APPLICATION TO PERMIT THE USE OF DIMETHYL ETHER AS AN EXTRACTION SOLVENT

A EXECUTIVE SUMMARY

Fonterra Co-operative Group Ltd (Fonterra), an individual organisation, requests that dimethyl ether be included as a permitted extraction solvent under Clause 13 of Standard 1.3.3 (Processing Aids).

Dimethyl ether has the unique ability to be able to extract all lipid classes (e.g. triglycerides, cholesterol and polar lipids) from dairy ingredients to produce:

1. Reduced/low fat dairy ingredients;
2. Dairy lipid ingredients rich in polar lipids (e.g. phospholipids).

None of the permitted extraction solvents can effectively perform this total lipid extraction. Dimethyl ether also has other advantages over permitted extraction solvents such as diethyl ether and hexane:

- It is a gas at room temperature and pressure so can easily be removed from the product streams and recycled through the extraction process;
- It is inert so produces products that are free of chemical artefacts or toxic residues;
- It allows food to retain its natural physical properties such as flavour, bioavailability and solubility.

Dimethyl ether does not pose a risk to safety as an extraction solvent for the production of dairy ingredients and should therefore be allowed in Standard 1.3.3 Processing Aids Clause 13 Permitted Extraction Solvents. Toxicity studies have shown dimethyl ether to be less toxic than the permitted extraction solvents diethyl ether and dibutyl ether. We therefore propose that the 2mg/kg limit applied to diethyl ether and dibutyl ether in the final food is also applied to dimethyl ether. In 2007 the EC requested that EFSA perform a scientific risk assessment on dimethyl ether as an extraction solvent for defatting meat proteins (Request number EFSA-Q-2007-186). EFSA's scientific panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) concluded that the use of dimethyl ether as an extraction solvent for defatting meat proteins is of no safety concern under the intended conditions of use (The EFSA Journal (2009) 984, 1-13). Consequently, Annex I to Directive 2009/32/EU has been amended to include dimethyl ether for the preparation of defatted animal protein products, with a maximum residue limit of 0.009 mg/kg (Commission Directive 2010/59/EU of 26 August 2010).

CEF acknowledged that in most cases inhalation exposure toxicity data cannot be directly extrapolated to an oral exposure situation. However, in this particular case, CEF considered that results from inhalation studies could be used to assess dimethyl ether oral toxicity because animal models show that dimethyl ether distribution in the body following inhalation exposure is similar to that following oral exposure. Substantial research into the health effects

of inhalation exposure to dimethyl ether has been carried out, and shows that dimethyl ether has no deleterious effects even at substantially high exposure levels in excess of 1000 ppm in air for prolonged periods of time. CEF estimated that the daily internal exposure to dimethyl ether arising from the lowest no-effect level identified in the embryo-foetal inhalation toxicity study was approximately 630 mg/kg of bodyweight per day. We calculate that in a worst case scenario of a 2.4 kg infant[1] consuming 1000 ml/day of infant formula containing 0.7% of dimethyl ether-processed dairy ingredient on a powder basis[2] the level of exposure to dimethyl ether (0.014 mg/infant/day) would be about 10^5 times lower than the lowest no-effect levels identified from the embryo-foetal inhalation toxicity study.

[1] 1 month-old girl 3 standard deviations below the median weight for her age (WHO Child Growth Standards)

[2] Based on a maximum recommended infant formula volume of 1000 ml/day for 1-4 month infants, addition of 141.67 grams of S-26 Newborn Formula (Pfizer Inc, leading Australasian brand) per 1000 ml of water, 50g of DME-processed dairy ingredient per kg of S-26 Newborn Formula powder (5% addition rate) and a residual DME level in the DME-processed dairy ingredient of 2 ppm.

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C GENERAL INFORMATION

1 Applicant Details

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2 Purpose of the application

The purpose of the application is to vary Standard 1.3.3 of the Australia New Zealand Food Standards Code on Processing Aids by including dimethyl ether as an approved extraction solvent (Clause 13 Permitted Extraction Solvents). We seek approval to use dimethyl ether as an extraction solvent for dairy ingredient manufacture. We propose a maximum permitted residue level of 2 mg/kg in the dairy ingredients, which corresponds with the maximum permitted residue levels of diethyl ether and dibutyl ether.

3 Justification for the application

3.1 Need and/or advantages for the proposed change

Dimethyl ether is the only solvent we have found that can effectively and efficiently extract both polar and non-polar lipid components from dairy materials without denaturing the milk proteins. None of the permitted extraction solvents listed under Clause 13 (Permitted Extraction Solvents) of Standard 1.3.3 (Processing Aids) can effectively perform this total lipid

extraction. Furthermore, no physical separation technologies (including membrane filtration, centrifugation, precipitation and combinations thereof) have been found that can effectively separate dairy polar lipids such as phospholipids from milk proteins.

Dimethyl ether also has a number of other benefits over the permitted extraction solvents listed under Clause 13 of Standard 1.3.3:

- It is a gas at room temperature and pressure so can easily be:
    - Removed from the product streams to produce virtually residue-free lipid extracts and lipid-depleted protein ingredients;
    - Recovered from the product streams and reused, thereby minimising solvent usage and solvent waste;
- It is inert so produces products that are free of toxic residues and chemical artefacts;
- It does not damage any of the components in powdered food materials under the mild extraction conditions used, thereby producing products that retain most, if not all, of their natural physical properties such as solubility, flavour and bioactivity;
- It can extract lipids from aqueous food materials.

3.2 Public health and/or safety issues related to the proposed change

EFSA's scientific panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids recently concluded that the use of dimethyl ether as an extraction solvent for defatting meat proteins is of no safety concern under the intended conditions of use[1]. Annex I to Directive 2009/32/EU has therefore been amended to include dimethyl ether for the preparation of defatted animal protein products, with a maximum residue limit of 0.009 mg/kg (Commission Directive 2010/59/EU of 26 August 2010)

Given that dimethyl ether distribution in the body following inhalation exposure is similar to that following oral exposure, it is worthy to note that dimethyl ether has been used for decades in the personal care industry as a benign aerosol propellant (e.g. in hair sprays), and that it is now increasingly being exploited for use as a clean burning alternative to LPG (liquefied petroleum gas), diesel and gasoline. In China, dimethyl ether is also blended with LPG (in a proportion of up to 20% by volume) and used for domestic cooking and heating.

More information on the safety of dimethyl ether is contained in section E of this document.

3.3 Nutrition issues relating to the proposed change

Because DME is not metabolised, there are no nutrition issues relating to the use of dimethyl ether as an extraction solvent for the manufacture of dairy ingredients.

3.4 Technological function and need for the processing aid

As highlighted in section 3.1 above, dimethyl ether has the unique ability to extract a broad range of lipid compounds from dairy materials, including valuable polar lipids such as phospholipids and glycolipids, while retaining the natural physical properties of the defatted dairy material, such as its solubility, flavour and bioactivity. No approved solvents or solvent mixtures, such as ethanol, diethyl ether, hexane and acetone, can perform this technological function.

Dimethyl ether also has the unique ability to extract both polar and non-polar lipids from aqueous dairy materials. Dimethyl ether extraction of aqueous dairy materials denatures the globular whey proteins, which in the case of whey protein concentrates can be desirable for specific applications such as nutrition bars or the production of (hypoallergenic) whey protein hydrolysates.

In addition dimethyl ether is:

- Easily removed from the products to produce virtually residue-free lipid extracts and defatted protein ingredients;
- Easily recovered from the product streams and reused, thereby minimising solvent usage and solvent waste;
- Inert so produces products that are free of toxic residues and chemical artefacts.

3.5 Potential impact on trade

The acceptance of dimethyl ether will result in an expanded range of premium dairy ingredients that will provide substantial earning potential.

3.6 Consumer choice issues related to the proposed change

Consumer choice will not be affected by the use of dimethyl ether as an extraction solvent for the manufacture of dairy ingredients.

3.7 Food industry support and interest

The approval of DME as an extraction solvent for the production of dairy ingredients will provide alternative options for manufacturing these types of products, and there is generic support from the food industry for the approval of DME as a food extraction solvent. Nutrizeal Ltd, Nelson, the main toll processor of ingredients produced using supercritical extraction in New Zealand, also supports the approval of this processing aid.

3.8 Costs and benefits for industry, consumers, and government associated with the proposed change

Industry benefits of dimethyl ether as a dairy ingredient processing aid

The use of dimethyl ether as a dairy processing aid enables:

- Removal of lipids (including triglycerides, cholesterol and polar lipids) from dairy materials, thereby enhancing the nutritional value and/or stability of the defatted dairy ingredients;
- Production of bioactive dairy lipid ("dairy lecithin") ingredients, which can be further concentrated or processed as required to deliver specific health benefits in a range of different food products.

Depending on the processing conditions used, dimethyl ether is able to either substantially reduce, or completely remove, lipids from dairy materials, resulting in dairy ingredients that have very low saturated fat contents. Furthermore, many dairy lipids are unstable in the presence of water, oxygen, light, heat and heavy metals, causing them to undergo a number of deteriorative reactions such as oxidation, Maillard browning and lipolysis, all of which have a detrimental effect on the flavour, appearance and nutritional value of dairy products. The ability to remove fat from high fat dairy materials, such as high fat whey protein concentrates, will enable the defatted dairy ingredients to be used in low fat and aqueous dairy products, such as cultured foods and beverages (e.g. yoghurt and fermented beverages).

Dairy lipid ingredient manufacture

Commercial vegetable oil-derived "unrefined lecithin" or "natural lecithin" contains 65 - 70% phospholipids and 30 - 35% crude oil, and is currently isolated as a gum through hydration of hexane-extracted soy, safflower, or corn oils. The gum is then (optionally) bleached using hydrogen peroxide and benzoyl peroxide and dried to reduce the moisture content to about 1%. The oil in unrefined lecithin can subsequently be removed by extraction with acetone (phospholipids are insoluble in acetone) to give a dry granular product called "refined lecithin". In contrast to current commercial lecithin products, dimethyl ether can be used to produce dairy lecithin products that are free from toxic residues and chemical artefacts (such as mesityl oxides in the case of acetone). Furthermore, refined dairy lecithin ingredients can be produced by extracting the neutral lipid (e.g. triglycerides and cholesterol) from dimethyl ether lipid extracts with supercritical CO_2 (rather than acetone), producing refined dairy lecithin products that are free from toxic residues and chemical artefacts. Approval of dimethyl ether as a dairy ingredient processing aid would therefore enable dairy ingredient manufacturers to produce natural, identity preserved dairy lecithin ingredients that can be used in a range of food and beverage products.

Dairy lecithin ingredients contain polar lipids, such as sphingomyelin, phosphatidylserine, cerebrosides and gangliosides, that are either unique to mammalian milk, or that are present in much higher levels than in soy- or egg-derived products. These polar lipids are important for human health, and it is envisaged that dimethyl ether extraction will enable the health benefits of these components to be delivered in a range of food and beverage formats that

would not be possible with less concentrated sources of these components (such as buttermilk powder or whey protein concentrate).

Defatted dairy protein ingredient manufacture

Dimethyl ether extraction of low moisture dairy materials does not affect the protein solubility of the defatted dairy ingredient or the integrity of the polar lipids in either the defatted dairy ingredient or the dairy lipid ingredient. Approval of dimethyl ether as a food processing aid would also enable dairy ingredient manufacturers to extract lipids from aqueous dairy streams such as whey protein concentrates to produce functional, low fat whey protein concentrates and dairy lecithin ingredients.

Consumer benefits of dimethyl ether as a dairy ingredient processing aid

Dimethyl ether as an extraction solvent is able to remove fat from dairy materials to produce low fat dairy ingredients. Low fat dairy ingredients are more stable than their full fat counterparts because milk fat will oxidise and become rancid unless stored under very low oxygen environments. Dimethyl ether has advantages over other solvents, such as diethyl ether and hexane, since it is a gas at room temperature and pressure and therefore volatilises off more readily from both the defatted dairy ingredients and the dairy lipid ingredients, leaving very low/undetectable levels in the final products. Defatted and functional lipid ingredients produced using dimethyl ether will be of superior quality to existing products because they will:

- Have superior compositions (based on dimethyl ether's ability to substantially remove all of the lipids from dairy materials);
- Be free of toxic residues and chemical artefacts;
- Retain most, if not all, of their natural physical properties, such as flavour, bioactivity and solubility;
- Not have been exposed to high temperatures during processing, which may give rise to thermal degradation products as well as affecting the natural physical properties of the ingredients.

Low fat products will also provide consumers a healthy alternative to higher fat products.

Government benefits of dimethyl ether as a food processing aid

The use of dimethyl ether is beneficial because it:

- Can be easily recovered and recycled, which reduces solvent usage (and therefore the amount of solvent waste);
- Replaces less environmentally friendly solvents such as hexane and ethanol.

4 Information to Support the Application

This application contains sufficient supporting information as detailed in Section D, to enable the objectives specified in section 18 of the FSANZ Act to be addressed. References are provided for all information that has been sourced externally to Fonterra Co-operative Group Limited.

5 Assessment procedure

This application is for a processing aid not currently approved and therefore should be assessed as a general level procedure up to 1000 hours.

6 Confidential Commercial Information (CCI)

This application does not contain any confidential commercial information.

7 Exclusive Capturable Commercial Benefit (ECCB)

This application does not confer an Exclusive Capturable Commercial Benefit to Fonterra Co-operative Group Limited. The application covers the extraction of any dairy material with dimethyl ether to produce a defatted dairy ingredient and a dairy lipid ingredient, and Fonterra Co-operative Group Limited has only patented the dimethyl ether extraction of some of these dairy materials, such as high fat whey protein concentrates, high fat buttermilk powders and beta serum streams. The relevant PCT applications that have been filed by Fonterra Co-operative Group are:

- WO 2004066744 (A1), Extraction of compounds from dairy products
- WO 2006041316 (A1), Beta-serum dairy products, neutral lipid-depleted and/or polar lipid-enriched dairy products, and processes for their production

Because of the limited patented applications, and the vast opportunity for other manufacturers to take advantage of DME approval, this application does not confer an ECCB.

8 International and other national standards

8.1 International Standards

We have no knowledge of any entry in the CODEX Alimentarius Commission Standards, nor has it been evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

8.2 Other National Standards or Regulations

Annex I to Directive 2009/32/EU has recently been amended to include dimethyl ether for the preparation of defatted animal protein products, with a maximum residue limit of 0.009 mg/kg (Commission Directive 2010/59/EU of 26 August 2010).

D TECHNICAL INFORMATION

1 Processing Aid type

Dimethyl ether (DME) falls under Standard 1.3.3 processing aid category (k) Extraction solvents.

Dimethyl ether is a powerful polar solvent when pressurised and heated close to its critical point. Supercritical and near-critical fluids (like dimethyl ether) are very powerful solvents because they have:

- The solute-carrying power of liquids (their density being similar to liquids);
- Similar mass-transfer rates to gases (their viscosity being similar to gases and their diffusivity being intermediate between that of the gas and liquid);

An example of a process used for extracting low moisture food materials with dimethyl ether is as follows:

1. The low moisture food material is loaded into stainless steel extraction baskets;
2. Liquid dimethyl ether is pressurised to 40 bar, heated to 40-50°C and then pumped through the extraction vessels containing the low moisture food material;
3. The dimethyl ether phase containing the dissolved polar and non-polar lipids enters one or more separation vessels;
4. The pressure in the separation vessels is lowered to a point where the lipids are no longer soluble in dimethyl ether. The lipid extract is then recovered from the bottom of the separator vessels and the dimethyl ether is recovered, repressurised, and recycled through the extraction vessels;
5. At the end of the extraction process, the extraction vessels are depressurised, the dimethyl ether is recovered for subsequent reuse, and the lipid-depleted food material is recovered from the extraction baskets.

2 Identity of the processing aid

Chemical name: Methoxymethane (IUPAC, CA)

Other names: Dimethyl Ether (DME)

Methyl Ether

Oxybismethane

Dimethyl Oxide

	Methyl oxide
	Wood Ether
Marketing names:	Demeon® D (AkzoNobel Industrial Chemicals B.V)
	Dymel® A (DuPont)
	Propel (Aerosol Supplies Australia)
CAS registry number:	115-10-6
Molecular formula:	C_2H_6O
Structural formula:	CH_3-O-CH_3
Molecular weight:	46.069 g/mol

3 Chemical and physical properties of the processing aid

Dimethyl ether is the simplest ether and is manufactured commercially from natural gas-derived methanol. It is a colourless gas at ambient temperature and pressure but is readily liquefied for ease of transport. It is also highly flammable, but has proven to be extremely safe when handled properly.

Boiling point: -24.8°C at 1 atmosphere [2-6]

Colour: Dimethyl ether is a colourless gas at room temperature and is easily compressed to a colourless liquid.[6-7]

Density of liquid: 0.66 g/cm^3 when liquefied at 25°C[4, 8].

Density of gas: 1.91855 g/cm^3 at 1 atmosphere and 25°C [5, 7]

Freezing (melting point):-141.5°C @ 1 atmosphere [2, 3, 5, 6, 7]

Octanol/Water partition coefficient: (Octanol-water) (log KOW): 0.10 [2, 7, 9, 10]

Odour: Dimethyl ether has a characteristic sweet ethereal odour (detectable at 0.33 ppm) [4, 6]

Oxidation stability (in air):[2, 4, 7] Autoignition temperature in air = 350°C.

Flash point = -41°C

Flammability limits in air, % by volume

LEL = 3.4

UEL = 18.0

Photolysis

The rate constant for the vapour-phase reaction of dimethyl ether with photochemically-produced hydroxyl radicals was 2.98 x 10^{-12} cm^3 $molecule^{-1}$ s^{-1} at 25°C [10]. This rate constant corresponds to an atmospheric half-life of about 5.4 days at an atmospheric concentration of 5 x 10^5 hydroxyl radicals per cm^3 [26]. Direct photolysis is not expected to be an important removal process since aliphatic ethers do not absorb light in the environmental spectrum[26]. The rate constant for the reaction of dimethyl ether with hydroxyl radicals in aqueous solution is 1.0 x 10^9 L/mol sec [26]. This rate constant corresponds to a half-life of about 2.2 years at an average aqueous hydroxyl radical concentration of 1 x 10^{-17} mol/L [11, 26]. The rate constant for the reaction of dimethyl ether with nitrate radicals is 2.6 x 10^{-16} cm^3/molecule-sec at 22°C [26]. This corresponds to an atmospheric concentration of 5 x 10^8 nitrate radicals/cm^3 [12, 13, 26].

Reliability: Estimated value based on accepted model.

Refractive index (liquid): 1.302 [26].

Solubility in organic solvents

Soluble in methanol, ethanol, isopropanol, diethyl ether, chloroform, acetone, chlorinated hydrocarbons and toluene [3].

3700cm^3 of dimethyl ether dissolves 100g of ethanol at 18°C.

Solubility in water

7% by weight at 18°C and 1 atmosphere[2, 4]

Thermal stability

Thermally stable under inert gas atmosphere, even under high temperatures of 400°C. Does not form measurable levels of peroxides under storage temperatures up to 353K[16]. Stable in neutral and dilute acidic and alkaline solutions.

Stability in water

The Henry's Law constant for dimethyl ether is estimated as 7.6 x 10^{-3} atm-m^3/mole from its vapour pressure, 4,450 mm Hg, and water solubility, 3.5 x 10^4 mg/L[26]. This Henry's Law constant indicates that dimethyl ether is expected to volatilise rapidly from water surfaces[26]. Based on this Henry's Law constant, the estimated volatilisation half-life from a model river (1m deep, flowing 1 m/sec, wind velocity of 3 m/sec) is approximately 2.1 hours[26]. The estimated volatilisation half-life from a model lake (1m deep, flowing 0.05 m/sec, wind velocity of 0.5 m/sec) is approximately 2.7 days[26].

Reliability: Estimated value based on accepted model.

Vapour pressure

4450 mm Hg (593 kPa) @ 25°C [2, 4, 15, 17, 18].

Bio-concentration

BCF 0.70 [26]

Method: The estimated value was calculated using a log KOW of 0.10 [9] and a regression-derived equation[26]. According to a classification scheme[18], this BCF suggests the potential for bioconcentration in aquatic organisms is low[9, 26].

Reliability: Estimated value based on accepted model.

Biodegradation

In an aerobic test, 2 mg/L of dimethyl ether was 5% degraded after 28 days. Methane-utilising microorganisms, abundantly present in nature, play a significant role in the removal of dimethyl ether from aquatic ecosystems and soils.

Method: Directive Test was under GLP working conditions, not yet certified[19-24].

Interaction in foods and metabolic fate

Dimethyl ether is stable and will not undergo degradation or form reaction products with any type of food[1] (excerpt taken from section 2.5 of The EFSA Journal (2009) 984, 1-3). See also section 3.1 of The EFSA Journal (2009) 984, 1-3, which covers the bioavailability, metabolic fate and biological distribution of DME.

4 Manufacturing process

Dimethyl ether is produced through the catalytic dehydration of methanol under high temperature and pressure conditions. The process is shown chemically as follows:

$$2CH_3OH \xrightarrow{\text{Catalyst}} CH_3OCH_3 + H_2O$$

In the commercial production of aerosol-grade dimethyl ether, satisfactory yields of high quality product are obtained by close attention to reactor design, catalyst selection and highly selective distillation design characteristics.

The manufacturing process can be summarised as follows:

1. Pure high-grade methanol is drawn from a bulk storage tank, passed through a heat recovery unit, and then vaporised in a pre-heater.
2. The methanol vapour under pressure and at elevated temperature is passed through a bed of catalyst in a specially designed reactor vessel.
3. The reaction products then go to a dimethyl ether distillation column via a heat recovery unit.

4. Methanol and water from the dimethyl ether distillation column pass to a methanol recovery distillation column. Here methanol and water are separated and the recovered methanol recycled to the reactor. The separated water is discarded.
5. Dimethyl ether product from the dimethyl ether distillation column passes through a condenser for storage and final product analysis.

Although the plant is designed to handle "off gas" and impurities, especially during start-up and shutdown operations, in practice it performs so well under normal production conditions that there are virtually no "off gas" or impurities produced.

5 Specification for identity and purity

Dimethyl ether is not covered in any of the relevant monographs listed in Standard 1.3.4. The proposed specification for identity and purity is a follows.

Appearance:	Clear, colourless liquefied gas
Odour:	Slight ethereal odour
DME Purity:	99.8% min
Methanol:	200 ppm max
Water:	500 ppm max
Air (O_2, N_2, CO_2)	100 ppm max
Total Residue	50 ppm max

5.1 Analytical method for measuring residual processing aid levels

Dimethyl ether is analysed by gas chromatography using flame ionisation or mass spectroscopy detection. Sample introduction is made by gas-tight syringes and a standard split port, or by head-space injection. The typical configuration and conditions of analysis developed and used by the Applicants are listed below:

Column:	BP-1 quartz capillary column (60m x 0.32mm, 0.25µ film, SGE, Australia)
Carrier solvent:	n-Butanol
Internal standard (IS):	Diethyl ether (and, optionally, n-propanol for ethanol)
Temperature:	Start at 40℃, increase by 2℃ per min to 50℃, then by 30℃ per minute to 100℃ and hold at 100℃ for 2.5 min.
Injector temperature:	200℃
Injection:	1 µL of solvent containing the IS and 50 mg/ml of test sample

Spilt ratio: 1:20

Column flow: Constant at 2.5 ml/min

Detector: Flame Ionisation Detector (FID), base temperature 200℃

Under these conditions retention times are as follows: dimethyl ether 3.40 min, ethanol 3.62 min, diethyl ether 3.86 min, n-propanol 4.21 min.

Procedure:

1. Add 1.8 ml of n-butanol (containing 100 ppm diethyl ether and 100 ppm n-propanol) to approximately 100 mg of the sample in a 2ml vial with a Teflon-lined cap;
2. Shake the mixture briefly and place in an ultrasonic bath for 5 min;
3. Precipitate out the insoluble material by centrifugation (Heraeus Megafuge 1.0, 4500 rpm for 5 min);
4. Perform the analysis under the conditions listed above.

Under such conditions, 1 ppm of dimethyl ether (and 1 ppm ethanol) in the butanol extract are reliably detected. A software subtraction of the baseline irregularities in the sample chromatograms (caused by impurities in the synthesis grade n-butanol used (99.9% purity, Merck)) improves the sensitivity to about 0.2-0.3 ppm of each analyte (figure 1). The estimated limit for quantitative dimethyl ether measurement of the sample (~19-fold diluted in the n-butanol) is therefore 5 ppm, with a detection limit of around 2 ppm.

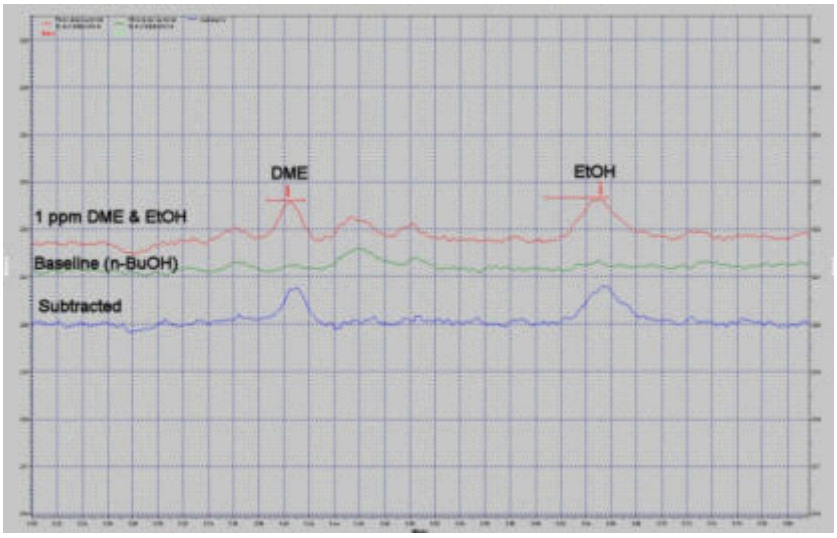

Figure 1. Gas chromatography calibration for dimethyl ether and ethanol with baseline correction

Under the conditions used, the peaks in the chromatograms are well separated and do not overlap with impurities in the n-butanol used, and the internal standards have the same peak shapes as their corresponding analytes.

The extraction effectiveness/overall analyte recovery from solid samples was tested by spiking dairy powder samples with known quantities of dimethyl ether. At least 90% of added dimethyl ether was recovered. The relative errors were estimated as better than ±10% for dimethyl ether.

Calibration curves were determined for both dimethyl ether and ethanol within the range of 1-600 ppm. The detector response was linear for both analytes from 1-200 ppm.

E SAFETY INFORMATION

Safety assessments have been based on high purity dimethyl ether and are therefore commercially representative of the dimethyl ether for which approval is sought.

1 General information on the industrial use of the chemical

Dimethyl ether has been used for decades in the personal care industry as a benign aerosol propellant, and is increasingly being exploited for use as a clean burning alternative to LPG (liquefied petroleum gas), diesel and gasoline. Dimethyl ether can be blended with LPG (in a proportion of up to 20%) and used for domestic cooking and heating, and China has recently issued the "DME Specification as Residential Gas in China" (Effective January 1st 2008).

Current uses of dimethyl ether are described in the document "INITIAL HUMAN HEALTH AND ENVIRONMENTAL SCREENING ASSESSMENT FOR DIMETHYL ETHER (DME) TECHNICAL SUMMARY", prepared by DuPont Company, August 29, 2001[25]. This document is supplied separately with the application.

2 General information on the use of the chemical as a food processing aid in other countries

Annex I to Directive 2009/32/EU has recently been amended to include dimethyl ether for the preparation of defatted animal protein products, with a maximum residue limit of 0.009 mg/kg (Commission Directive 2010/59/EU of 26 August 2010).

3 Data on the toxicogenetics and metabolism of the processing aid

Dimethyl ether is not metabolised and disperses naturally from the body. Rat studies have shown that elevated dimethyl ether levels in tissue and organs, recorded after high inhalation exposure to dimethyl ether, returned to background levels within 90 minutes largely by respiratory action[1].

4 Information on the toxicity of the processing aid

Extensive studies on the toxicity of dimethyl ether have been summarised in a report prepared by DuPont (Robust Summary for Dimethyl Ether, 11 October 2000, DuPont SHE Excellence Center) and published by the United States Environmental Protection Agency[26].

Further detail is contained in the report "Initial Human Health and Environmental Screening Assessment Assessment for Dimethyl Ether (DME)", prepared by DuPont Company, August 29, 2001[25]. These documents are included with this submission for reference.

Dimethyl ether has very low toxicity. Table 1 compares some inhalation toxicity measures for dimethyl ether with those of the approved food processing aids (permitted extraction solvents) diethyl ether and dibutyl ether.

Table 1 Comparison of dimethyl ether toxicity with that of diethyl ether and dibutyl ether[25-28]

Toxicity model	Dimethyl ether	Diethyl ether	Dibutyl ether
Inhalation LC50/mouse (15 minutes)	494 000 ppm		40 000 ppm
Inhalation LC50/mouse (30 minutes)	386 000 ppm	31 000 ppm	
Inhalation LC 50/rat (4 hours)	164 000 ppm		4 000 ppm
DFG MAK	1000 ppm	400 ppm	

In beagle dogs, dimethyl ether has been shown to produce cardiac sensitisation following inhalation of 200,000 ppm (20%) dimethyl ether, but not at 10% dimethyl ether. In a lifetime inhalation study in rats, dimethyl ether produced slight haemolytic effects at 25,000 ppm (2.5%) and was negative for carcinogenicity. The no-observable-adverse-effect-level (NOAEL) for this lifetime study was 2,000 ppm (0.2%) and was based on an increase in body weight and a decrease in survival in male rats exposed to 10,000 and 25,000 ppm, and on the blood effects seen at the 25,000 ppm exposure level. In developmental studies, pregnant rats exposed by inhalation to atmospheres containing 2% dimethyl ether (20,000 ppm) over gestation days 6 - 15 exhibited mild anaesthetic effects. The foetal NOAEL was 0.125% dimethyl ether (1,250 ppm) based on an increased incidence of skeletal variations at the 0.5% dimethyl ether dose level. However, dimethyl ether was not teratogenic at concentrations of up to 2% (20,000 ppm). Following exposure to dimethyl ether in air for 2 years, no reproductive toxicity was noted at dose levels up to 2.5% (25,000 ppm). Dimethyl ether is non-mutagenic and non-clastogenic when tested *in vitro* and was negative in the *in vivo* sex-linked recessive lethal assay with *Drosphila melanogaster.*

In humans, current exposure to dimethyl ether occurs principally by the inhalation route. Under controlled laboratory exposures of up to 100,000 ppm (10% dimethyl ether), mild yet reversible central nervous system effects were noted. Human exposure to atmospheres containing greater than 144,000 ppm (14.4%) resulted in unconsciousness after approximately 26 minutes. The current exposure standards for both the American Industrial

Hygiene Association (AIHA) 8 hours TWA and the German MAK, which are based on the NOAEL in rats following lifetime exposure to 2,000 ppm (0.2%) dimethyl ether, has been set at 1,000 ppm (or 0.1%) dimethyl ether for an 8 hours daily lifetime exposure. The studies listed below were selected to represent the best available study design and execution for toxicity endpoints.

Recommended Exposure Limits:

- DuPont Acceptable Exposure Limit (AEL): 1000 ppm, 8 hours and 12 hours TWA
- AIHA WEEL: 1,000 ppm (1880 mg / m^3), 8 hours TWA
- MAC (NL): 1,000 mL/m^3 Limit value; TWA = 1,000 ppm or 1,910 mg/m^3
- MAC(DE): 1,000 mL/m^3 Limit value; Short term limit value = 2,000 mL/m^3 for 60 minutes, three times/shift skin notation

The majority of studies on dimethyl ether toxicity are related to inhalation exposure. Studies have shown that atmospheric exposure of 1000ppm results in accumulation of dimethyl ether at levels up to 22mg/kg in different organs and tissues in rats[1]. The distribution of dimethyl ether in the organs and tissue is similar to that expected to result from oral exposure, so that results from inhalation studies may be extrapolated to assessments of oral toxicity[1]. Studies have shown that elevated levels of dimethyl ether in organs and tissue reverts to background levels within 90 minutes of removing the dimethyl ether exposure, largely by respiratory processes[1].

DuPont calculates that their acceptable 8 hour exposure limit (AEL) of 1000 ppm amounts to an exposure of 664 mg per kg of body weight per day[25]. In comparison to this, consumption of 1kg of food product containing less than 2 ppm dimethyl ether would amount to exposure of less than 2 mg of dimethyl ether, or less than 0.04 mg per kg body weight for a 50 kg person. This is 10^5 times lower than recommended AEL's by DuPont and AIHA WEEL.

Dimethyl ether is not expected to accumulate in the environment. If released into rivers or lakes, dimethyl ether is expected to volatilise with estimated half-lives of 2.1 hours and 2.7 days respectively[26]. Dimethyl ether exhibits low toxicity to fish and aquatic invertebrates with a low bio-concentration potential in aquatic organisms.

5 Safety assessment reports prepared by international agencies or other national government agencies

The EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing aids (CEF) has published a recommendation on the use of dimethyl ether as an extraction solvent[1]. This document is attached to the application.

F INFORMATION RELATED TO DIETARY EXPOSURE

1 Foods or food groups likely to contain the processing aid

Dairy ingredients processed with dimethyl ether will contain less than 2 ppm of dimethyl ether. In the majority of cases, the levels of dimethyl ether (DME) in foods containing dimethyl ether-processed dairy ingredients will be negligible (<<2 ppm) because food manufacturing processes such as pasteurisation, evaporation and drying will volatilise all, or almost all, of the residual DME present in the dairy ingredient.

Foods that may contain dairy ingredients processed with dimethyl ether are

- Liquid milk and liquid milk based drinks (toddler milks only)
- Fermented and rennetted milk products
- Dried milk, milk powder, cream powder (toddler milk powders only)
- Cheese and cheese products
- Ice cream and edible ices
- Chocolate and cocoa products
- Infant formula products
- Foods for infants
- Formula meal replacements and formulated supplementary foods

2 Level of residues in each food group

2.1 Proposed processing aid residue levels

Dimethyl ether-processed dairy ingredients will contain less than 2 ppm dimethyl ether (i.e. less than the detection limit of the method described in section D5.1). This is because the ingredients will be gas flushed prior to packing which will remove the DME.

2.1.1 Measured residue levels

Table 2 shows the residual dimethyl ether levels (ppm) in the defatted protein powder and lipid extract produced by extracting a buttermilk powder with dimethyl ether (refer section D5.1 for the analytical method).

Table 2 Residual dimethyl ether levels (ppm) after dimethyl ether extraction, and removal of dimethyl ether by various methods. ND = Not detected (<2 ppm). A range of values indicates the range of multiple experiments.

Processing method to remove dimethyl ether	Defatted protein powder (ppm)	Lipid extract (ppm)
None (levels in product immediately after processing, before evaporation of the solvent)	11,000-13,000	300
Standing at room temperature for 16h	42-50	ND
Standing at room temperature for 24h	ND	ND
Standing at room temperature for 48h	ND	ND
Standing at 45℃ for 16h	ND	ND
Circulation of CO_2 gas through extraction bed, 35 bar, 40℃, 10 min	ND	
Fluidisation with compressed air, atmospheric pressure and temperature, 30 min	ND	

Table 2 shows that:

- Dimethyl ether naturally dissipates from defatted protein powders and lipid extracts over time to undetectable levels (<2ppm), so it is not strongly bound to the products;
- Powder fluidisation for ≤ 30 min, either with CO_2 gas in the extraction plant or with compressed air after removing the powder from the extraction vessels, is sufficient to reduce residual dimethyl ether to undetectable levels (<2ppm).

Similarly, dimethyl ether extraction of an aqueous dairy material followed by recovery of the lipid extract and spray drying of the defatted protein stream resulted in undetectable (<2 ppm) levels of dimethyl ether in both the defatted dairy ingredient and the dairy lipid ingredient.

2.1.2 Analytical method for dimethyl ether by-products

Dimethyl ether is inert, and so there will be no by-products to analyse.

3 The percentage of the food group in which the processing aid is likely to be found or the percentage of the market likely to use the processing aid

DME-processed dairy ingredients will primarily be used in foods intended for particular dietary use, such as infant formula, follow-on formula and toddler milk powders. These foods are subjected to high heat pasteurisation during manufacture, which would drive off all, or virtually all, of the residual DME in the DME-processed dairy ingredient. We calculate that in a worst case scenario of a 2.4 kg infant[3] consuming 1000 ml/day of infant formula containing 0.7% of dimethyl ether-processed dairy ingredient[4] the level of exposure (0.014 mg/infant/day) would be about 10^5 times lower than the lowest no-effect levels identified from the embryo-foetal inhalation toxicity study.

Defatted DME-processed dairy ingredients will also be used in dairy products and nutritional products such as nutrition bars, which are also subjected to pasteurisation steps. Table 3 gives estimated percentages of each food group that will contain dimethyl ether- processed dairy ingredients.

Table 3 Maximum percentage of each food group likely to contain a DME-processed dairy ingredient and the expected levels of DME-processed ingredients in these food groups.

Food group	**Max percentage likely to contain DME-processed ingredient (wt %)**	**Expected level of DME-processed ingredient in food product (wt %)**
Dairy Products		
Liquid milk and liquid milk based drinks (toddler milk products only, 1+ years)	5 (5% of toddler milks, 0% of other liquid milk products)	0.5-5.0
Fermented and rennetted milk products	1	0.5-5.0
Dried milk, milk powder, cream powder (toddler milk products only, 1+ years)	5 (5% of toddler milks, 0% of other milk or cream powders)	0.5-5.0

[3] 1 month-old girl 3 standard deviations below the median weight for her age (WHO Child Growth Standards)

[4] Based on a maximum recommended infant formula volume of 1000 ml/day for 1-4 month infants, addition of 141.67 grams of S-26 Newborn Formula (Pfizer Inc, leading Australasian brand) per 1000 ml of water, 50g of DME-processed dairy ingredient per kg of S-26 Newborn Formula powder (5% addition rate) and a residual DME level in the DME-processed dairy ingredient of 2 ppm.

Cheese and cheese products	1	0.5-5.0
Ice-cream and edible ices	1	0.5-5.0
Confectionery		
Chocolate and cocoa products	0.5	1-3
Nutrition bars	1	1-10
Foods intended for particular dietary uses		
Infant formula products	10	0.5-5.0
Foods for infants	5	0.5-5.0
Formula meal replacements and formulated supplementary foods	1	0.5-5.0

4 Levels of processing aid residues in foods in other countries

Annex I to Directive 2009/32/EU has recently been amended to include dimethyl ether for the preparation of defatted animal protein products, with a maximum residue limit of 0.009 mg/kg (Commission Directive 2010/59/EU of 26 August 2010).

G CHECKLIST

General Requirements (3.1)

☑ Form of application *☑Executive Summary* *☑Relevant sections of part 3 identified* *☑Pages sequentially numbered* *☑Hard copies capable of being laid flat* *☑Electronic and hard copies identical*	☑ Assessment procedure
☑ Applicant details	☑ Confidential Commercial Information *☐ Confidential material separated in both electronic and hard copy* *NO CONFIDENTIAL INFORMATION*
☑ Purpose of the application	☑ Exclusive Capturable Commercial Benefit
☑ Justification for the application	☑ International standards
☑ Information to support the application	☑ Statutory Declaration

Processing Aids (3.3.2)

☑ Type of processing aid	☑ Toxicokinetics and metabolism information (chemical only)
☑ Identification information	☑ Toxicity information (chemical only)
☑ Chemical and physical properties	☑ Safety assessments from international agencies (chemical only)
☑ Manufacturing process	☑ List of foods likely to contain the processing aid
☑ Specification information	☑ Anticipated residue levels in foods
☑ Industrial use information (chemical only)	☑ Percentage of food group to use processing aid
☑ Information on use in other countries (chemical only)	☑ Information on residues in foods in other countries (if available)

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