

## **Supporting Document 1**

### **RISK AND TECHNICAL ASSESSMENT REPORT**

#### **APPLICATION A1062**

#### **DIMETHYL ETHER AS A PROCESSING AID FOR NON-DAIRY INGREDIENTS & PRODUCTS**

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##### **Executive Summary**

Dimethyl ether is proposed for use as an extraction solvent for the separation of lipids from a range of non-dairy foods. At ambient pressure (1 atmosphere), dimethyl ether exists as a gas at temperatures above  $-24^{\circ}\text{C}$ . It is compressed, under high pressure, for use as a liquid extraction solvent in the course of food processing. The evidence assessed provided adequate assurance that the proposed use of dimethyl ether is technologically justified and has been demonstrated to be effective in achieving its stated purpose.

Animal and human data on inhalational exposure to dimethyl ether indicate a very low degree of toxicity. Adverse effects have been reported only at atmospheric concentrations greater than 20,000 parts per million (ppm) for acute exposure and 2,000 ppm for chronic exposure. Because of its low boiling point, dietary exposure to dimethyl ether will be negligible due to rapid evaporation of any residual dimethyl ether present in food following processing. A maximum permitted level (MPL) for dimethyl ether of 2 mg/kg is proposed which is equivalent to the MPL for the two ether extraction solvents that are currently permitted for use in food manufacture: diethyl ether and dibutyl ether. This MPL is considered to be appropriate. Dimethyl ether is considered to pose no public health and safety issues associated with its proposed use.

The overall conclusion of this risk and technical assessment is that the use of dimethyl ether as a processing aid is technologically justified and raises no public health and safety issues.

## Table of Contents

<b>RISK AND TECHNICAL ASSESSMENT REPORT .....</b>	<b>1</b>
<b>EXECUTIVE SUMMARY .....</b>	<b>1</b>
<b>TABLE OF CONTENTS .....</b>	<b>2</b>
<b>1. INTRODUCTION.....</b>	<b>3</b>
1.1 BACKGROUND.....	3
1.2 RISK ASSESSMENT QUESTIONS & SCOPE .....	3
<b>2. FOOD TECHNOLOGY ASSESSMENT.....</b>	<b>4</b>
2.1 DIMETHYL ETHER CHARACTERISTICS.....	4
2.1.1 <i>Identity</i> .....	4
2.1.2 <i>Chemical and physical properties</i> .....	4
2.1.3 <i>Production</i> .....	5
2.1.4 <i>Specifications</i> .....	5
2.1.5 <i>Methods of analysis</i> .....	5
2.2 TECHNOLOGICAL FUNCTION.....	5
2.2.1 <i>Examples of use of dimethyl ether for non-dairy products</i> .....	7
2.3 FOOD TECHNOLOGY CONCLUSION.....	7
<b>3. HAZARD ASSESSMENT .....</b>	<b>8</b>
3.1 INTRODUCTION .....	8
3.2 HISTORY OF USE .....	8
3.3 OVERSEAS APPROVALS .....	8
3.4 ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION .....	8
3.5 TOXICITY .....	8
3.5.1 <i>Acute toxicity</i> .....	8
3.5.2 <i>Sub-chronic toxicity</i> .....	9
3.5.3 <i>Chronic toxicity and carcinogenicity</i> .....	9
3.5.4 <i>Genotoxicity</i> .....	9
3.5.5 <i>Reproductive and developmental toxicity</i> .....	9
3.6 RESIDUAL LEVELS IN FOOD .....	9
3.7 DIETARY EXPOSURE .....	10
3.8 DISCUSSION .....	10
3.9 HAZARD ASSESSMENT CONCLUSION .....	10
<b>4. REFERENCES.....</b>	<b>10</b>

# **1. Introduction**

## **1.1 Background**

On 16 May 2011, Food Standards Australia New Zealand (FSANZ) received an Application from Industrial Research Limited, New Zealand, seeking an amendment to Schedule 13 of Standard 1.3.3 of the *Australia New Zealand Food Standards Code* (the Code) to permit the use of dimethyl ether as an extraction solvent processing aid.

Dimethyl ether is proposed for the extraction of lipids from a range of non-dairy foods. The Code currently includes two ether compounds permitted as extraction solvents: diethyl ether and dibutyl ether. Both of these extraction solvents are permitted for use in the manufacture of all foods. Residual levels of extraction solvents may remain in treated foods and the maximum permitted level (MPL) for each of these extraction solvents is 2 mg/kg. For dimethyl ether, the proposed MPL is also 2 mg/kg.

## **1.2 Risk Assessment Questions & Scope**

The following questions are addressed in this Risk and Technical Assessment Report:

- Is the use of dimethyl ether as an extraction solvent technologically justified?
- Are foods produced through the use of dimethyl ether safe for consumption?

This Risk and Technical Assessment Report addresses the above questions in order and comprises the following components:

- (1) Food Technology Assessment, which describes the chemical properties of the compound and considers whether the use of dimethyl ether as an extraction solvent is technologically justified.
- (2) Hazard Assessment, which evaluates the intrinsic toxicity of dimethyl ether and the potential for residual dimethyl ether to remain in food produced through its use.

## 2. Food Technology Assessment

### 2.1 Dimethyl Ether Characteristics

The following information regarding the identity and chemical and physical properties of the extraction solvent dimethyl ether has been taken from the Application and various references.

#### 2.1.1 Identity

Common name:	dimethyl ether
Chemical name (IUPAC):	methoxymethane
Other names:	methyl ether, oxybismethane, dimethyl oxide, wood ether
C.A.S. registry number:	115-10-6
Molecular formula:	C <sub>2</sub> H <sub>6</sub> O
Structural formula:	CH <sub>3</sub> -O-CH <sub>3</sub>
Molecular weight:	46.069 g/mol
Marketing names:	Dymel A <sup>®</sup> , Demeon D <sup>®</sup> , Propel

#### 2.1.2 Chemical and physical properties

Dimethyl ether is a colourless gas at room temperature and pressure with a characteristic sweet ethereal odour. It is readily liquefied when compressed to produce a colourless liquid. It is highly flammable but is safe when handled appropriately.

Relevant chemical and physical properties for dimethyl ether are provided in Table 1.

**Table 1:** Chemical and physical properties of dimethyl ether

Characteristic	Property
Boiling point	-24.8°C at 1 atmosphere
Freezing point (melting point)	-141.5°C at 1 atmosphere
Flash point	-41°C
Density of liquid	0.665 g/cm <sup>3</sup> at 25°C, when liquefied
Density of gas	1.92 g/L at 1 atmosphere and 25°C
Octanol/water partition coefficient	Log KOW 0.10
Vapour pressure	4450 mmHg (593 kPa) at 25°C
Solubility in water	7% by weight at 18°C and 1 atmosphere

As can be seen from Table 1, dimethyl ether is partially soluble in water. It is also soluble in organic solvents that are relatively polar, such as methanol, ethanol, isopropanol, diethyl ether, chloroform, acetone, chlorinated hydrocarbons and toluene.

Dimethyl ether is quite stable under an inert atmosphere. It also does not form any reaction products when it is used to treat food.

### 2.1.3 Production

Dimethyl ether is produced from the catalytic dehydration of methanol under conditions of high temperature and pressure.

### 2.1.4 Specifications

There are no specifications for dimethyl ether in the relevant monographs of clause 2 and 3 of Standard 1.3.4 – Identity and Purity. Therefore a specification monograph for dimethyl ether is required to be added to the Schedule of Standard 1.3.4.

FSANZ has amended the Applicant's proposed specification based on that used for aerosol grade dimethyl ether (used as a propellant for various uses for commercial care products such as hairspray). FSANZ has removed reference to appearance and odour and some parameters as these are not important for regulatory specifications. The proposed specification for dimethyl ether is provided in Table 2, to be added into the Schedule of Standard 1.3.4.

**Table 2:** Proposed specification for dimethyl ether

Characteristic	Specification
Purity	Minimum of 99.8%
Methanol	Not greater than 200 mg/kg

### 2.1.5 Methods of analysis

The Application contains details of an analytical method for dimethyl ether residues on treated food.

The method used is a gas chromatography method (GC) with detection via flame ionisation (FID) or mass spectroscopy. The Applicant notes that the limit of detection for their analytical method for determining dimethyl ether residues in treated food is 2 mg/kg, while the limit of quantification is estimated to be 5 mg/kg.

## 2.2 Technological function

Dimethyl ether is proposed by the Applicant as a new extraction solvent processing aid. Extraction solvent processing aids used during the manufacture and processing of foods are regulated by clause 13 – Permitted extraction solvents of Standard 1.3.3. There are already a number of permitted extraction solvents including two ethers, diethyl ether and dibutyl ether.

The Applicant, supported by scientific literature, claims dimethyl ether has a number of advantages over other extraction solvents that make it the solvent of choice for a number of specific uses.

The main purpose of using dimethyl ether as an extraction solvent is to extract lipids from both liquid and dry foods. The solvent has unique properties that make it an effective solvent for extracting both polar and non-polar lipids from food. One of these properties is that it can extract lipids without denaturing the residual proteins in the food, which for some uses is a

very important and useful attribute.

Dimethyl ether has unique extraction properties compared to other extraction solvents due to the following attributes:

- It is a gas at room temperature and pressure so residues can be easily removed from treated food.
- It is a powerful polar solvent when it is compressed to a liquid and used for extraction near its critical point (40-50° C).
- It is inert, so there are no by-products produced during extraction.
- Because it is used at relatively mild extraction conditions of temperature and pressure its use does not damage the foods it is extracting, which retain most, if not all, of their natural properties such as appearance, flavour, solubility and bioactivity.
- Since it is partially soluble in water it is able to extract lipids from aqueous foods.

Dimethyl ether is considered a near-critical liquid when used as an extraction solvent. Near-critical liquids are found to be very powerful extraction solvents when used as pressurised extraction solvents because of the dual properties:

- They have the solute carrying capacity of a liquid (similar density).
- They have similar mass-transfer rates to gases (their viscosity is similar to gases and diffusivity is intermediate between a gas and a liquid).

The Application explains the general process used to extract solid food with dimethyl ether.

- The food is loaded into stainless steel extraction baskets.
- Dimethyl ether is liquefied by being compressed to 40 bar, heated to 40-50°C and then pumped through the vessels containing the food.
- The dimethyl ether phase containing the extracted and dissolved polar and non-polar lipids pass into one or more separation vessels.
- The separation vessel has its pressure lowered so that the lipids are no longer soluble in dimethyl ether and so precipitate out of solution. The lipid extract is recovered from the base of the vessel and the dimethyl ether gas is recovered, re-pressurised and recycled through the process.
- Once the extraction process has been completed the extraction vessels are depressurised, the dimethyl ether is recovered for reuse, the lipid extract is obtained and the lipid-depleted original food is also recovered from the extraction baskets.

There are two categories of food applications for which dimethyl ether could be used as an extraction solvent. The first is to remove polar lipids from the food so producing a lower fat version of the food. The second category is to extract a valuable lipid extract from one source of food and then use this as a value-added ingredient in other foods, often to produce food with added proposed health benefits.

The following examples of food that have been extracted by dimethyl ether in trials and pilot

plant studies have been provided in the Application. As well there are various literature studies (some recent examples are provided in the reference section at the end of the report) on the use of dimethyl ether as an extraction solvent for various foods.

### **2.2.1 Examples of use of dimethyl ether for non-dairy products**

The Applicant has requested approval for use of dimethyl ether as an extraction solvent for non-dairy foods, to complement the concurrent dimethyl ether Application (A1056) that is seeking permission for use of dimethyl ether for dairy based foods.

The Application describes a large range of possible uses of dimethyl ether as an extraction solvent for various non-dairy foods. It describes these food categories as marine and animal products, plants, fruit, seeds and microorganisms (including algae, fungi and bacteria).

The Application listed various lipid extracts from sources such as marine, egg, bacteria, algae and plant that could potentially be added to margarine, bread, ice-cream, chocolate, sauces, drinks, various meat and fish products and infant formula and food for infants.

Reduced fat (lipid extracted) ingredients that could be added to food include egg proteins, plant proteins, fruit sugars and meat proteins added to a variety of other foods such as drinks or powders for formulated supplementary sports foods, infant formula products, juice products, drink products, dried fruit products and various dried meat products.

The Application provided analytical results of dimethyl ether residue amounts for various treated food and lipid extracts produced using dimethyl ether extraction. The residue levels were all below the detection limit of 2 mg/kg of the treated food after they had been further treated such as standing at room temperature after processing. Further downstream processing of the treated extracts and foods such as fluidisation, spray drying or vacuum drying will often be undertaken and will further reduce dimethyl ether residue levels.

The examples of food and food extracts treated by dimethyl ether reported in the Application are an enzyme (lipase) powder (treated to remove extraneous lipids derived from the production process), fermented bacterial biomass and the dimethyl ether extract from the fermented bacterial biomass, and aqueous protein/lipid solution and the dimethyl ether extract of this aqueous solution, both after further treatment. The Application reported residue data on the treated foods and also extracts from the foods.

Various studies in the literature and examples provided in the Application support the conclusion that dimethyl ether performs its function as an extraction solvent and it has unique properties that means it has advantages over other approved extraction solvents for different uses.

## **2.3 Food Technology Conclusion**

Dimethyl ether has been shown to function as an extraction solvent for treating various food matrices. The technological function as an extraction solvent processing aid is to extract polar lipids from both solid and aqueous foods when it is used as a near critical liquid produced by compressing the gas and slightly heating it. The analysis concludes that dimethyl ether performs the technological function as an extraction solvent processing aid, which is the stated purpose of the Application.

## **3. Hazard Assessment**

### **3.1 Introduction**

The pharmacokinetic and toxicological properties of dimethyl ether have been investigated in inhalation studies in animals and humans (summarised below). EFSA recently published a scientific opinion on the safety of dimethyl ether when used as an extraction solvent in food manufacturing (EFSA 2009). US EPA has evaluated unpublished inhalation toxicity studies on dimethyl ether and concluded that there is no need to establish a maximum permissible level for residues of dimethyl ether arising from its use in pesticide formulations (US EPA 2005).

### **3.2 History of Use**

Dimethyl ether has a long history of use as an aerosol propellant in personal care products and in pesticide formulations. The use of dimethyl ether as a food extraction solvent is recent (see Overseas Approvals, below).

### **3.3 Overseas Approvals**

Dimethyl ether was recently approved for use in the European Union as a food extraction solvent (EC 2010). It is approved for the removal of fat from animal protein raw materials. The approved 'maximum residual limit' of dimethyl ether is 9 µg/kg in the defatted protein product. This limit corresponds to the detection limit of the analytical method provided to EFSA (EFSA 2009).

The US EPA has granted an exemption from the requirement of a tolerance for residues of dimethyl ether arising from its use as an inert ingredient (propellant) in pesticide formulations applied to growing crops or raw agricultural commodities (US EPA 2005).

### **3.4 Absorption, Distribution, Metabolism and Excretion**

EFSA reviewed unpublished inhalation data in rats and stated that dimethyl ether is rapidly absorbed and distributed in various tissues and organs, reaching a steady state concentration 30 minutes after exposure. It is reported to be excreted unchanged, largely via exhaled air within a very short time, with levels returning to background levels within 90 minutes. Further, in rats exposed to 1000 ppm of dimethyl ether for 60 minutes, concentrations of dimethyl ether ranged from 14 to 22 mg/kg in muscle, fat, lungs, liver, spleen, kidney, heart, brain and blood. Concentrations in organs appeared to be directly proportional to atmospheric concentrations of dimethyl ether in the range 750 to 2000 ppm (EFSA 2009).

### **3.5 Toxicity**

Unpublished inhalational toxicity studies have been evaluated by US EPA (2005) and EFSA (2009). Information from these evaluations is summarised below.

#### **3.5.1 Acute toxicity**

The most obvious acute effect of inhalational exposure to high concentrations of dimethyl ether is anaesthesia, as is the case with diethyl ether which was once used as a general anaesthetic. Narcotic effects have been reported in humans at an atmospheric concentration of 120000 ppm.



Rats exposed for four hours to an atmosphere containing dimethyl ether at a concentration of 20000 ppm did not show any effect, while the lethal concentration for 50% of the rats (LC<sub>50</sub>) was 164000 ppm.

### **3.5.2 Sub-chronic toxicity**

Four- and 13-week inhalation studies have been conducted in rats and hamsters. Animals were exposed for six hours per day. In both species there were no biologically significant effects on any of the parameters investigated (behaviour, body weight, clinical chemistry, haematology, urinalysis, gross pathology, organ weights and histopathology) at atmospheric concentrations as high as 20000 ppm, the highest concentration tested.

### **3.5.3 Chronic toxicity and carcinogenicity**

A two-year inhalation study in rats exposed to atmospheres of dimethyl ether at concentrations up to 25000 ppm for six hours per day, five days per week, showed no evidence for carcinogenicity potential. Clinical chemistry, haematology and histopathology findings were unremarkable. A slight decrease in survival was observed in the 10000 ppm group compared to the control group. The next lowest concentration level of 2000 ppm was considered to be the no observed adverse effect concentration (NOAEC) in this study.

### **3.5.4 Genotoxicity**

Unpublished *in vitro* and *in vivo* studies with dimethyl ether have shown no evidence for genotoxicity potential, with or without metabolic activation. Bacterial mutagenicity assays involved incubation of plates in atmospheres containing dimethyl ether at concentrations up to 120000 ppm. Concentrations tested *in vivo* were up to 20000 ppm.

### **3.5.5 Reproductive and developmental toxicity**

Two unpublished studies in pregnant rats have been evaluated by US EPA and EFSA. Inhalation exposure to dimethyl ether was from days 6 to 15 of gestation. The maximum concentration tested was 20000 and 28000 ppm in the respective studies. The rat strain differed for each study (Wistar and Sprague-Dawley) and no teratogenic effects were observed in either strain. In Sprague-Dawley rats, an increased incidence of skeletal variations was reported at the two highest concentrations tested (5000 and 20000 ppm). The NOAEC was therefore proposed to be the next lowest concentration of 1250 ppm.

## **3.6 Residual Levels in Food**

The Applicant proposes a maximum permitted level (MPL) for dimethyl ether of 2 mg/kg which is equivalent to the detection limit of the method described by the Applicant. It was stated that no residual dimethyl ether was detectable in the following: lipase enzyme powder exposed to dimethyl ether (24 h after processing); fermented bacterial biomass extracted with dimethyl ether (24 h after processing); dimethyl ether extract from fermented biomass (immediately after processing), aqueous protein/lipid solution defatted using dimethyl ether (after spray drying); extract from aqueous protein/lipid solution fraction using dimethyl ether (after rotary evaporation of water). Incorporation of the ingredient in final food products will further dilute any residual dimethyl ether.

### 3.7 Dietary Exposure

FSANZ considers that a dietary exposure assessment for dimethyl ether is not necessary because of its low toxicity and the negligible levels that will be present in food.

### 3.8 Discussion

While the inhalational toxicity of dimethyl ether is not directly relevant to potential exposure to trace amounts of dimethyl ether present in food matrices, the data indicate that the compound is of very low toxicity with regards to all toxicological aspects investigated. Data on acute, sub-chronic, chronic and reproductive/developmental toxicity via the inhalation route indicate that adverse effects are only evident at exceedingly high atmospheric concentrations. Because of its low boiling point, dietary exposure to dimethyl ether will be negligible due to rapid off-gassing of any residual dimethyl ether present in food following processing.

The proposed MPL for dimethyl ether is 2 mg/kg, which is equivalent to the limit of detection of the method described by the Applicant. The presence of dimethyl ether in food at levels below the MPL raises no public health and safety concerns.

### 3.9 Hazard Assessment Conclusion

Data on inhalation exposure to dimethyl ether indicate a very low degree of toxicity and dietary exposure to the compound will be negligible.

The use of dimethyl ether as an extraction solvent processing aid raises no public health and safety issues.

## 4. References

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