dossier blijkt dat betaïne niet acuut toxisch is en niet mutageen in de gebruikelijke onderzoeken naar genotoxiciteit. In subchronisch toxiciteitsonderzoek bij ratten, die betaïne gedurende 90 dagen in het voer kregen toegediend, werden echter wel behandelingsgerelateerde effecten waargenomen bij alle geteste doseringen waarvan de laagste 0,8 g/kg/dag en de hoogste 4,4 g/kg/dag was (overeenkomend met respectievelijk 56 g en 308 g bij een lichaamsgewicht van 70 kg). Deze hematologische een hepatologische veranderingen zijn volgens de aanvrager het gevolg van de onfysiologisch hoge blootstellingen waardoor de normale evenwichten worden verstoord en zijn derhalve niet relevant bij gewone menselijke consumptie die de aanvrager voorstelt. Uit de resultaten van een zogeheten reversibiliteitsonderzoek bij ratten, met een gemiddelde dagelijkse dosis van ten hoogste 5,7 g/kg, concludeert de aanvrager dat de door betaïne te weeg gebrachte effecten omkeerbaar zijn; de veranderingen in de lever zouden het gevolg zijn van intermediair metabolisme. De Commissie VNV onderschrijft de mening van de NFB dat, alhoewel de geïnduceerde effecten mild en reversibel lijken, het moeilijk is in te schatten wat hiervan de betekenis zal zijn voor de gezondheid van de consument.

Om deze metabole aspecten beter te onderzoeken zijn er op de Brandeis Universiteit in de Verenigde Staten vervolgonderzoeken uitgevoerd met alleen vrouwelijke ratten die gedurende 28 en 90 dagen voer met betaïne kregen toegediend. Dit mechanistisch voedingsonderzoek, waarvan de uitkomsten in het dossier zijn opgenomen, was voor wat betreft de rattenstam en het betaïnegehalte van het voer vergelijkbaar met de voornoemde toxicologische onderzoeken. Ook bleek dat de effecten die in de lever optraden vergelijkbaar waren, maar minder ernstig. De onderzoekers schrijven dit verschil in effect toe aan verschillen in de samenstelling van de gebruikte standaard rattenvoeren. De Commissie VNV acht dit een plausibele verklaring, maar blijft van mening dat de waargenomen afwijkingen in de lever moeten worden toegeschreven aan betaïne en als ongewenst moeten worden beschouwd. Zij stemt derhalve niet in met de wijze waarop de aanvrager deze proefdierresultaten gebruikt om een voor de mens veilige bovengrens van betaïne af te leiden.

Samenvattend stelt de Commissie VNV dat er onvoldoende gegevens zijn om een veilig niveau van inneming betrouwbaar te kunnen vaststellen. In het dossier ontbreekt bovendien een duidelijk betoog, gebaseerd op het totaal aan resultaten van mensgebonden en proefdieronderzoeken. De commissie meent dat vaststelling van een veilige bovengrens noodzakelijk is gezien het feit dat betaïne een specifieke bio-actieve verbinding is en zal worden toegevoegd aan producten die voor de algemene bevolking beschikbaar komen. Gebaseerd op het huidige totaal aan beschikbare gegevens concludeert de Commissie VNV dat er vooralsnog

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Onderwerp : Tweede beoordeling veiligheid Betaïne
Uw kenmerk : VGB/VL 2407857
Ons kenmerk : 2003/03VNV, U-1520/MR/cv/622-CM
Datum : 23 oktober 2003

onvoldoende zekerheid is dat nadelige effecten op de gezondheid achterwege zullen blijven door het gebruik van betaïne, waarbij de commissie anticipeert op een langdurige dagelijkse inneming door voedingsbewuste consumenten.

Toepassing

In het licht van de hierboven genoemde beschouwing over een veilig niveau van betaïne inneming concludeert de Commissie VNV dat het productassortiment, dat de aanvrager voorstelt, veel te breed is, mede gezien het feit dat er geen resultaten beschikbaar zijn van chronisch proefdieronderzoek die zo'n algemene toepassing rechtvaardigen. Door consumptie van meerdere betaïne-houdende producten op één dag, overschrijdt de inneming de hoeveelheid die de aanvrager aanbeveelt, te weten 4 g betaïne, en deze kan zelfs oplopen tot zo'n 8 à 12 g. De Commissie VNV licht hieronder haar kantekeningen verder toe.

Voor de levensmiddelen waaraan betaïne zou kunnen worden toegevoegd in concentraties variërend van 2,0-6,7 %, stelt de aanvrager de volgende categorieën voor (zie paragraafnummer 29 in Bijlage E voor meer details):

- dranken variërend van mineraalwater, frisdrank, koffie, thee tot alcoholische dranken
- graanproducten zoals müsli, cornflakes, energierepen
- zuivelproducten
- snoepgoed

Voor elk van deze productcategorieën vermeldt het rapport van de eerste beoordeling het gemiddelde en de 90 percentiel van de dagelijkse inneming. Op basis hiervan is berekend dat mensen die op één dag producten uit alle categorieën consumeren (stapeling), respectievelijk 21 en 39 g betaïne zullen binnenkrijgen. Hiervoor zijn consumptiegegevens uit Finland, Zweden en Denemarken gebruikt, aangevuld met informatie over inneming van zuivelproducten in het Verenigd Koninkrijk, Duitsland, Spanje en Nederland. Het is de Commissie VNV echter niet duidelijk hoe de verschillende sets van consumptiegegevens uit deze zeven Europese lidstaten zijn gecombineerd om de innemingen af te leiden.

De Commissie VNV constateert dat de consumptie van bepaalde producten, die met betaïne verrijkt zullen gaan worden, zeer sterk uiteen kan lopen in de verschillende Europese lidstaten of zelfs onbekend is. Zij stemt in met de NFB dat, mede ook vanwege nationale verschillen in de samenstellingen van de geanalyseerde productcategorieën, de innemingsgegevens van betaïne niet meer dan een globale indicatie zijn en benadrukt dat gemiddelden van de Europese innemingen niet gerechtvaardigd zijn.

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Gezondheidsraad **Vice-voorzitter**
Health Council of the Netherlands

Onderwerp : Tweede beoordeling veiligheid Betaïne
Uw kenmerk : VGB/VL 2407857
Ons kenmerk : 2003/03VNV, U-1520/MR/cv/622-CM
Datum : 23 oktober 2003

De Commissie VNV meent dat dranken als categorie geheel zou moeten worden uitgesloten gezien de zeer lastig in te schatten dagelijkse inneming. Omdat betaïne niet in gezonde kinderen is onderzocht, vindt de Commissie VNV het niet acceptabel om snoepgoed te verrijken met betaïne.

In aanvulling op de eerste beoordeling merkt de Commissie VNV nog op dat het de verantwoordelijkheid is van de producent-en-aanvrager Finnfeeds om de eindfabrikanten van betaïne verrijkte voedingsmiddelen te adviseren inzake het juiste gebruik en een goede etikettering van het nieuwe ingrediënt. Bij onduidelijkheid hierover, of als de aanvrager dit niet accepteert, is volgens de commissie deze firma niet de juiste aanvrager voor markttoelating van betaïne in levensmiddelen. De Commissie VNV onderschrijft de mening van de NFB die nadere etiketteringsvoorschriften nodig vindt, en voegt toe dat de consument geïnformeerd dient te worden over hoeveel van de aanbevolen dagelijkse hoeveelheid betaïne één portie bevat. Dit alles overwegende lijkt het de commissie volstrekt onduidelijk, hoe de aanvrager wordt geacht zicht te houden op alle mogelijke toepassingen van het nieuwe ingrediënt.

Op grond van bovenstaande argumenten maakt de commissie VNV bezwaar tegen het op de markt brengen van betaïne als voedselingrediënt. Zij stelt twee mogelijkheden voor om een veilig gebruik van betaïne door de consument te realiseren. De eerste mogelijkheid is een gelimiteerde toepassing van betaïne in een beperkt en goed gedefinieerd productassortiment waarbij een veilige bovengrens zal moeten worden vastgesteld op grond van de uitkomsten van adequaat klinisch onderzoek dat nog uitgevoerd dient te worden. Met postmarketing onderzoek kan gecontroleerd worden of de hoeveelheden betaïne die de consument dagelijks binnenkrijgt onder deze bovengrens blijft. De tweede mogelijkheid is het bepalen van een ADI (acceptable daily intake of wel ‘maximaal toegestane hoeveelheid’). Hiervoor is een zeer omvangrijk veiligheidsdossier vereist, gelijk aan dat voor voedseladditieven, met de resultaten van onder andere onderzoek naar reproductie, teratogeniteit, chronische toxiciteit en carcinogeniteit. Als deze ADI voldoende hoog uitvalt zou een breder productassortiment mogelijk zijn.

Ik onderschrijf de conclusies en aanbevelingen van de Commissie VNV.

Hoogachtend,

prof. dr JGAJ Hautvast

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Letter to the Dutch Minister of Health, Welfare and Sport

On October 23, 2003, professor JGAJ Hautvast, Vice-president of the Health Council of the Netherlands wrote as follows to the Minister of Health, Welfare and Sport:

This letter has been prepared in reply to your request for advice regarding the safety of novel foods and food ingredients, also made on behalf of the Minister of Agriculture, Nature and Food Quality. The subject in question is a second opinion, in accordance with European Regulation 258/97, concerning betaine, the chemical name for which is trimethylglycine. The applicant wishing to market this novel ingredient is the company Finnfeeds Finland Ltd. Betaine will not be directly available for consumers, but will be incorporated in foods of various categories. This assessment has been carried out by the Committee on Safety Assessment of Novel Foods (VNV Committee) of the Health Council of the Netherlands.

The initial assessment of the application for market introduction was carried out in Finland by the Novel Food Board (NFB). The major conclusion of the NFB is that, in spite of the fact that the applicant has provided extensive information about the effect of betaine in certain patients, data from scientific studies with healthy subjects is limited. The NFB therefore states that a reliable assessment of consumer safety is not possible.

The VNV Committee objects to market authorisation of betaine as a food ingredient. The Committee bases its opinion on the report of the initial assessment by the NFB (see Annex E), the information in the dossier (for a summary, see Annex D) and the scientific literature. The VNV Committee agrees in part with the assessment from Finland and has itself a number of criticisms of the dossier. It is not always clear to

the VNV Committee when the comments made by the NFB should be considered essential to the assessment. The VNV Committee's main criticism of the safety dossier is that the safe upper intake limit is inadequately supported. This criticism is based on the lack of adequate studies in healthy subjects and because adverse metabolic effects have been observed in laboratory animals. Considering these uncertainties, the VNV Committee also expresses a negative opinion on the wide range of products that the applicant is proposing. The text below sets out the assessment of the VNV Committee in greater detail.

General product information

The three products the applicant wishes to market, namely Betafin BF20, AP and TMG20, consist of pure betaine (at least 99%) and contain no undesirable ingredients or microbiological impurities. The VNV Committee agrees with the NFB that the product information in the dossier is representative for the betaine food ingredients to be marketed. This information is adequate as a basis for the safety assessment.

Given the stability of betaine, the Committee VNV notes that the new ingredient should not be added to foods that may be heated at home to temperatures above 200 °C (oven dishes, for example) because of the increased possibility of undesirable pyrolytic esterification. Nor does the VNV Committee consider betaine suitable for use in foods that are a potential source of *Lysteria* contamination (such as dairy products made from untreated milk), because under osmotic or cold stress these bacteria in food are being protected by the presence of betaine.

Betaine is obtained from an extract of sugar beet molasses, mainly using standard techniques. The VNV Committee agrees with the NFB that the safeguards for the quality of the industrial production process are adequate. Like its Finnish colleagues, the VNV Committee accepts that products from genetically-unmodified sugar beet have a long history of use in human food. Sugar beet molasses is considered to be a safe raw material for foods.

Safety and efficacy

The VNV Committee has only assessed the safety, and not the efficacy, of the bio-active ingredient betaine. According to the applicant, a daily intake of 4 grams of betaine is sufficient for the effective decrease of blood homocysteine concentrations. It is claimed that this prevents cardiovascular disease. Given the fact that the applicant considers the assumed beneficial effects on health of betaine to be important, the VNV Committee refers to the definitive proposal from the European Commission for a Regulation on nutrition and health claims made on foods (EC03).

Safe upper intake limit

The VNV Committee agrees with the assessment of the NFB that the dossier contains enough nutritional information on the new food ingredient. The Committee wishes to point out that betaine is part of the normal methylation cycle in the human body; it is a metabolite of choline and serves as a methyl group donor. Exposure to betaine is not new. It is naturally present in certain vegetable and animal products and is also used as a technical additive in certain foods (for details, see Annexes D and E). The daily intake proposed by the applicant is approximately two to four times more than the intake from a normal diet. In the US, the latter ranges from an average of 1.0 g to 2.5 g for a high seafood diet.

In the EU, food supplements with betaine in the form of the hydrochloride salt have been on the market since 1982, with a daily recommended dose level varying from 7 to 324 mg. The NFB points out that there is no documented data about the consequences of using these supplements. It is also not known to what extent undesirable effects may occur if consumption exceeds the dose proposed by the applicant.

In 1996, betaine was approved in America by the Food and Drug Administration as an orphan drug* (trade name 'Cystadane') for the treatment of homocystinuria, a rare metabolic disorder. It was also registered later in Canada and Australia. As a medicine, the daily dose is usually 6 g, but it can increase to 20 g. The VNV Committee supports the criticism of the NFB that the dossier does not contain information about the safety assessments made during these registration procedures. In addition to the information given in the dossier and the assessment report of the NFB, the VNV Committee reports that, in the EU, betaine was designated as an orphan medicine in July 2001, but the market authorisation procedure is still in progress (EU01). On the basis of product information (Can03) the VNV Committee notes that the toxicological data required for the registration as an orphan drug (outside Europe) is limited. For example, no reproduction or carcinogenicity studies were required in laboratory animals. Nor were there any human pharmacokinetic studies.

Clinical research. The VNV Committee finds there is no adequate justification of the conclusion of the applicant that consumption of up to 30 g betaine extra a day involves no health or nutritional risk. The applicant discusses the results of 43 clinical studies, 36 of which were conducted in different types of patients. One fifth studied the effect of chronic exposure (lasting at least one year) to relatively high doses of betaine (6 – 20 g a day). Although no acute symptoms were reported, the VNV Committee notes that undesirable side-effects were not systematically explored in these patient studies.

Most of the seven studies with healthy volunteers examined the effect of a single exposure to betaine (2 - 6 g), whereas two studies evaluated exposure of 6 g a day during

* Medicines for rare disorders

a period of several weeks. The VNV Committee notes that, although these studies were designed to test efficacy, the results can be used as supporting material for the safety assessment of betaine. Annex 14 of the dossier contains the results of a placebo-controlled, randomised and double-blind study with 48 obese subjects (Sch02). According to the applicant, there were no side-effects at an exposure of 6 g a day for 12 weeks. Also in another study with 15 healthy volunteers who consumed 6 g daily for three weeks no adverse effects occurred. However, there was no placebo control group in the latter study and this undermined the power of the study.

Although the VNV Committee has found no indications on the basis of the limited clinical research that clear symptoms will result from a maximum daily intake of an added 6 g betaine, it does not agree with the conclusion of the applicant that there are no harmful side-effects. Researchers do have observed significant changes in cholesterol metabolism as a result of betaine intake. This has been reported not only in various studies included in the dossier that were conducted with volunteers (Sch02) and with patients (Abd01, McG02), but also in another study, the unpublished results of which have been made available to the Committee on a confidential basis. The VNV Committee concludes that the ratio 'total to HDL cholesterol' is affected adversely, and considers this to be a harmful side-effect. It also points out that this is opposed to the beneficial effect that the applicant has in mind. In order to be able to assess the safety of betaine for consumers, the VNV Committee demands more extensive studies with healthy volunteers using a dose that is as high as responsibly possible. In addition, alongside the various liver enzymes, all the usual cardiovascular risk factors should be studied.

Animal studies. The dossier shows that betaine is not acutely toxic or mutagenic in the usual tests for genotoxicity. In a subchronic toxicity study with rats given betaine in feed for 90 days, however, treatment-related effects were observed at all tested doses, the lowest of which was 0.8 g/kg/day and the highest of which was 4.4 g/kg/day (corresponding to 56 g and 308 g respectively at a body weight of 70 kg). These hematological and hepatological changes are, according to the applicant, the result of the unphysiologically high level of exposure, resulting in disturbances of normal balances so that they are unlikely to be relevant to normal human intake. On the basis of the results of a reversibility study in rats, with a maximum average daily dose of 5.7 g/kg, the applicant concludes that the effects induced by betaine are reversible; the changes in the liver are thought to be caused by intermediary metabolism. The VNV Committee shares the opinion of the NFB that, although the induced effects appear to be mild and reversible, it is difficult to assess their significance for consumer health.

In order to study these metabolic issues better, the Brandeis University in the United States has conducted follow-up trials in which female rats alone were given feed with betaine for 28 and 90 days. This mechanistic feeding study, the results of which have

been included in the dossier, was comparable in terms of the rat strain and the betaine levels in the feed with the toxicological studies referred to above. The effects on the liver were comparable but less severe. The researchers ascribe this variance to differences in the composition of the standard rat feeds used. The VNV Committee considers this a plausible explanation, but remains of the opinion that the observed disorders in the liver must be ascribed to betaine and considered to be adverse. It does not therefore agree with the way in which the applicant uses these animal results to derive an upper limit for betaine that is safe for humans.

In summary, the VNV Committee finds that there is inadequate data for determining a safe level of intake in a reliable way. Furthermore, the dossier does not contain any clearly argued reasoning that is based on the entire body of data from human and animal studies. The Committee is of the opinion that a safe upper limit is necessary in view of the fact that betaine is a specific bio-active compound and will be added to products that will be available to the general population. On the basis of all the currently available data, the VNV Committee concludes that, for the time being, it cannot be stated with certainty that there will be no adverse health effects as a result of the use of betaine. Here, the Committee anticipates chronic daily intake by nutritionally conscious consumers.

Application

Given the risk analysis referred to above with respect to a safe level of betaine intake, the VNV Committee concludes that the product range proposed by the applicant is much too broad, partly given the fact that no results are available from chronic animal studies that justify a general application of this kind. The consumption of several products containing betaine in a single day would result in intake exceeding the amount recommended by the applicant, in other words 4 g betaine, and even rising to approximately 8 à 12 g. The VNV Committee discusses its reservations in greater detail below.

For the foodstuffs to which betaine would be added in concentrations varying from 2.0-6.7 %, the following categories are proposed (see paragraph 29 in Annex E for more details):

- beverages varying from mineral water, soft drinks, coffee and tea, to alcoholic beverages;
- cereal products such as muesli, corn flakes and energy bars;
- dairy products;
- sweets.

For each of these product categories, the report of the first assessment states the average and the 90 percentile for the daily intake. On this basis, it is calculated that people who consume products from all categories in a single day, will ingest 21 and 39 g of betaine respectively (cumulative intake). This calculation uses consumption data from Finland, Sweden and Denmark, supplemented by information about the intake of dairy products

in the United Kingdom, Germany, Spain and the Netherlands. However, it is unclear to the VNV Committee how the various sets of consumption data from these seven European member states were combined to derive the intakes.

The VNV Committee notes that the consumption of certain products that will be enriched with betaine can vary greatly in the various European member states or is even unknown. It agrees with the NFB that, in part because of national differences in the composition of the analysed product categories, the intake data for betaine is no more than a general indication and emphasises that averages for European intake levels are not justified.

The VNV Committee is of the opinion that beverages should be excluded altogether as a category in view of the extreme difficulty of estimating daily intake. Because betaine has not been studied in healthy children, the VNV Committee does not consider the enrichment of sweets with betaine to be acceptable.

In addition to the initial assessment, the VNV Committee notes that the producer/applicant Finnfeeds ought to be responsible for advising end-producers of betaine-enriched food about the correct use and the proper labelling of the new ingredient. If there are any ambiguities in this respect, or if the applicant does not accept this condition, the Committee believes that this company is not the right applicant for market authorisation for betaine in foodstuffs. The VNV Committee shares the opinion of the NFB that more detailed labelling conditions are necessary and adds that the consumer should be informed about how much of the recommended daily amount of betaine is contained in one portion. Given all this, it is by no means clear to the Committee how the applicant can be expected to monitor all possible uses of the new ingredient.

Based on the arguments outlined above, the VNV Committee objects to introduction of betaine as a food ingredient on the European market. It proposes two options to realize a safe use of betaine by the consumer. The first option is a limited application of betaine in a restricted and well-defined product range, for which a safe upper limit needs to be determined on the basis of the results of adequate clinical research to be conducted in the future. Post-marketing research can be used to establish whether the daily intake of betaine by consumers remains below this upper limit. The second option is to determine an acceptable daily intake (ADI). This requires a highly detailed safety dossier on the lines of dossiers for food additives, containing the results of, amongst other, studies into reproduction, teratogenicity, chronic toxicity and carcinogenicity. If this ADI turns out to be sufficiently high, betaine might be incorporated in a wide range of products.

I endorse the conclusions and recommendations of the VNV Committee,

(signed) professor JGAJ Hautvast

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A	De adviesaanvraag/Request for advice
B	De commissie/The committee
C	EU-procedure/EU-procedure
D	Samenvatting van het dossier/Executive summary of the dossier
E	Eerste beoordeling/First assessment

Bijlagen/Annexes

Bijlage **A**

De Adviesaanvraag/Request for advice

Op 18 augustus 1999 schreef de Minister van Volksgezondheid, Welzijn en Sport aan de Voorzitter van de Gezondheidsraad (brief kenmerk GZB/VVB 993428):

Sinds mei 1997 is in de Europese Unie de Verordening (EG) 258/97 van kracht inzake nieuwe voedingsmiddelen en nieuwe voedselingrediënten. Daarmee werd de veiligheidsbeoordeling onderdeel van een communautaire procedure.

Met u is reeds de mogelijkheid besproken de beoordeling door de Gezondheidsraad te laten uitvoeren. Ik verzoek u dan ook mede namens de Staatssecretaris van Landbouw, Natuurbeheer en Visserij, in deze eerste fase van uitvoering van de Europese Verordening (EG) 258/97 gedurende een aantal jaren, de veiligheidsbeoordeling gestalte te geven. Voor het onderbrengen bij de Gezondheidsraad pleit het experimentele karakter dat de beoordeling de eerste jaren zal hebben. Dit experimentele karakter komt voort uit het feit dat het een nieuw soort beoordeling betreft van deels nieuwe categorieën van voedingsmiddelen of voedselingrediënten. Het is namelijk een veiligheidsbeoordeling vóór het op de markt brengen van met name voedingsmiddelen van een genetisch gemodificeerde oorsprong en zogenaamd functional foods (nutriceutica). Daarnaast ga ik ervan uit dat de onafhankelijke wetenschappelijke advisering door de Gezondheidsraad het vertrouwen van de Europese Commissie en de andere lidstaten in het Nederlandse oordeel nog versterkt.

Mijn beleid is erop gericht een zo groot mogelijke openheid en transparantie te realiseren van de gevolgde procedure en de beoordeling om de consument vertrouwen te geven in de veiligheid van de

nieuwe voedingsmiddelen. Ik verzoek de Gezondheidsraad hieraan bij te dragen door bijvoorbeeld inzage te geven in de dossiers waarvoor een aanvraag wordt ingediend, waarbij uiteraard bedrijfsvertrouwelijke gegevens worden beschermd en door de criteria, waarop de veiligheid zal worden beoordeeld, te publiceren.

De Minister van Volksgezondheid, Welzijn en Sport,
w.g. dr E Borst-Eilers

English translation

On 18 August 1999, the Minister of Health, Welfare and Sport wrote as follows to the President of the Health Council of the Netherlands (under reference GZB/VVB 993428):

Since May 1997, Regulation (EC) 258/97 concerning novel foods and novel food ingredients has been in force in the European Union. Under the Regulation, the safety of novel foods has to be assessed as part of a community procedure.

Following discussions regarding the possibility of the Health Council making such assessments, the State Secretary for Agriculture, Nature Management and Fisheries and I wish the Council to take responsibility for safety assessment for a period of several years during the fist phase of implementation of European Regulation (EC) 258/97. It is considered appropriate that the Health Council should initially take on this role because the assessment activities will be of an experimental nature, involving both a new form of assessment (i.e. pre-marketing assessment) and, in many cases, new categories of foodstuff (primarily foodstuffs with a genetically modified basis and functional foods or nutraceuticals). We also feel that if assessments are made by a body with the Council's independent scientific status, this will support the validity of the Netherlands' opinion in the eyes of the European Committee and other member states.

My wish is to make the procedure and the assessment as open and transparent as possible, so as to enhance consumer trust in the safety of novel foods. I would like the Health Council to support this objective by, for example, allowing perusal of the application dossier (insofar as consistent with the need to protect the confidentiality of commercially sensitive information) and publishing the criteria upon which safety assessments are made.

The Minister of Health, Welfare and Sport,
(signed) dr E. Borst-Eilers

Bijlage **B**

De commissie/The committee

- Prof. dr LM Schoonhoven, *voorzitter/chairman*
  emeritus hoogleraar entomologie; Wageningen Universiteit en Researchcentrum/
  emeritus professor of entomology; Wageningen University and Research centre
- Prof. dr CAFM Bruijnzeel-Koomen
  hoogleraar dermatologie/allergologie; Academisch Ziekenhuis Utrecht/
  professor of dermatology/allergology; Academic Hospital Utrecht
- Ir EJ Kok
  toxicoloog; RIKILT-DLO Wageningen/
  toxicologist; State Institute for Quality Control of Agricultural Products, Wageningen
- Dr CF van Kreijl
  moleculair-bioloog; RIVM Bilthoven/
  molecular biologist; National Institute of Public Health and the Environment, Bilthoven
- Prof. dr P van der Laan
  hoogleraar statistiek; Technische Universiteit Eindhoven/
  professor of statistics; Technical University Eindhoven
- Dr FM Nagengast
  gastro-enteroloog; Academisch Ziekenhuis Nijmegen/
  gastro-enterologist; Academic Hospital Nijmegen

- Dr ir JMA van Raaij
  voedingsfysioloog; Wageningen Universiteit and Researchcentrum/
  food physiologist; Wageningen University and Research centre
- Prof. dr ir G Schaafsma
  hoogleraar voeding; TNO Voeding, Zeist/
  professor of nutrition; TNO Nutrition and Food Research, Zeist
- Prof. dr EG Schouten, *adviseur/advisor*
  hoogleraar epidemiologie; Wageningen Universiteit and Researchcentrum/
  professor of epidemiology; Wageningen University and Research centre
- Dr GJA Speijers
  toxicoloog; RIVM Bilthoven/
  toxicologist; National Institute of Public Health and the Environment, Bilthoven
- Prof. dr WJ Stiekema
  hoogleraar bioinformatica; Wageningen Universiteit en Researchcentrum/
  professor of bioinformatics; Wageningen University and Research centre
- Ir R Top, *adviseur/advisor*
  Ministerie van VWS; Den Haag/
  Ministry of Health, Welfare and Sport; The Hague
- Prof. dr WM de Vos
  hoogleraar microbiologie; Wageningen Universiteit en Researchcentrum/
  professor of microbiology; Wageningen University and Research centre
- Dr RA Woutersen, *adviseur/advisor*
  toxicoloog; TNO Voeding, Zeist/
  toxicologist; TNO Nutrition and Food Research, Zeist
- Dr ir F van der Wilk, *adviseur/advisor*
  COGEM, Bilthoven/
  Committee on Genetic Modification, Bilthoven
- Dr ir M Rutgers, *secretaris/scientific staff member*
  Gezondheidsraad, Den Haag/
  Health Council of the Netherlands, The Hague

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Layout: J van Kan; Gezondheidsraad, Den Haag/Health Council of the Netherlands, The Hague.

Bijlage **C**

EU-procedure/EU-procedure

Als een fabrikant een nieuw voedingsmiddel op de markt brengt, dient de veiligheid voor de consument gewaarborgd te zijn. In 1997 werd de Europese verordening van kracht waarin de procedure is geregeld voor de goedkeuring voor marktintroductie van een nieuw voedingsmiddel (EG97). Bij deze procedure zijn verschillende actoren betrokken. De aanvrager moet beoordelen of het product werkelijk 'nieuw' is, dat wil zeggen dat het nog niet eerder in de Europese Unie in substantiële mate voor menselijke voeding is gebruikt en ook niet wezenlijk gelijkwaardig is aan een bestaand product. (Voor een wezenlijk gelijkwaardig product kan worden volstaan met een kennisgeving van de marktintroductie.) Ook moet het niet gaan om een levensmiddelenadditief, aroma of extractiemiddel, omdat deze producten op een andere wijze worden beoordeeld. Voor een nieuw voedingsmiddel in de zin van de Europese verordening moet de aanvrager een veiligheidsdossier overleggen volgens aanbevelingen van de Europese Commissie (EG97a). Deze aanbevelingen zijn gebaseerd op rapporten van verschillende instanties die zich met het onderwerp nieuwe voedingsmiddelen bezighouden, te weten de OECD (OECD93, OECD96) en de WHO/FAO (FAO96, WHO91). Ook de Gezondheidsraad heeft zich al eerder over dit onderwerp gebogen (GR92). Sinds het verschijnen van de aanbevelingen van de EU wordt in internationaal verband gewerkt aan explicitering en aanpassing aan de stand van de wetenschap (FAO01, OECD98, OECD00, SCF99, SSC99, WHO00).

De fabrikant levert het volgens de richtlijnen samengestelde dossier in bij het land waar het product het eerst op de markt zal komen. Daarop komt de nationale veiligheids-beoordelingsautoriteit in actie. In Nederland is dat de Minister van Volksgezondheid,

Welzijn en Sport. Zij heeft de Gezondheidsraad verzocht haar van advies te dienen. De Voorzitter van de Gezondheidsraad heeft hiertoe de commissie Veiligheidsbeoordeling nieuwe voedingsmiddelen (commissie VNV) ingesteld.

De commissie beoordeelt op basis van de huidige stand van de wetenschap of de door de fabrikant geleverde gegevens juist en volledig zijn en of zij het eens is met diens conclusies. Zij maakt een verslag van haar bevindingen — ook volgens de Europese aanbevelingen (EG97a, deel III) — en biedt dat de minister aan. De minister formuleert het Nederlandse oordeel over een voedingsmiddel en brengt dat in bij het Europese overleg in het Permanent Comité voor de voedselketen en de diergezondheid. Alle Europese lidstaten worden uitgenodigd hun oordeel (de zogeheten tweede beoordeling) te geven over het dossier en over de eerste beoordeling alvorens genoemd Comité een eindoordeel velt. Als een dossier veel vragen oproept, gaat er een adviesvraag van de Europese Commissie naar het Wetenschappelijk Comité voor de menselijke voeding. Komt men dan nog niet tot overeenstemming dan beslist de Europese Ministerraad.

English translation

When manufacturers bring novel foodstuffs onto the market, consumer safety has to be ensured. In 1997, a European Regulation (EG97) came into force, laying down the procedure for approving the market introduction of novel foodstuffs. The procedure recognizes various actors. The applicant must decide whether a product is a novel foodstuff, i.e. a substance that has not previously been available for human consumption to any substantial extent within the European Union and is not substantially equivalent to any existing product. (If a foodstuff is substantially equivalent to any existing product, it is sufficient to inform the authorities of its market introduction). Food additives, aromas and extracts are excluded from the provisions of the directive, since they fall within the scope of an established assessment regime. Before marketing a novel foodstuff, the applicant must compile a safety dossier that complies with the Recommendations of the European Commission (EG97a). These Recommendations are based on reports by a number of bodies that have studied the issue of novel foodstuffs, in particular the OECD (OECD93, OECD96) and the WHO/FAO (FAO96, WHO91). The Health Council of the Netherlands has also considered the question earlier (GR92). Since publication of the EU recommendations, international efforts have been made to clarify and adapt the latest scientific knowledge in the field (FAO01, OECD98, OECD00, SCF99, SSC99, WHO00).

Having compiled a dossier in line with the guidelines, the manufacturer has to submit it to the competent authority in the country where the product is to be marketed first. This dossier is assessed by the national safety assessment authority. In the Netherlands, this is the Minister of Health, Welfare and Sport, who is advised by the Health Council.

The President of the Health Council has created a Committee on the Safety Assessment of Novel Foods (VNV Committee) to advise the minister on behalf of the Council.

On the basis of the scientific state of the art, the committee has to decide whether the information provided by the manufacturer is accurate and complete and whether the manufacturer's conclusions are sound. The committee then draws up a report on its findings for the minister; this report must also comply with the European Recommendation (EG97a, part III). After considering the report, the minister formulates the Netherlands' opinion regarding the foodstuff in question, which is discussed at European level in the Standing Committee on the Food Chain and Animal Health. All other European member states are invited to express a 'second opinion' regarding the dossier and the first opinion. The Standing Committee then arrives at a final judgement. If a dossier is particularly contentious, the European Commission calls upon the Scientific Committee on Food for advice. If consensus still cannot be reached, the issue is referred to the European Council of Ministers.

Bijlage **D**

Samenvatting van het dossier/Executive summary of the dossier

SUMMARY BY APPLICANT

(for the further circulation to the Member States of European Union)

An application to place betaine as a food ingredient on the EU Novel Food Market

TABLE OF CONTENTS

APPENDICES

1 Introduction

The novel food application on which this summary is based, has been made to place the novel food ingredient, betaine, both in anhydrous and monohydrate form, to be used in beverages, confectionary, cereal and dairy products on the EU novel food market.

Betaine (chemical name: 1-Carboxy-N,N,N-trimethylmethanaminium hydroxide inner salt) is categorised as novel food ingredient because it has not previously been used for human consumption to a significant degree within the European Community.

Betaine, also known as trimethylglycine or glycine betaine, is a quarternary amine, closely related to the amino acid glycine. It is naturally present at varying concentrations, in most living organisms, including sugar beet and other plants belonging to the *Chenopodiaceae* family. Naturally occurring betaine concentrations in plants and animals generally vary along with growing and osmotic stress conditions. Betaine has been found at relatively high concentrations in common foods and/or foodstuffs such as cereals (e.g. wheat, oats), seafood, clams, vegetables and common edible mushrooms.

Betaine was first isolated in 1866, from sugar beet (*Beta vulgaris*) juice concentrate. Until 1960, betaine was used mainly in pharmaceutical applications. Today, it is widely used in dietary supplements, dental products, cosmetics, for fermentation purposes as well as in animal feed. In these applications, betaine is used to serve a technical function such as moisture control and/or for its nutritional benefits, particularly as a methyl donor.

In recent years, betaine has been actively investigated for its health-promoting potential. In clinical studies it has been shown that betaine successfully lowers serum elevated homocysteine levels in humans. High serum homocysteine levels have been shown to be a risk marker to cardiovascular disease and thus, betaine-enriched foods may help to lower the risk of cardiovascular disease. Other investigators have studied betaine metabolism, including its role in the methionine cycle and betaine's potential to protect the liver from ethanol induced liver injury and non-alcoholic steatohepatitis. To date, there is a

wealth of human clinical studies discussing the benefits of betaine supplementation at dose levels ranging from 2 to 30 g/day; 6 g/day being the most common dose.

The table of contents of the original application is presented in appendix 1.

2 Scientific classification

According to European Commission's recommendations on the Assessment of Novel foods (Part I), the novel food ingredient, betaine, is classified under

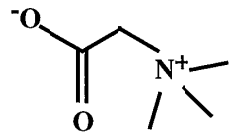
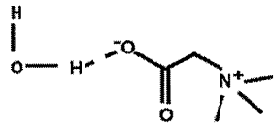
Class 1: **Pure Chemicals or simple mixtures from non-GM sources.**
Sub class 1.1: **The sources of the novel foods have a history of food use in the Community.**

According to the categorisation in the EC Novel Foods and Novel Food Ingredients Regulation 258/97, the present novel ingredient falls into the following category:

e) foods and food ingredients consisting of or isolated from plants and food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagating or breeding practices and having a history of safe food use.

3 Description of betaine

Betaine is 99 % pure compound of which chemical structure is presented below. Specifications of betaine (Betafin BF 20, TMG 20 and Betafin AP) are presented in appendix 2. Betaine as such does not have a traditional counterpart. The nutritional value of betaine is comparable to amino acids, which are parts of proteins. Betaine is derived from non-genetically modified source.

Betaine:	$(CH_3)_3N^+CH_2COO^-$	$(CH_3)_3N^+CH_2COO^- \times H_2O$
		
	Anhydrous betaine	Betaine monohydrate

Anhydrous betaine and betaine monohydrate have similar chemical structure except water (H_2O) molecule which is attached into the carbonyl group in monohydrate form. Physicochemical characteristics of anhydrous betaine and betaine monohydrate are similar. Anhydrous betaine is gradually converted to betaine monohydrate when the relative humidity of environment is more than 7 %. Both betaine forms dissolve in water when the relative humidity is more than 46 %. Nutritional, microbiological and toxicological properties of anhydrous betaine and betaine monohydrate are equal. **In the present application, word 'betaine' means both betaine anhydrous and monohydrate form.**

4 Production process of betaine

Sugar beet is containing 0.2 - 0.3 % betaine. Extraction of betaine from sugar beet can be divided into three main stages – production of sugar beet molasses from sugar beet, extraction of betaine rich fraction from sugar beet molasses and finally refining and crystallisation of betaine rich fraction to crystalline betaine. Betaine is extracted from sugar beet molasses by liquid chromatography method. This method is generally well known and the same method is used for example in fructose or xylitol production. Food grade betaine has been produced since 1983 to be sold in Japan and Korea by using this process. Betaine marketed by Finnfeeds Finland Ltd is extracted at Naantali, Finland, from sugar beet based concentrated liquids of betaine.

5 Anticipated use of betaine

Betaine will be used as an ingredient in beverages, confectionary, cereal and dairy products. These foods are produced by using the traditional ingredients except the enrichment with betaine. Proposed new uses for betaine in foods and maximum application levels are as follows:

- beverages, max 2,0 %
- confectionary, max 6,7 %
- cereal products, max 4,0 %
- dairy products, max 2,7%.

Betaine does not replace any particular ingredient of foods, but it replaces evenly all other ingredients. Betaine enriched foods are manufactured as traditional foods. According to study results, betaine is a stabile ingredient in food processing and no decomposition happens.

Anticipated intake of betaine from the previous-mentioned betaine-enriched foods is 4 grams per day. The recommendations on package labelling of betaine-enriched foods will advise to consume betaine-enriched products so that not more than 4 g betaine will be obtained daily. This is because already 3 g of betaine has been shown to be effective to decrease blood homocysteine concentrations.

6 Purpose of betaine enrichment

In clinical studies it has been shown that betaine successfully lowers serum elevated homocysteine levels in humans. High serum homocysteine levels have been shown to be a risk marker to cardiovascular disease and thus, betaine-enriched foods may help to lower the risk of cardiovascular disease. Traditionally betaine has been used for enhancing seafood flavourings, particularly crab meat substitutes. Betaine is also used as a preservative for shrimps by lowering the water activity.

7 Safety aspects concerning betaine

7.1 General

A safety evaluation of novel food ingredient betaine has been prepared according to the European Commission's Recommendations on the assessment of novel foods (97/618/EY). In respect to betaine, based on the results of clinical studies presented previously, nutritional impact of betaine and betaine-enriched foods happens mainly in blood homocysteine concentrations, which decrease due to betaine enrichment. Based on the results of several studies, betaine does not affect the bioavailability of nutrients from the diet. No adverse effects except mild gastrointestinal symptoms have occurred in the studies made with betaine or betaine-enriched foods. Microbiological tests show that betaine does not cause any microbiological risks. Also toxicological tests of betaine show that no safety concern is apparent. As an amino acid, betaine has no allergenic potential.

7.2 Nutritional information

Betaine is a normal constituent of human blood and urine and accumulates in kidney renal medullary cells where it functions as a protective osmolyte. Betaine levels in the blood appear to be homeostatically controlled and typical betaine plasma concentrations (20-60 µmol/l) are relatively stable.

In the diet, betaine is obtained either directly from ingesting foods containing betaine or indirectly via metabolism of foods containing choline, and choline derivatives such as lecithin. Dietary betaine is absorbed via the small intestine into the enterocytes. It is then released into the portal circulation and carried to the liver where significant first pass extraction and metabolism of betaine occurs. Betaine is also metabolised in the kidneys. *In vivo*, choline is largely converted to either acetylcholine and/or phospatidylcholine or oxidized to betaine. According to kinetic studies, betaine is primarily catabolized *in vivo*, urinary excretion being negligible.

To date there are over 40 published human clinical studies (some of which comprise several case studies on betaine); in total, more than 700 people have been studied. In those studies, the effect of betaine to decrease the serum homocysteine concentrations both in people with homocysteinemia and healthy people is reported. Reported betaine dose levels range from 2 to 30 g per day; 6 g/day being the most common dose. The period of betaine intake ranges from 1 day to 16 years. There has been no evidence of organ toxicity, and adverse reactions to betaine have been minimal, including anecdotal reports of nausea, diarrhoea and gastrointestinal distress. No other types of adverse effects have been found.

7.3 Microbiological information

Betaine is manufactured under sanitary conditions and in conformance to health and safety conditions established by the Finnish authorities. The applicant's facility is subjected to inspections and monitoring by local health inspectors. HACCP and other internal quality management programs have been established to ensure good manufacturing practice. In addition, the facility has been ISO 9001 certified since September 1997.

The preservation tests of betaine-enriched beverages are being made and the results of the tests will be attached into the present application later.

According to studies conducted by the applicant, betaine itself has some antimicrobial effects when concentrated. As a hygroscopic product betaine tends to bind water molecules from the surroundings. The antimicrobial effects are based on the fact that betaine can lower the free water activity so that the growth of microbes is delayed or inhibited.

7.4 Toxicological information

In the literature, the safety of betaine in rats has been reported in several studies. In addition, the applicant has had toxicological studies made by expert research institutions: short-term genotoxicity studies, acute toxicity study, A 14-day range finding study and a

90-day sub-chronic toxicity study, 28-day sub-acute toxicity and reversibility study, 28-day & 90-day metabolic feeding studies and sensitization / irritability studies. All studies have been conducted in accordance with the Principles of Good Laboratory Practice (GLP).

To present one of the studies in which the NOAEL (no adverse effects level) was set: In the 28-day and 90-day feeding studies in rats carried out with betaine as the test substance, fifty 3-wk old Sprague-Dawley female rats were studied. As a result, no significant adverse clinical effects were observed at any betaine dose level. Based on modest perturbation of red blood cell physiology in growing animals and considerations for protein metabolism, the NOAEL for betaine was set at 150 mg/g protein consumed by growing rats fed a normal diet. The equivalent NOAEL for casually exposed adult humans was determined to be 9-15 g betaine/day, based on the typical range of protein intake by adult humans.

List of references of an original application is presented in appendix 3.

8 Conclusion

Based on literature, human clinical studies and toxicological tests, the novel food ingredient betaine, is unlikely to give any rise to nutritional, microbiological or toxicological problems. Therefore, it is considered safe for use at the anticipated consumption levels of beverages, confectionary and cereal and dairy products as a part of the daily diet of healthy people and especially people with risk of atherosclerosis.

Summary:

APPENDIX 1

Table of contents of the original novel food application

TABLE OF CONTENTS

Appendix 12	**Betaine intake from natural sources**
Appendix 13	**The list of human clinical studies with betaine**
Appendix 14	**Final report: The effect of betaine supplementation on plasma homocysteine concentrations, body weight, body composition and resting energy expenditure in human subjects.**
Appendix 15	**Amendment to final report:** The effect of betaine supplementation on plasma homocysteine concentrations, body weight, body composition and resting energy expenditure in human subjects
Appendix 16	**Effect of betaine supplementation on hematology - will be completed later. Study report: Dose-response study of betaine and homocysteine**
Appendix 17	**- will be completed later. Research report: preservation tests of betaine-enriched beverages**
Appendix 18	**Research report: Determination of microbiological stability of betafin solutions**
Appendix 19	**Short-term genotoxicity studies:** **Bacterial reverse mutation assay** **Mouse micronucleus test** **Metaphase analysis of human lymphocytes**
Appendix 20	**Acute oral toxicity study in the rats**
Appendix 21	**Report: Validation of the determination of betaine in diet**
Appendix 22	**Final report: A 14-day range finding study and a 90-day sub-chronic toxicity study in the rat with betaine**
Appendix 23	**Final report: A 28-day sub acute toxicity and reversibility study in the rat with betaine**
Appendix 24	**Study report: Metabolic aspects of betaine supplementation in rats**
Appendix 25	**Sensitization/irritability studies:** **Human patch test for skin irritation** **Sensitisation test in the guinea pig** **Acute eye irritation study**

APPENDIX 2

Product specifications of Betafin BF 20, TMG 20 and Betafin AP

finnfeeds
DANISCO CULTOR

product specification

BETAFIN BF 20

Betaine anhydrous food grade

C10A0

Formula	$(CH_3)_3$-N^+-CH_2-COO^-
Molecular weight	117.15

Specification

Betaine (HPLC)	min. 99 % d.s.
Moisture (Halogen drying)	max. 2 % when packed
Ash (conductometric)	max. 0.1 %
Chloride (titration)	max. 50 ppm
Sulphate (limit test)	max. 100 ppm
Heavy metals (limit test)	max. 10 ppm
Arsenic (ICP-MS)	max. 1 ppm
Lead (ICP-MS)	max. 1 ppm
Colour (ICUMSA)	max. 20
pH (5 % solution)	5 - 7
Total viable count	max. 100 cfu/g
Yeast	max. 10 cfu/g
Mold	max. 10 cfu/g
Coliforms	not detected
E-coli	not detected
Salmonella	not detected

Other properties

Appearance	Free-flowing, white crystals, faint characteristic odour.
Particle size	Typically 90% < 0,5 mm
Bulk volume	Typically 0.6 - 0.8 kg/l
Solubility at 25°C	Water 160 g/100 g H_2O Methanol 55 g/100 g MeOH Ethanol 8.7 g/100 g EtOH
	Hygroscopic, absorbs humidity from air
Stability	Heat stable up to 200°C

Finnfeeds Finland Limited
Naantali Plant, Satamatie 1, FIN-21100 NAANTALI, Finland
Telephone +3582 4393 300, Fax +358 2 4393 333
Trade reg.no. 751.670, Domicile Helsinki, Business ID FI15081982

finnfeeds
DANISCO CULTOR

Shelf life	3 years from the manufacturing date
Packaging	20 kg cartons with polyethylene inner bag, shrinkwrapped on one-way pallet. Standard pallet 1000 kg.
Storage	In unopened bags, protected from humidity

Finnfeeds Finland Limited
Naantali Plant, Satamatie 1, FIN-21100 NAANTALI, Finland
Telephone +3582 4393 300, Fax +358 2 4393 333
Trade reg.no. 751.670, Domicile Helsinki, Business ID FI1508198-2

DANISCO

product specification

TMG 20

Betaine anhydrous food grade
C10B0

Formula	$(CH_3)_3$-N^+-CH_2-COO^-
Molecular weight	117.15

Specification

Betaine (HPLC)	min. 99 % d.s.
Moisture (Halogen drying)	max. 2 % when packed
Ash (conductometric)	max. 0.1 %
Chloride (titration)	max. 50 ppm
Sulphate (limit test)	max. 100 ppm
Heavy metals (limit test)	max. 10 ppm
Arsenic (ICP-MS)	max. 1 ppm
Lead (ICP-MS)	max. 1 ppm
Colour (ICUMSA)	max. 20
pH (5 % solution)	5 - 7
Total viable count	max. 100 cfu/g
Yeast	max. 10 cfu/g
Mold	max. 10 cfu/g

Other properties

Appearance	Free-flowing, white crystals, faint characteristic odour	
Bulk volume	0.5 - 0.6 kg/l	
Solubility at 25°C	Water	160 g/100 g H_2O
	Methanol	55 g/100 g MeOH
	Ethanol	8.7 g/100 g EtOH
	Hygroscopic, absorbs humidity from air	
Stability	Heat stable up to 200°C	
Shelf life	3 years from the manufacturing date	
Packaging	20 kg cartons with polyethylene inner bag, shrinkwrapped on one-way pallet. Standard pallet 1000 kg.	

Storage	In unopened bags, protected from humidity

DANISCO

product description

BETAFIN AP

Betaine monohydrate pharmaceutical and food grade
C13N0

Formula	$(CH_3)_3$-N^+-CH_2-COO^- x H_2O
Molecular weight	135.16
Specification	
Eetaine (HPLC)	min. 99 % d.s.
Moisture (Halogen drying)	max. 15 % when packed (includirg water of crystallization)
Ash (conductometric)	max. 0.1 %
Chloride (titration)	max. 50 ppm
Sulphate (limit test)	max. 100 ppm
Heavy metals (limit test)	max. 10 ppm
Arsenic (ICP-MS)	max. 1 ppm
Colour (ICUMSA)	max. 20
pH (5 % solution)	5 - 7
Total viable count	max. 100/ g
Other properties	
Appearance	Free-flowing, white crystals, faint characteristic odour
Bulk volume	0.7 - 0.75 kg/l
Betaine solubility at 25°C	Water 160 g/100 g H_2O Methanol 55 g/100 g MeOH Ethanol 8.7 g/100 g EtOH
	Hygroscopic, absorbs humidity from air
Stability	Heat stable up to 200°C
Shelf life	3 years from the manufacturing date
Packaging	25 kg multiwall laminated white paper bags with polyethylene inner bag, shrinkwrapped on one-way pallet. Standard pallet 1000 kg.
Storage	In unopened bags, protected from humidity

APPENDIX 3

List of references of an original novel food application

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Bijlage **E**

Eerste beoordeling/First assessment

MINISTRY OF
TRADE AND INDUSTRY

FINLAND

Novel Food Board

(Courtesy Translation)

Dno 1/618/2003
12 June 2003

INITIAL ASSESSMENT REPORT
under Article 4 of Regulation (EC) No 258/97 of the European Parliament and the Council concerning novel foods and novel food ingredients

"AN APPLICATION TO PLACE BETAINE AS A FOOD INGREDIENT ON THE EU NOVEL FOOD MARKET"

1. On 24 January 2003, Finnfeeds Finland Ltd submitted an application to place betaine as a food ingredient on the EU novel food market to the National Food Agency. Betaine is intended for use in drinks, cereal products and dairy products. The application was forwarded to the Novel Food Board on 30 January 2003. The Board has requested the applicant to provide further clarification on 25 February 2003, 6 May 2003, 19 May 2003 and 10 June 2003. The applicant has responded to the requests on 31 March 2003, 7 May 2003, 13 May 2003, 3 June 2003 and 11 June 2003.

2. The Novel Food Board has examined the application in accordance with the Commission Recommendation 97/618/EC concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients and the preparation of initial assessment reports under Regulation (EC) No 258/97 of the European Parliament and of the Council.

3. The application is considered to belong to class (e) in Article 1.2 of the Regulation, foods and food ingredients consisting of or isolated from plants or animals. In accordance with the Commission Recommendation 97/618/EC, the ingredient concerned by the application has been identified as belonging to class 1.1 "Pure chemicals or simple mixtures from non-GM sources; the source of the NF has a history of food use in the Community". Accordingly, the examination of this application proceeds in accordance with the schemes I, II, III, IX, X, XI, XII, XIII presented in the Commission Recommendation.

OPINION OF THE NOVEL FOOD BOARD ON THE SAFETY OF THE FOODS CONCERNED BY THE APPLICATION

SUMMARY

4. **Betaine (synonyms glycine betaine and trimethyl glycine), intended for use as an ingredient in the foods concerned by the application, is a compound that is commonly found in animals and plants. The products concerned by the application (Betafin BF20, TMG20 and AP) consist up to 99% of betaine. In the products, betaine is either in anhydrous from or in form of betaine monohydrate. The foods for which the ingredient is intended correspond as to their composition otherwise to foods that already are on the market.**

5. **The information submitted by the applicant on the composition of the betaine ingredient has been sufficient. The calculations on anticipated consumption has been adequately**

made. The Novel Food Board states however that it is very difficult to give estimates on the intake of betaine from foods to which betaine has been added, and that the calculations have mainly been based on the applicant's own estimates on the consumption of single products.

6. The source of betaine, molasses from sugar beet, has a long history use as a safe raw material for foodstuffs. The betaine ingredient isolated from sugar beet can be regarded as fit for human consumption. According to a testimonial presented by the applicant, no genetically modified sugar beets are used in the production of the food ingredient concerned.

7. The production processes used in the manufacture of the foods concerned are traditional food processes, and the Board has no objection to them. On the basis of what is said in the application, the processes of manufacture of the final foods cannot be expected to have any marked effect on the content or the quantity of the betaine ingredient. Neither are any problems of microbiological nature to be expected.

8. Foods containing the ingredient concerned by the application are not expected to be nutritionally disadvantageous even when replacing traditional foods used for comparative purposes.

9. The results of the safety evaluation studies provided by the applicant indicate that liver is the target organ of possible betaine toxicity. The observed effects on animals were minor and at least largely reversible. The effects on the health of the consumer cannot, however, be assessed with adequate reliability on the basis of the material presented by the applicant. Betaine has not been proved to cause allergies or reactions of hypersensitisation.

10. Based on the existing knowledge presented in the application and in the light of other existing knowledge of betaine, it can be assumed that a daily intake of 20-30 grams of the new ingredient in the foods concerned by the application would not be nutritionally disadvantageous for consumers.

11. The Board holds the view that foods to which betaine has been added should not be marketed to pregnant women, breastfeeding mothers or infants, because no data on the long-term effects of betaine on these user groups are available.

12. The Board considers that food labels should provide the consumer with information on the betaine ingredient of the product. The applicant has presented a draft of a product label to be affixed on packages intended for sale to food manufacturers. The applicant does not present any proposal on how information on the new ingredient should be disseminated to consumers on the package of the final product.

DETAILED EXAMINATION OF THE APPLICATION

I. Specification of the Novel Food

13. The information received on the products concerned by the application and on the betaine ingredient of them has been sufficient. On the basis of the material presented, the products can be considered suited for food use.

14. Betaine is produced of the secondary flow of sugar beet intended for the production of sugar. An assessment of the manufacturing process and its effects on the products is presented in Chapter III.

15. Betaine is planned to be marketed under three different brand names: Betafin BF20 (anhydrous form of edible quality, a description of the product in Annex 1a to the application), Betafin TMG20 (anhydrous form of edible quality corresponding to the above product, a description of the product in Annex 1b to the application) and Betafin AP (betaine monohydrate of edible and pharmaceutical quality, a description of the product presented in Annex 1d). A safety data sheet for all the three products is presented in Annex 1d. Annex 2 contains a description of the method used in the determination of the quantity of betaine mentioned in the product specification.

16. In the light of the information presented in product specifications and in Annexes 5-6, it can be stated that the products concerned are suited for food use as concerns residual materials.

17. The data presented in product specifications are obtained from production on an industrial scale. Betaine has been produced in commercial scale since 1979 and betaine for food grade betaine since 1983. Reference materials related to the products are available.

18. Betaine is known under its chemical names glycine betaine or trimethyl glycine. Its chemical structure is simple – a glycine basis plus three methyl groups that are attached to one nitrogen atom. In betaine monohydrate, one water molecule is attached to a group of carbonyls. The anhydrous form and the hydrated form of betaine are comparable as to their physical and chemical properties. In the application, the concept "betaine" is used to describe both these forms.

19. Betaine products are highly hygroscopic. The stability of the products has been ensured by packaging them in moisture-resistant, food quality material.

20. Betaine is intended for use in drinks, sweets, cereal products and dairy products. The applicant states that betaine will be added to normal foods that are already on the market. The proposed maximum betaine content of the products concerned is as follows: drinks 2%, sweets 6.7%, cereal-based products 4% and milk-based products 2.7%.

II. Effect of the Production Process Applied to the Novel Food

21. The methods used in the production of betaine and betaine products can be considered acceptable. Betaine is considered to be able to endure the manufacturing process of the foods to which betaine is intended to be added.

22. The production methods of betaine products have been presented in the application. The production process is conducted according to GMP requirements and by applying the Hazard Analysis and Critical Control Points (HACCP) principles. The quality system for production and the environmental management system have been certified in accordance with the ISO 9001:1994 and 14001:96 standards (Annex 2 to the Application).

23. Betaine can be crystallized from sugar molasses produced from sugar beet either in an anhydrous form or as betaine monohydrate. Anhydrous betaine has been proved to remain stable over the time set out for the products concerned, namely three years (Annex 8 to the application).

24. For anhydrous betaine, the degradation process or the esterification process starts first at a temperature exceeding 245°C, and betaine monohydrate is still more stable than that. The core temperature of foods to which betaine is going to be added does not exceed 200°C during the manufacture, which means that degradation or esterification of betaine is not to be expected.

25. The stability of crystalline betaine and of a solution with a betaine content by weight of 50% has been tested during 2-24 hours at temperatures between 80°C and 200°C (Annex 9 to the Application). The quantity of crystalline betaine remained unchanged under test conditions, even though a slight change of colour could be observed at 120°C and especially at 200°C. Clear degradation was observed in the aqueous solution of betaine at 200°C and an indefinable odour already at 120°C. However, the foods to which betaine will be added can be expected to endure the manufacturing process for such foods.

26. The method of manufacturing cookies did not have any effect on the betaine added (Annex 10).

III. History of the organism used as Novel Food source

27. Betaine is produced from sugar beet, *Beta vulgaris sp.*, which is used in the production of sugar and which has a long history as a food source. No genetically modified varieties are used in the production, the applicant presents a testimonial of that in Annex 11. Sugar molasses from which betaine is being isolated is well-known as a food ingredient throughout the EU.

IX. Anticipated intake / extent of use of the Novel Food

28. The consumption calculations presented in the application are adequate. For many foodstuffs, the calculations are based on the applicant's own judgment. The fact that the applicant intends to add betaine to certain groups of foodstuffs, and not to specific foods, makes the estimation of intake levels more difficult. There are necessarily no data available on the consumption of single foodstuffs belonging to certain food categories, and foods categories on the other hand vary from country to country within the EU, which also makes it more difficult to make reliable estimates of consumption. Any specific estimates of consumption by children have not been presented.

29. The applicant proposes that betaine be used as an ingredient in the following foodstuffs:

- beverages, such as soft drinks and mineral waters, non-diluted fruit juices, ready-to-serve coffee and tea drinks, alcoholic drinks - excluding beer - with an alcoholic strength by volume of less than 22% vol (such as long drink, cider, wine, bitter, sherry or liqueur)
- cereal products, such as Müsli, breakfast cereals, oat, rye, barley and wheat flakes and snack-bars ("energy bars")
- dairy products such as sour milk products
- confectionary such as hard candies (pastilles) and chewing gum

The maximum betaine content of the products concerned by the application is planned to be as follows: for drinks 2%, for cereal-based products 4%, for sour milk products 2.7% and for confectionary 6.7%.

30. Data on the use of foodstuffs to which betaine is planned to be added in some EU countries (Finland, Sweden, Denmark, Great Britain, Germany, the Netherlands and Spain) is presented in the application and in the supplementary information submitted on 31 March 2003 and 3 June 2003. The applicant presents in the following data on very high consumption of the foods to which betaine is planned to be added at the level of the 90th percentile (intake g/day):

	Drinks	Sweets	Cereal products	Dairy products
Sweden[1]	1250	13	176	224
Denmark[2]	1250	15	163	230

[1] Riksmaten 1997-1998. Kostvanor och näringsintag i Sverige. Method and result analysis. Livsmedelsverket 2000
[2] Andersen et al, Publ. 235, Levnedsmiddestyrelsen 1996

31. The table below presents an estimate of the intake of betaine that has been made on the basis of the recommended daily intake of foods to which betaine is added and on the consumption data on corresponding foods without betaine (g/day):

	Recommended daily intake of a foodstuff	Intake of betaine at recommended dosage	Average consumption of a foodstuff	Intake of betaine at average consumption	Maximum consumption of a foodstuff	Intake of betaine at maximum consumption
Drinks	200	4	493-739	10-15	1250	25
Confectionary	60	4	4-8	0.2-0.5	13-15	1
Cereal products	100	4	27-45	1-2	163-176	6.5-7
Dairy products	200	4	65-115	2-3	224-230	6
Cumulative intake		16		13-20.5		39

32. It appears from the table above that the total daily intake of betaine from all groups of foodstuffs containing betaine at recommended intake levels may be up to 16 grams. If the intake is calculated on the basis of the average intake of the foodstuffs concerned, the daily intake of betaine is estimated to be about 13-20 grams, and at large consumption about 39 grams.

33. It is, however, improbable that a consumer would eat all foodstuffs containing betaine continuously and in large quantities. The applicant considers that a continuous high intake of betaine could result in intestinal trouble, which would have a dampening effect on the consumer's desire to use the products concerned continuously. A study published in 2002 . (Abdelmalek et al) reveals that a continuous daily consumption of 20 grams during a year did not cause harm to the health of seven patients who suffered from non-alcoholic fatty liver disease i.e. non-alcoholic steatohepatosis. Similar results have been obtained in a study published in 1951 where the intake level was 20-30 grams per day (Borsook & Borsook).

34. The applicant proposes that adults, old people and particularly persons who are otherwise healthy but are running a risk of heart disease should be target groups for the products concerned. The products are not intended for children or pregnant women or breast-feeding mothers, and for that reason, the applicant has not considered it necessary to make a safety evaluation especially with a view to these groups of consumers. Betaine is, however, proposed to be added to groups of foodstuffs that children consume in larger quantities than adults in relation to their weight (e.g. sweets and soft drinks).

35. Vegetarians and persons suffering from under-nourishment constitute a potential risk group if betaine increases the need for methionine. A study reveals that the need for methionine by healthy men increased already after quite a reasonable increase of betaine. The results of this study cannot, however, be directly applied to persons suffering from methionine deficiency, and tests on animals do not support this observation.

36. Foodstuffs to which betaine has been added will replace similar foodstuffs without betaine, but this is not considered to be nutritionally disadvantageous for user groups. The foodstuffs areequivalent, apart from betaine.

X. Information from previous human exposure to the NF or its source

37. The applicant presents data on the previous exposure to betaine, for instance, from plant products that are a natural element of our diet and from dietary supplements. There are no results from a systematic follow-up of the use of betaine available. These new foodstuffs containing betaine may lead to a markedly higher intake of betaine, and therefore the ingredient is subjected to a safety assessment in accordance with the Novel Food Regulation.

38. Betaine is a compound commonly found in plants and animals. It is accordingly also a natural element of our diet. Studies of literature reveal that an analysis of the betaine content is available for more than 50 foodstuffs. The application presents examples of them, such as prawns (0.25-0.96 g/100 grams), spinach (0.41-0.91 g/100 grams), edible mushrooms (0.32-0.69 g/100 grams), breakfast cereals (0.05-29 mg/100 grams), biscuits (5-34 mg/100grams) and wine (about 1 mg/100 ml). Annex 12 to the Application contains calculations on the intake of betaine from different natural sources and different diets. The intake varied between 1 g and 2.5 g per day.

39. Betaine hydrochloride is used also in dietary supplements. The doses vary between 7 and 324 mg/tablet. Most products have also been available via Internet within the EU (a list of them is presented in the application). It must however be observed that betaine hydrochloride differs from betaine as to its physical and chemical properties.

40. Betaine has been marketed as food supplement in the USA since the 1960's and the FDA has approved it for medical use in 1996 (orphan drug, dose 6-20 grams per day).

41. Betaine is also used as flavour enhancer and as preservative for prawns. As an ingredient in feeds, betaine has been used worldwide over 25 years.

42. Betaine has been used in clinical tests some of which have contained analysis of the impact of betaine on the homocystein content of serum.

43. No results of a systematic follow-up of the use of betaine after the products concerned have been introduced to the market are available.

XI. Nutritional information on the Novel Food

44. The use of foodstuffs with added betaine concerned by the application is not expected to have disadvantageous nutritional effects. The intended group of users comprises adults and old people.

45. Betaine is not available for traditional comparison. Betaine is not intended for use as such but as an ingredient in certain categories of foodstuffs that already are on the market.

46. Anhydrous betaine and betaine monohydrate are physiologically similar. Already with the relative humidity at 7%, anhydrous betaine turns into betaine monohydrate.

47. Betaine occurs in human blood and the concentration of betaine in blood is usually quite stable. It is found in urine and stored in renal medullar cells providing a source of osmotic protection.

48. Intake of betaine takes place either directly from foodstuffs containing betaine or indirectly via foodstuffs containing choline/derivates of choline as metabolic products of them.

49. Betaine comprises three methyl groups that participate in methylation. The application presents a description of the metabolic routes of betaine in man. Metabolization mainly takes place in the liver and kidney. It is further stated in the application that betaine is catabolized mainly *in vivo* and is eliminated to a very little extent in urine.

50. The application makes reference to many scientific publications (Annex 13 to the Application) where betaine has been studied in clinical trials. On the basis of these analyses it can be stated that betaine has been widely tested and is considered to be well tolerated at dosages up to 30 g. The literature reveals that only few cases of nausea, diarrhoea or gastro-intestinal troubles have been reported.

51. Tests have been conducted on adults running the risk of a heart attack, on healthy adults and on old people. Old people's tolerance to betaine has been equal to that of adults in general.

52. As to its nutritional effects, betaine mainly has a lowering effect on the serum homocystein concentration. A diet based on the recommendations on the intake of betaine does not involve any changes compared with a normal diet. The consumption volumes of sweets may, however, increase because the upper limit of the recommended daily intake of sweets containing betaine is planned to be set at 60 g per day.

XII. Microbiological information on the Novel Food

53. The applicant has presented a sufficient explanation of the source of betaine and the manufacturing process of the betaine ingredient. The production process or the sources of raw materials do not give any reason to expect problems with the microbiological quality.

XIII. Toxicological assessment of the Novel Food

54. **Results of safety evaluation studies provided by the applicant indicated that liver is the target organ of betaine toxicity. The observed effects were relatively mild and mainly reversible, but their clinical significance is difficult to assess only on the basis of animal experiments. Liver toxicity has not been reported in human trials. However, the applicant has provided only a very limited set of data on the safety and liver effects of betaine in patients. Therefore, the statistical power of the data is limited. Betaine did not show allergenic or hypersensitizing potential.**

55. The applicant has carried out a set of toxicity studies with betaine. In these studies the acute oral toxicity was low in rats. Betaine did not show eye irritating potential in rabbits, and it did not cause skin sensitization in guinea pigs. In the human patch test betaine was not a skin irritant. In addition, betaine was not proved to be genotoxic in the bacterial reverse mutation assays, the metaphase analysis of human lymphocytes *in vitro*, and the mouse micronucleus test *in vivo*.

56. Subchronic toxicity studies in rats revealed basically mild, but consistent and dose-dependent changes in liver. These changes included increased liver weight, increased serum levels of gamma-glutamyl transpeptidase (GGT) and alkaline phosphatase (AP), as well as increased incidence of hepatocellular microvacuolization. The vacuoles were shown to contain lipids. These changes were present already after a treatment period of 14 days, and they were more pronounced in female rats. A 28-day study with a 28-day recovery phase indicated that these changes were largely reversible. The liver changes were observed at all dose levels studied, and therefore it was not possible to set a NOAEL value. The lowest doses studied were equivalent to ca. 800 mg/kg/day corresponding to 56 g/day in a 70 kg human. Although the liver changes observed in toxicity studies were relatively mild and reversible, their relevance for the human use of betaine is difficult to assess. Therefore, for the assessment of human safety of betaine, a systematic and careful analysis of all human trials should be carried out. For this purpose placebo controlled double blind studies and studies that utilized high dose levels are most valuable.

57. Subchronic toxicity studies revealed also dose-dependent decreases in mean corpuscular volume and haemoglobin concentration, and increases in blood fibrinogen concentration.

58. Betaine has been on market as a dietary supplement in the USA since the 1960's. It has been used as a methyl donor for controlling serum homocysteine levels. The recommended dosage has been 0.5-1.5 g/day. Betaine has also been approved by the FDA in 1996 as an orphan drug for treatment of homocysteinuria. The dose levels have typically been 6 g/day, but doses as high as 20 g/day have also been recommended. However, the applicant has not referred to the safety evaluation studies used for registration, and no systematic post-marketing follow-up data on possible side effects is available.

59. For the safety of betaine the applicant has referred to 43 published clinical trials with over 700 subjects. Only a few of these studies were placebo controlled double blind studies. Most of the

subjects were patients with a variety of illnesses, and there are only a few reports on healthy subjects. The dose-range has been 2-30 g/day (typically 6 g/day), and treatment times range from 1 day to 16 years. Reported side effects include isolated cases of nausea, diarrhoea and gastrointestinal disorders, but there are no reports on adverse organ toxicity.

60. Safety issues have not been the main objective in most of the trials, and they have not necessarily been adequately monitored in all the trials. In addition, it is problematic to demonstrate possible mild liver toxicity of betaine for patients with pre-existing liver disease. In the material presented by the applicant effects of betaine on enzyme levels indicating liver damage have been monitored only in a few studies that included about thirty patients. Due to the low number of patients the statistical power of the data is limited. In addition, data on the safety of betaine in healthy subjects is limited for a reliable consumer safety assessment.