INDUSTRIAL RESEARCH LIMITED

Te Tauihu Pūtaiao

Application to have dimethyl ether approved for use as a food processing solvent under standard 1.3.3 processing aids, clause 13 permitted extraction solvents

A. EXECUTIVE SUMMARY

This application requests that dimethyl ether be permitted as an extraction solvent for the production of food products under Standard 1.3.3 Processing Aids, Clause 13 Permitted Extraction Solvents, with a maximum permitted residue level of 2 mg/kg of processed product. Foods for which approval is sought are those derived from plants, animal tissue, ova, marine organisms, and micro-organisms including algae, fungi, and bacteria.

Dimethyl ether is a unique solvent that has several advantages over similar and already approved 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 due to the low processing temperature that is possible and the inertness of the solvent
- It has solvent properties that allows fractionation of a range of compounds that is not possible with other common solvents
- It can extract lipid compounds from aqueous systems

Toxicity studies have shown dimethyl ether to be non toxic even under high exposure levels. 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). 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). We are not aware of any other national standards relating to the use of dimethyl ether as a food processing aid.

Dimethyl ether is approved for use as an aerosol propellant for consumer products, including personal care products such as hair sprays. 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, in their assessment of DME noted that although the majority of studies on dimethyl ether toxicity have been inhalation studies they consider the results to be applicable because animal models show that dimethyl ether distribution through the body after oral exposure is similar to that after inhalation exposure. CEF further noted that the lowest no-effect level identified in an embryo-foetal inhalation toxicity study was approximately 630 mg/kg of bodyweight per day. As an extreme example, dietary exposure of a 50 kg adult to 1 kg per day of dimethyl ether processed food containing the maximum proposed limit of 2 ppm residue would give exposure of 0.04 mg/kg bodyweight per day, more than 10^5 times less than the lowest no-effect level identified.

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C. GENERAL INFORMATION

1. Applicant Details

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Nature of Business:	Industrial research and development
Other associated companies:	None

2. Purpose of the application

This application seeks to vary Standard 1.3.3 of the Australia New Zealand Food Standards Code 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 manufacture of food products derived from plants, animal tissue, ova, marine organisms, and micro-organisms with a maximum permitted residue level of 2 mg/kg of processed product.

Dimethyl ether has been successfully used for the extraction of lipids (fats and oils) from a broad range of natural materials, including seed and nut meals, animal and fish tissues, herbs and spices, plant material, and biomass produced by micro-organisms. The applicant wishes to use dimethyl ether in the production of food products and food ingredients derived from these materials.

Dimethyl ether has already been approved by the European Food Standards Authority (EFSA). Under Annex I to Directive 2009/32/EU, dimethyl ether is approved 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).

The applicant is aware of an existing application to FSANZ to have dimethyl ether approved for use in Australia and New Zealand for dairy-derived food ingredients.

The applicant is not aware of any further applications or approvals in any other jurisdiction.

3. Justification for the application

3.1 Need for and/or advantages of the proposed change

Dimethyl ether is a unique and very effective solvent for extraction of both polar and non-polar lipid components from source materials. It is possible to extract lipids from either dry or wet substrates. It is also possible to extract lipids without denaturation of residual proteins, and to remove both lipid and water from an aqueous stream leaving a dry lipid free residual fraction. None of the permitted extraction solvents listed under Clause 13 (Permitted Extraction Solvents) of Standard 1.3.3 (Processing Aids) can give the same total lipid profile of extracted compounds, or selectively extract the same range of compounds directly from an aqueous solution.

Dimethyl ether also has a number of physical property benefits over other solvents:

- It is a gas at room temperature and pressure so can easily be:
  - Removed from the product streams to produce virtually solvent 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 products 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 is partially miscible with water and can extract lipids and water from aqueous raw materials.

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

Dimethyl ether has been widely used for decades as a propellant in personal care products, and significant studies into potential health effects have demonstrated no safety issues even after very high exposure.

EFSA have recently amended Annex 1 to Directive 2009/32/EU 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), following advice from EFSA's scientific panel on food contact materials, enzymes, flavourings and processing aids.[1] The applicant believes that this limit is unnecessarily tight, and that such a limit would impose an unreasonable compliance cost on industry without any functional benefit in public health and safety. The applicant proposes that a maximum permitted residue limit of 2 mg/kg (2 ppm) be applied in Standard 1.3.3 of the Australia New Zealand Food Standards Code. Maximum residue limits of 2ppm apply to similar solvents currently permitted in Standard 1.3.3 of the Australia New Zealand Food Standards Code, including dibutyl ether and diethyl ether, and higher limits apply for solvents such as hexanes and methanol. The applicant believes that the use of dimethyl ether will not pose a health risk with a maximum permitted residue limit of 2 ppm. Due to the more volatile nature of dimethyl ether it is expected that, in practice, residue levels in dimethyl ether processed foods and food ingredients will be substantially lower than this limit, and inherently lower than for food products produced using liquid solvents, but the applicant asserts that establishing a lower limit than 2ppm is neither necessary nor desirable. Furthermore, the applicant believes that accurate measurement of residue levels of 0.009 mg/kg is difficult to achieve without unreasonable effort in calibration and care in the method applied, and that results measured at this level could potentially be inaccurate or misleading. In contrast, the applicant proposes a simple and reliable method for measuring residual dimethyl ether at levels of 2ppm, and this is disclosed later in this application.

If this application is successful, new products that are produced using dimethyl ether are expected to displace products that are already solvent extracted, so the total quantity of solvent processed foods is not expected to increase significantly. Dimethyl ether has a higher volatility than liquid solvents that are more commonly used and the overall solvent residue levels in processed foods is expected to be correspondingly lower.

Dimethyl ether is known to be less flammable than propane, an allowed food processing aid. Dimethyl ether is used extensively as an aerosol propellant for materials that are too polar to dissolve in propane or propane/butane mixtures. Dimethyl ether can also be blended with LPG (in a proportion of up to 20%) and used for domestic cooking and heating without modifications to equipment or distribution networks. Growth in dimethyl ether's use for domestic applications is expected to increase as dimethyl ether use and blending becomes more widespread within the large and growing LPG market – especially in developing countries where portable (bottled) fuel is providing a safer, cleaner and more environmentally benign fuel for cooking and heating (see http://www.aboutdme.org/).

Further safety information is described in later sections.

3.3 Nutritional issues relating to the proposed change

Dimethyl ether is not metabolised and disperses naturally from the body by respiratory action, so presents no nutritional issues.[2]

3.4 Technological function and need

Dimethyl ether has the ability to extract a broad range of lipid compounds from natural materials, including valuable polar lipids such as phospholipids and glycolipids, which other gaseous solvents are not able to accomplish alone. For example supercritical CO_2 and near critical propane both require a polar co-solvent, such as ethanol, in order to extract a limited range of polar lipids. Additionally, the use of ethanol as a co-solvent results in lipid extracts and lipid-depleted products that contain ethanol residues.

The liquid solvent diethyl ether is a poor solvent for lipids on its own and is a liquid under ambient conditions, so leaves solvent residues in the final food products that must be removed. Traditional extraction solvents, such as diethyl ether, hexane, acetone and ethanol, also affect the solubility of the lipid-depleted food products by denaturing a significant proportion of the protein present. In contrast, dimethyl ether extraction of low moisture food products does not affect the solubility of the resulting lipid-depleted food products.

Dimethyl ether is also partially soluble in water and can be used to extract lipids from aqueous (as well as low moisture) food products, such as un-dried marine or animal tissue, plant materials, fermentation broths, or fruit juices. Dimethyl ether extraction of wet or high moisture content products (in contrast to low moisture content products) under certain conditions can result in partial denaturation of proteins, which in some cases produces desirable textural and functional properties in the food product.

Removal of dimethyl ether from food products or food ingredients is easily achieved by returning them to ambient temperature and pressure at the end of the extraction process. In contrast, the removal of traditional extraction solvents (e.g. hexane) requires the addition of heat, which can have undesirable effects on the flavour, bioactivity and solubility of many food products, and may also lead to the formation of chemical artefacts. Dimethyl ether extraction avoids thermal degradation of the food products because both processing and solvent removal are carried out at moderate temperatures (typically ≤ 60°C). The applicant has demonstrated that residual levels of dimethyl ether below the detection limits of the measurement method used can be achieved in the processed ingredient (see analytical method in Section D5 and process residue levels in Section F2). Incorporation of the ingredient in final food products will further dilute any residual solvent levels, and the product handling involved in additional processing of the ingredient should also result in complete volatilisation of dimethyl ether out of the product.

3.5 Potential impact on trade

The registration of dimethyl ether is expected to result in an expanded range of food products, including novel and niche products with substantial earning potential. If subsequent approval is gained for use of dimethyl ether in other jurisdictions then significant export earnings potential is also envisaged.

3.6 Consumer choice issues

The use of dimethyl ether is expected to provide a greater range of choice in both the composition of products available, and in the way in which the products are made; extraction with compressed liquid gases is expected to give lower solvent residues in the products, and to be a more environmentally benign method of processing over traditional solvent extraction processes because it has the potential to significantly reduce or eliminate the large volumes of organic solvent used in current processing methods, and the gases can easily be recycled and reused. Consumers may make a conscious decision to purchase products manufactured using solvents that are more easily removed and a process that is more environmentally friendly.

3.7 Food industry support and interest

A letter of support from Nutrizeal, Nelson, New Zealand, is attached to this application. Nutrizeal has an established interest in high pressure processing technologies and is interested in commercialising dimethyl ether processed products as well as provision of processing services for other manufacturers.

Fonterra, New Zealand, have a declared interest in processing dairy materials using dimethyl ether.[3,4,5]

The applicant has an ongoing research programme[6] related to processing using dimethyl ether, and as part of this programme is working with a number of New Zealand and Australian companies to develop applications that depend on the successful result of this application.

3.8 Industry, consumer, and government costs and benefits

Industry benefits

The use of dimethyl ether as a processing aid enables:

- Removal of lipids (including fats, oils and polar lipids) from food products, thereby enhancing the nutritional value and/or stability of the lipid-depleted food products;
- Production of (polar) lipid extracts, which can be further concentrated or processed as required to deliver specific nutritional 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 foods, resulting in products that have very low saturated fat contents. Furthermore, many lipids (e.g. phospholipids and oils) 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 and lipolysis, which have a detrimental effect on the flavour, appearance and nutritional value of the food products. For example, complete removal of oil from linseed or sesame meal is desirable to ensure that the product does not become oxidised (or rancid) during storage. Furthermore, extraction of a greater proportion of the oil present in certain products (e.g. linseed and soy beans) will make the total oil production process more viable. Lipid-depleted products can be used for example in low fat products and aqueous food products, such as cultured foods and beverages.

Commercial "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 benzyl 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 lecithin products that are free from toxic residues and chemical artefacts (such as mesityl oxides in the case of acetone). Furthermore, refined 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), once again producing lecithin products that are free from toxic residues and chemical artefacts. Approval of dimethyl ether as a food processing aid would therefore enable food manufacturers to produce natural, identity preserved lecithin products that can be used in a range of food and beverage products.

Dimethyl ether can extract a range of nutritionally beneficial lipids from animal, plant, and marine material. These beneficial lipids include polar lipids such as phospholipids, sphingolipids, gangliosides, carotenoids and lipids high in polyunsaturated fatty acids. High quality products can be extracted due to the anaerobic environment, the low temperatures used, and the non-reactivity of dimethyl ether. Extracted lipids can be further concentrated or used in a bulk form for nutritional fortification of foods. Efficient and high quality extraction of these lipids will enable the nutritional benefits of these compounds to be more fully realised. Dimethyl ether also enables efficient recovery of valuable lipids from marine and plant materials that are currently considered waste material. This improves the overall productivity of these sectors. Examples include fish oil products rich in phospholipids and in omega-3 fatty acids from waste fish material.

For food products, hexane-extracted soy flakes (from which the soy oil has been removed) are typically flash-desolventised, then carefully steam-heated to the desired Nitrogen Solubility Index (NSI) value (typically 80%). However the three commonly used extraction techniques for producing soy protein concentrates from the desolventised soy flour (the aqueous alcohol wash process, the acid wash process, and the heat denaturation/water wash process) all render the soy proteins insoluble. In contrast, dimethyl ether extraction of low moisture food products does not affect the protein solubility of the lipid-depleted food product or the integrity of the polar lipids in either the lipid-depleted food product or the lipid extract.

Industry costs

Manufacturing costs associated with the use of dimethyl ether as a food processing aid are expected to be comparable to existing processing methods. Cost of capital equipment is expected to be comparable. Cost of the solvent, storage and freight is expected to be comparable, although overall solvent use is expected to be lower. Lower energy consumption and smaller plant footprint is expected for some processes due to high extract solubility in dimethyl ether and favourable kinetics. Lower rates of solvent loss/consumption are expected due to ease of recycling in a closed extraction system.

Processing using dimethyl ether will require a plant designed for operation with flammable materials. This places some design constraints and health and safety requirements on the process, but standard industry practice for managing this will be entirely adequate. Comparable design criteria are required for use of other approved solvent systems where flammable vapours are present, including for ethanol.

Consumer benefits

Dimethyl ether as an extraction solvent is able to remove fats and oils from certain foods to produce reduced fat products and products that contain less oil. Reduced oil products have advantages of improved quality and shelf life since excess oil can oxidise and become rancid, causing deleterious effects with storage. 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 more readily from both the lipid-depleted food products and the food lipid extracts, leaving very low/undetectable solvent levels in the final products. Defatted and functional lipid food products 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 food products);
- 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 food.

Consumer costs

No consumer costs directly associated with use of dimethyl ether are anticipated.

Government benefits

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.

Government costs

Many of the products that could be manufactured using dimethyl ether would displace existing products that are currently manufactured using other extraction solvents. There is no expected net increase in industry or government costs for such products, except through natural expansion of the overall size of the processing industry that may occur. Any regulatory expenses, for example associated with atmospheric release monitoring, health and safety compliance, or food safety compliance, are expected to be in line with existing industrial processing expenses.

4. Information to support the application

Information required to support the application is given in later sections, and in other attached documentation.

5. Assessment procedure

The applicant believes that a General Level Procedure would be required to assess this application.

6. Confidential commercial information

This application does not contain any confidential commercial information.

7. Exclusive capturable commercial benefit (ECCB)

In our opinion this application is not expected to confer an Exclusive Capturable Commercial Benefit to the Applicant.

The applicant, Industrial Research Limited (a Crown Research Institute), has a proprietary position on the production and use of dimethyl ether to process materials including marine, plant, seed, nut, animal tissue and fish tissue. This position includes the following patent:

WO 2007136281 (A1), Extraction of highly unsaturated lipids with liquid dimethyl ether.[7]

We believe that an exclusive capturable commercial benefit is not conferred because there is opportunity for independent persons or bodies to benefit without the agreement of the applicant in areas not covered by the above patent. Evidence of these opportunities can be found in relevant intellectual property rights held by other parties.[4,5,8,9,10] Akzo Nobel also successfully applied on behalf of a commercial client to have dimethyl ether approved by EFSA for use with meat products, and this application has no connection with the applicant. We further believe that there is substantial growth potential outside of the proprietary positions of the applicant and other bodies listed above. This growth would be further encouraged by approval of dimethyl ether as a processing solvent.

8. International and other national standards

International Standards

We have no knowledge of any entry in the CODEX Alimentarius, in the Joint FAO/WHO Expert Committee on Food Additives (JECFA), or in the United States Pharmacopoeia.

National standards or regulations

We have no knowledge of dimethyl ether being rejected or withdrawn for registration with any international body. DuPont successfully submitted an application to the United States Environmental Protection Agency (U.S. EPA) to establish an exemption from the requirement of a tolerance for residues of dimethyl ether as an inert ingredient (propellant) in pesticide formulations applied to growing crops or raw agricultural commodities.[11] The application was submitted under the Federal Food, Drug and Cosmetic Act (FFDCA), as amended by the Food Quality Protection Act 1996 (FQPA). Dimethyl ether also appears in the U.S. EPA List 4B: "Other ingredients for which EPA has sufficient information to reasonably conclude that the current use pattern in pesticide products will not adversely affect public health or the environment".[12]

Annex 1 to Directive 2009/32/EU includes 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), following advice from EFSA's scientific panel on food contact materials, enzymes, flavourings and processing aids.[1]

D. TECHNICAL INFORMATION ON DIMETHYL ETHER AS A PROCESSING AID

1. Type of processing aid

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 materials with dimethyl ether is as follows:

1) The low moisture 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 material;

3) The dimethyl ether phase containing the dissolved polar and non-polar extracts enters one or more separation vessels;

4) The pressure in the separation vessels is lowered to a point where the extracts are no longer soluble in dimethyl ether. The extract is then recovered from the bottom of the separation 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 extract-depleted 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
	Wood Ether
Marketing names:	Dymel A ®
	Demeon D ®
	Propel
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

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 and storage. It is highly flammable, but has proven to be extremely safe when handled properly (http://www.aboutdme.org/).

Boiling point: -24.84°C at 1 atmosphere [13,14,15,16,17]

Colour: Dimethyl ether is a colourless gas at room temperature and is easily compressed to a colourless liquid.[18,19]

Density of liquid: 0.665 g/cm^3 when liquefied at 25°C.[13]

Density of gas: 1.92 g/L at 1 atmosphere and 25°C.[13,15,18,19,20,21]

Freezing (melting point): -141.49°C @ 1 atmosphere [13,14,17]

Octanol/Water partition coefficient: (Octanol-water) (log KOW): 0.10 [13]

Odour: Dimethyl ether has a characteristic sweet ethereal odour [18]

Oxidation stability (in air):[15] Autoignition temperature 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 2.98×10^{-12} cm^3/molecule sec at 25°C.[22] This rate constant corresponds to an atmospheric half-life of about 5.4 days at an atmospheric concentration of 5×10^5 hydroxyl radicals per cm^3.[23] Direct photolysis is not expected to be an important removal process since aliphatic ethers do not absorb light in the environmental spectrum. The rate constant for the reaction of dimethyl ether with hydroxyl radicals in aqueous solution is 1.0×10^9 L/mol sec.[24] This rate constant corresponds to a half-life of about 2.2 years[23] at an average aqueous hydroxyl radical concentration of 1×10^{-17} mol/L.[25] The rate constant for the reaction of dimethyl ether with nitrate radicals is $\leq 3 \times 10^{-15}$ cm^3/molecule-sec at 25°C.[26] This corresponds to an atmospheric concentration of 5×10^8 nitrate radicals/cm^3.[26]

Reliability: Estimated value based on accepted model.

Refractive index (liquid):

1.302.[17]

Solubility in organic solvents

Soluble in methanol, ethanol, isopropanol, ether, chloroform, acetone, chlorinated hydrocarbons and toluene.

Solubility in water

35-46 g/L at 18-25°C.[13,15,17,18,27,28]

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.[29] Stable in neutral and dilute acidic and alkaline solutions.

Stability in water

The Henry's Law constant for dimethyl ether is estimated as 7.6×10^{-3} atm-m^3/mole[23] from its vapour pressure, 4,450 mm Hg, and water solubility, 3.5×10^4 mg/L.[17] This Henry's Law constant indicates that dimethyl ether is expected to volatilise rapidly from water surfaces.[23,30] 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.[23,30] 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.[23,30]

Reliability: Estimated value based on accepted model.

Vapour pressure

4450 mm Hg (593 kPa) @ 25°C [19,28]

Bio-concentration

BCF 0.70 [23]

Method: The estimated value was calculated using a log KOW of 0.10 [13] and a regression-derived equation.[30] According to a classification scheme,[31] this BCF suggests the potential for bioconcentration in aquatic organisms is low.

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. [32,33,34,35,36,37]

Interaction in foods and metabolic fate

Dimethyl ether is stable and does not form reaction products with any type of food.[1]

4. Manufacturing process

Dimethyl ether is most commonly 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:

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

5. Specification for identity and purity

Specification

Aerosol grade dimethyl ether is manufactured and supplied by Aerosol Supplies Australia (Propel), Dupont (Dymel A) and Akzo Nobel Base Chemicals (Demeon D), amongst others. Table 1 gives the manufacturer's product specifications for Propel and Dymel A, and Table 2 gives typical analyses for Propel and Dymel A.

***Table 1**. Product specifications for Dymel A and Propel*

Test	Dymel A	Propel
Purity (vol%)	99.8 (min)	99.5 (min)
Methanol (ppm)	200 (max)	10 (max)
Water (ppm)	500 (max)	500 (max)
Air (O_2, N_2, CO)	100 ppm (max)	0.5 vol% (max)
Residue (ppm)	50 (max)	500 (max)
Oil (ppm)	-	30 (max)

Table 2. Typical analyses for Dymel A and Propel

Test	Dymel A	Propel
Dimethyl ether purity (% vol)	99.973	99.8
Methanol (ppm)	130	0
Water (ppm)	120	77
Air (O_2, N_2, CO)	80 ppm	0.1 vol%
Residue (ppm)	<20 ppm	83
Oil (ppm)	-	5

Dimethyl ether is not covered in any of the relevant monographs listed in Standard 1.3.4, Identity and Purity. Based on currently available aerosol grade supplies, the proposed specification for identity and minimum purity is as follows:

Appearance:	Clear, colourless liquefied gas
Odour:	Slight ethereal odour
DME purity:	99.8% minimum
Methanol:	<200 ppm
Water:	<500 ppm
Air (O_2, N_2, CO_2):	<100 ppm
Non-volatile residues:	<50ppm

Purity standard

A high purity standard for reference is available from chemical suppliers including Condea, Germany.

Analytical method for measuring residual processing aid levels

Dimethyl ether can be analysed by gas chromatography using flame ionisation or mass spectroscopy detection. Sample introduction can be made by gas-tight syringes and a standard split port, or by head-space injection. A typical configuration used by the applicant is 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°C, increase by 2°C per min to 50°C, then by 30°C per minute to 100°C and hold at 100°C for 2.5 min.
Injector temperature:	200°C
Injection:	1 µL of solvent containing the internal standard and 50 mg/ml of test sample
Split ratio:	1:20

Column flow:	Constant at 2.5 ml/min
Detector:	Flame Ionisation Detector (FID), base temperature 200°C

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:

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;

Shake the mixture briefly and place in an ultrasonic bath for 5 min;

Precipitate out the insoluble material by centrifugation (Heraeus Megafuge 1.0, 4500 rpm for 5 min);

Perform the analysis under the conditions listed above (We performed our analyses using a TraceGC equipped with a TriPlus auto sampler, Thermo Finnigan, USA).

Under such conditions, both 1 ppm of dimethyl ether and ethanol in the butanol extract were 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)) improved 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.

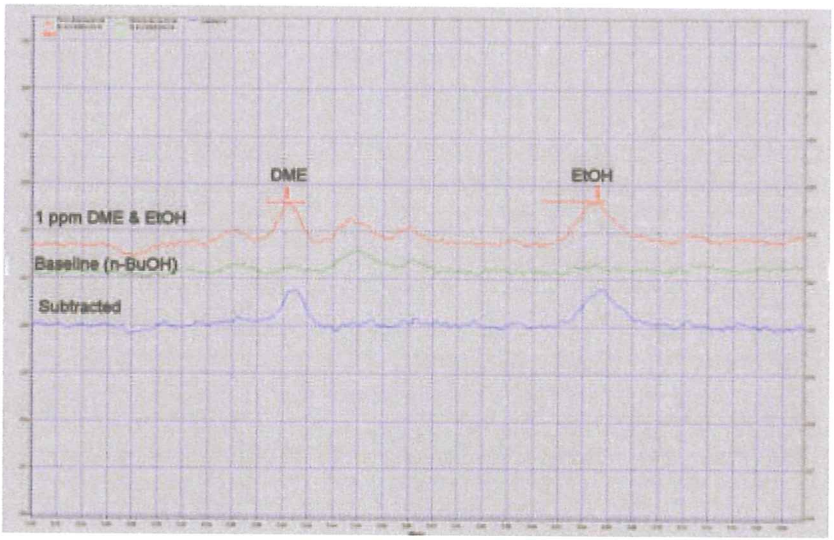

Figure 1. Gas chromatography calibration for dimethyl ether and ethanol with baseline correction

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 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

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 (http://www.aboutdme.org/). 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.[38]

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

We are not aware of any current use of dimethyl ether in food processing. However, AKZO NOBEL Chemicals Holding GmbH requested, on behalf of a customer, authorisation of dimethyl ether as an extraction solvent to de-fat meat proteins according to the provisions of Council Directive 88/344/EEC. This request resulted in a scientific risk assessment by EFSA on dimethyl ether as an extraction solvent (Request number EFSA-Q-2007-186), who 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]

3. Data on the toxicokinetics 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.[1,2]

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 Du Pont (ROBUST SUMMARY FOR DIMETHYL ETHER, 11 October 2000, Du Pont SHE excellence center) and published by the United States Enviromental Protection Agency.[23] Further detail is contained in the report "INITIAL HUMAN HEALTH AND ENVIRONMENTAL SCREENING ASSESSMENT FOR DIMETHYL ETHER (DME) TECHNICAL SUMMARY", prepared by DuPont Company, August 29, 2001.[38]

Dimethyl ether has very low toxicity. Table 3 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 3**. Comparison of dimethyl ether toxicity with that of diethyl ether and dibutyl ether[28,39,40,41,42,43]*

Toxicity model	Dimethyl ether	Diethyl ether	Dibutyl ether
Inhalation LC50/mouse (15 minutes)	494 000 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.[1,2] 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.[1,2]

DuPont calculate 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.[38] 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. [23,30] 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]

The U.S. EPA granted an exemption from the requirement of a tolerance for residues of dimethyl ether as an inert ingredient (propellant) in pesticide formulations applied to growing crops or raw agricultural commodities.[11] Dimethyl ether also appears in the U.S. EPA List 4B: "Other ingredients for which EPA has sufficient information to reasonably conclude that the current use pattern in pesticide products will not adversely affect public health or the environment".[12]

F. INFORMATION RELATED TO DIETARY EXPOSURE TO DIMETHYL ETHER

1. Foods or food groups likely to contain the processing aid

Dimethyl ether has application in processing of a wide range of foods including those from marine and animal products, plants, fruit, seeds, and micro-organisms. After processing, DME will potentially be present in both the extracts and in the defatted source materials, either or both of which could potentially be included in foods. Food groups from Standard 1.3.1 – food additives – that are likely to contain DME processed products are given in Table 4 below, which are separated into lipid extracts and de-fatted products.

Table 4*. Food groups likely to contain material processed using the processing aid.*

DME processed product	Food groups (according to standard 1.3.1 – Food Additives) likely to contain the product	Example(s)
	Lipid extracts	
Marine lipids	2.2 oil emulsions	Omega-3 for fortified margarine
	7.1 fancy breads	Omega-3 or phospholipids for fortified breads
	13.1 Infant formula products	Omega-3 fortification
	13.2 Food for infants	Omega-3 fortification
Egg phospholipids	3 ice cream and edible ices	Emulsifiers in ice cream
	5.1 chocolate and cocoa products	Emulsifiers in chocolate
	20.2 mixed foods, food other than beverages	Emulsifiers in sauces and toppings
Bacteria derived lipids	7.2.2 Biscuits, cakes, and pastries	Natural colouring for baked goods
	14.1.2.2 Fruit and vegetable juice products	Natural colouring agent for drinks
	20.2 Mixed foods, food other than beverages	Natural colouring agent for desserts and snacks
Algae derived lipids	7.1 fancy breads	PUFA fortified breads
Plant lipids	8.1 Raw meat, poultry, game	Natural antioxidant preservatives
	9.4 Fully preserved fish, canned fish	Natural antioxidant preservatives
	13.1 Infant formula products	Soy lecithin additive, omega-3

		fortification
	13.2 Food for infants	Natural plant flavourings, plant lecithin additive, omega-3 fortification
De-fatted (non-lipid) products		
Egg proteins	13.4 Formulated supplementary sports foods	Protein ingredient for protein drinks or powders
Plant proteins	13.1 Infant formula products	Soy protein additive
	13.4 Formulated supplementary sports foods	Protein ingredient for protein drinks or powders
	14.1.2.2 Fruit and vegetable juice products	Soy proteins for soy based drinks
Fruit sugars	4.3.1 dried fruits and vegetables	Dried fruit snacks
	14.1.3 Water based flavoured drinks	Sweetener and flavouring for drinks.
Meat proteins	8.2 dried meat	Dried fat-free meat products
	8.5 animal protein products	Dried fat-free meat products

2. Residue levels for each food group

Proposed residue levels

The applicant proposes that dimethyl ether be approved as a processing aid with a maximum permitted residue limit of 2 ppm dimethyl ether (i.e. less than the detection limit for the method described above).

Measured residue levels

Table 5 shows the residual dimethyl ether levels (ppm) measured by the applicant in a range of dimethyl ether processed food substrates.

***Table 5**. Residual dimethyl ether levels in various materials processed using dimethyl ether. ND=not Detected (<2 ppm)*

Product and process	DME residue (ppm)
Lipase enzyme powder exposed to dimethyl ether, 24 hours after processing	ND
Fermented bacterial biomass extracted with dimethyl ether, 24 hours after processing	ND
Dimethyl ether extract from fermented biomass, immediately after processing,	ND

Aqueous protein/lipid solution defatted using dimethyl ether, after spray drying	ND
Extract from aqueous protein/lipid solution fraction using dimethyl ether, after rotary evaporation of water	ND

This table shows that dimethyl ether naturally dissipates from both lipid extracts and residual lipid-depleted biomass to undetectable levels (<2 ppm), so it is not strongly bound to the products.

Standard downstream processing methods including fluidisation, spray drying, or vacuum drying, can also be applied to more rapidly remove any residual dimethyl ether traces that may be present.

Analytical method for dimethyl ether by-products

Dimethyl ether is inert, so there are 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 ingredients are expected to be used in premium foods, and in particular, premium foods that are sold on the basis of their nutritional quality. Food products are expected to contain 0.5-10 wt% of a dimethyl ether processed ingredient depending on the type of ingredient used (lipid ingredient or a reduced lipid protein or carbohydrate ingredient). Some dehydrated or de-fatted foods may contain higher levels of processed material. Table 6 gives estimated percentages of each food group that will contain dimethyl ether processed ingredients.

***Table 6**. Maximum percentage of each food group likely to contain a dimethyl ether (DME) processed ingredient.*

Food group (according to standard 1.3.1 – Food additives)	Max. percentage likely to contain DME-processed food (wt %)	Expected level of DME- processed food in final food product (wt %)
2. Edible oils and emulsions	1	1-10
3. Ice cream and edible ices	0.5	5-10
4. Fruits and vegetables		
4.3.1 Dried fruits and vegetables	0.5	50-100
5. Confectionary		
5.1 Chocolate and cocoa products	0.5	1-3
7. Breads and bakery products		

7.1 Fancy breads	0.1	1-5
7.2 Biscuits, cakes and pastries	0.1	1-5
8. Meat and meat products		
8.1 Raw meat, poultry, game	1	1
8.2 Processed meat, poultry, game	0.1	100
8.5 Animal protein products	0.1	50-100
9. Fish and fish products		
9.4 Fully preserved fish, canned fish	1	1
13. Foods for particular dietary use		
13.1 Infant formula products	0.5	0.5-5
13.2 Foods for infants	1	1-3
13.4 Formulated supplementary sports foods	2	50-100
14. Non-alcoholic and alcoholic beverages		
14.1.2.2 Fruit and vegetable juice products	0.1	1-2
14.1.3 Water based flavoured drinks	0.1	5
20. Mixed foods		
20.2 Food other than beverages	2	1-20

4. Levels of processing aid residues in foods in other countries

Annex 1 to Directive 2009/32/EU includes 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. STATUTORY DECLARATION – NEW ZEALAND

STATUTORY DECLARATION

Oaths and Declarations Act 1957

I, Owen Catchpole, Group Manager Integrated Bioactive Technologies, Industrial Research Ltd, 14/189 Jellicoe Towers, The Terrace, Wellington, New Zealand, solemnly and sincerely declare that:

The information provided in this application fully sets out the matters required; and

the information is true to the best of my knowledge and belief; and

no information has been withheld which might prejudice this application to the best of my knowledge and belief.

I make this solemn declaration and conscientiously believing the same to be true and by virtue of the Oaths and Declarations Act 1957.

Declared at LOWER HUTT

On the 11th day of MAY 2011

Signature

Declared before me* J M Woodward

Title Solicitor

Wellington

*A statutory declaration must be made before a person authorised to take a statutory declaration under the *Oaths and Declarations Act 1957*, available online at http://www.legislation.govt.nz

H. Check List

CHECKLIST FOR STANDARDS RELATED TO SUBSTANCES ADDED TO FOOD

This checklist will assist you in determining if you have met the information requirements as detailed in the Application Handbook. Section 3.1 – General Requirements is mandatory for all applications. Sections 3.3.1-3.3.3 are related to the specifics of your application and the information required is in addition to section 3.1.

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*
- ☑ Applicant details
- ☑ Purpose of the application
- ☑ Justification for the application
- ☑ Information to support the application
- ☑ Assessment procedure
- ☑ Confidential Commercial Information
  - ☐ *Confidential material separated in both electronic and hard copy*
- ☑ Exclusive Capturable Commercial Benefit
- ☑ International standards
- ☑ Statutory Declaration

Food Additives (3.3.1)

- ☐ Nature and technological function information
- ☐ Identification information
- ☐ Chemical and physical properties
- ☐ Impurity profile
- ☐ Manufacturing process
- ☐ Specifications
- ☐ Food labelling
- ☐ Analytical detection method
- ☐ Toxicokinetics and metabolism information
- ☐ Toxicity information
- ☐ Safety assessments from international agencies
- ☐ List of foods likely to contain the food additive
- ☐ Proposed levels in foods
- ☐ Percentage of food group to contain the food additive
- ☐ Use in other countries (if applicable)

Processing Aids (3.3.2)

- ☑ Type of processing aid
- ☑ Identification information
- ☑ Chemical and physical properties
- ☐ Information on enzyme use on other countries (enzyme only)
- ☐ Toxicity information of enzyme (enzyme only)
- ☐ Information on source organism (enzyme from micro-organism only)

☑	Manufacturing process	☐	Pathogenicity and toxicity of source micro-organism (enzyme from micro-organism only)
☑	Specification information	☐	Genetic stability of source organism (enzyme from micro-organism only)
☑	Industrial use information (chemical only)	☐	Nature of genetic modification (PA from GM micro-organism only)
☑	Information on use in other countries (chemical only)	☑	List of foods likely to contain the processing aid
☑	Toxicokinetics and metabolism information (chemical only)	☑	Anticipated residue levels in foods
☑	Toxicity information (chemical only)	☑	Percentage of food group to use processing aid
☑	Safety assessments from international agencies (chemical only)	☑	Information on residues in foods in other countries (if available)

Nutritive Substances (3.3.3)

☐	Identification information	☐	Proposed maximum levels in food groups or foods
☐	Information on chemical and physical properties	☐	Percentage of food group anticipated to contain nutritive substance
☐	Impurity profile information	☐	Food consumption data for new foods
☐	Manufacturing process information	☐	Nutritional purpose
☐	Specification information	☐	Need for nutritive substance in food
☐	Analytical detection method	☐	Demonstrated potential deficit or health benefit
☐	Proposed food label	☐	Consumer awareness and understanding
☐	Statement that the product being assessed is representative of the commercial product	☐	Actual or potential behaviour of consumers
☐	Toxicokinetics and metabolism information	☐	Demonstration of no adverse effects on any population groups
☐	Animal or human toxicity studies	☐	Impact on food industry
☐	Safety assessments from international agencies	☐	Impact on trade
☐	List of food groups or foods likely to contain the nutritive substance		

I. References

1. Scientific Opinion of the Panel on Food Contact Materials, Enzymes, Flavourings and Processing aids (CEF) on dimethyl ether as an extraction solvent. The EFSA Journal (2009) 984, 1-13.

2. Kemper F.H. and Eckard R. (1979). Mass fragmentographic study of the pharmacokinetics and tissue distribution of dimethyl ether (DME). Nauyn-Schmiedeberg's Arch. Pharmacol., Suppl., 307, R19.

3. FSANZ, Application – Administrative Assessment PA1056, dimethyl ether as a processing aid(solvent), assessment completed 14 december 2010.

4. WO 2004066744 (A1), Extraction of compounds from dairy products.

5. WO 2006041316 (A1), Beta-serum dairy products, neutral lipid-depleted and/or polar lipid-enriched dairy products, and processes for their production.

6. Foundation for Research Science and Technology, Research Programme CO8X0709, High Value Lipids, awarded to Industrial Research Ltd.

7. Catchpole et al. Patent WO 2007136281 (A1), Extraction of highly unsaturated lipids with liquid dimethyl ether.

8. Yano et al, Patent US 4157404 (A) , Process for obtaining yolk lecithin from raw egg yolk.

9. Yano et al, Patent US 4234619 (A), Decholesterolized and defatted egg powder and method for producing same.

10. Schonemann et al. Patent US 7329789 B1, Method for extraction and concentration of carotenoids using supercritical fluids.

11. U.S. Environmental Protection Agency. (2005). Dimethyl ether: exemption from the requirement of a tolerance. Federal Register, 70(95). Retrieved April 14th 2011, from http://www.epa.gov/EPA-PEST/2005/May/Day-18/p9475.htm

12. U.S. Environmental Protection Agency , August 2004, List of Inert Pesticide Ingredients. Retrieved April 14th 2011 from http://www.epa.gov/opprd001/inerts/inerts_list4Bcas.pdf

13. Yaws, C.L. 7th Edition, pp. 322, (2001). Matheson gas data book. New York: McGraw-Hill.

14. Lide, D.R. (Ed.). (2005-2006). CRC handbook of chemistry and physics (86th ed.) (pp.3-198). Boca Raton: Taylor and Francis.

15. Du Pont Co. (1999, March 24). Material safety data sheet No. DU001206.

16. Kennedy, et al. (1941). The heat capacity and entropy, heats of fusion and vaporisation, and the vapour pressure of dimethyl ether. The density of gaseous dimethyl ether. JACS 63, 2267.

17. Riddick, J.A. et al. (1986). Techniques of chemistry (4th ed.) (pp. 281-282 and pp. 923). New York: Wiley Interscience.

18. Merck Index (12th ed.). 1996, CD-ROM Version 2:1.

19. Braker, W., & Mossman, A.L. (Eds.). (1974). Matheson Unabridged Gas Data Book. Vol 3.

20. IUCLID (International Uniform ChemicaL Information Database) (18 February 2000). IUCLID data sheet: dimethyl ether.

21. Bobbo, S., Scattolini, M., Fedele, L., Camporese, R. (2005). Compressed liquid densities and saturated liquid densities of dimethyl ether. Journal of Chemical and Engineering Data, 50, 1667-1671.

22. Atkinson, R. (1994). Gas phase tropospheric chemistry of organic compounds, Journal of Physical and Chemistry Reference Data, Monograph 2, 132.

23. United States Environmental Protection Agency, Robust Summaries & Test Plans: Dimethyl Ether.

24. Buxton, G.V. et al. (1988). Critical review for rate constants for reactions of hydrated electrons, hydrogen atoms and hydroxyl radicals in aqueous solution. Journal of Physical and Chemistry Reference Data, 17, page 716.

25. Mill, T. et al. (1980). Free-radical oxidants in natural water. Science, 207(4433), 886-7.

26. Atkinson, R. (1991). Kinetics and mechanisms of the gas phase reactions of the NO_3 radical with organic compounds. Journal of Physical and Chemistry Reference Data, 20, 459-507.

27. Hine, J., & Mookerjee, P.K. (1975). Structural effects on rates and equilibriums. XIX. Intrinsic hydrophilic character of organic compounds. Correlations in terms of structural contributions. Journal of Organic Chemistry, 40(3), 292-298.

28. Daly, J.J., & Kennedy, G.L. (1987). Dimethyl ether: As safety evaluation. Chemical Times and Trends, 10(1), 40-44.

29. Michie Naito et al. A comparative study on the autoxidation of dimethyl ether (DME) comparison with diethyl ether (DEE) and diisopropyl ether (DIPE), Journal of Loss Prevention in the Process Industries, Volume 18, Issues 4-6, 2005, Pages 469-473.

30. Lyman, W.J. et al. (1990). Handbook of chemical property estimation methods, Chapter 15 (calculation method on pp. 15-29). Washington D.C. American Chemistry Society.

31. Franke, C. et al. (1994). The assessment of bioaccumulation. Chemosphere, 29(7), 1501-1514.

32. Stirling, D.I., & Dalton, H. (1979). The fortuitous oxidation and cometabolism of various carbon compounds by whole cell suspensions of *methylococcus capsulatus* (Bath). FEMS Microbiology Letters, 5, 315-318.

33. Stirling, D.I. & Dalton, H. (1980). Oxidation of dimethyl ether, methyl formate and bromomethane by *methylococcus capsulatus* (Bath). Journal of Genetic and Molecular Microbiology, 116, 277-283.

34. Colby, J. Stirling, D.I., Dalton, H (1977). The soluble methane mono-oxygenase of *methylococcus capsulatus* (Bath) Biochemical Journal, 165, 395-402.

35. Patel, R.N. et al. (1978). Microbial oxidation of methane and methanol: Isolation of methane utilizing bacteria and characterisation of a facultative methane-utilisaing isolate. J. Bacteriol., 136:352-358.

36. Patel, R.N. et al. (1982). Microbial oxidation of hydrocarbons: Properties of a soluble methane monooxygenase from a facultative methane-utilising organism, *Methylobacterium* sp. Strain RL-26. Appl. Environ. Microbio., 44(5):1130-1137.

37. Hazeu, W. (1975). Some cultural and physiological aspects of methane-utilising bacteria. Antonie van Leeuwenhoek, International Journal of General and Molecular Microbiology, 41,121-134.

38. Du Pont, INITIAL HUMAN HEALTH AND ENVIRONMENTAL SCREENING ASSESSMENT FOR DIMETHYL ETHER (DME) TECHNICAL SUMMARY Prepared by DuPont Company, 2001, retrieved from http://www.chemicalawareness.org/toolkit/advanced/technical_exam.pdf

39. L. Caprino; G. Togna, Toxicological aspects of dimethyl-ether, European Journal of Toxicology, 8(5), 1975, 287-290.

40. Kobayashi, K. 1985, Strain differences of ether susceptibility in mice, Exp. Anim., vol. 34, no. 4, pp. 379-386.

41. Data taken from online database: Hazmat Navigator, Elsevier Inc., 2011.

42. Marsh, D. F.; Leake, C. D.; The Comparative Anesthetic Activity of the Aliphatic Ethers, Anesthesiology. 11(4):455-463, July 1950.

43. Lewis, R.J., Sax's dangerous properties of industrial materials, 10th edition, John Wiley and Sons, 1999.