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**ORIGINAL SUBMISSION**

**000001**



2001 9<sup>th</sup> AVENUE  
SUITE 301  
VERO BEACH, FL 32960  
p•772.562.390 / f•772.562.3908  
e•gburdock@burdockgroup.com

July 11, 2007

Laura Tarantino, Ph.D.  
Office of Food Additive Safety (HFS-200)  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
5100 Paint Branch Parkway  
College Park, MD 20740-3835

RE: Methylsulfonylmethane (OptiMSM<sup>®</sup>) GRAS Notification

Dear Dr. Tarantino:

In accordance with proposed 21 CFR § 170.36 (a notice of a claim for exemption based on a Generally Recognized As Safe (GRAS) determination) published in the Federal Register (62 FR 18937-18964), I am submitting in triplicate, as the representative of the notifier, Bergstrom Nutritional, 1000 West Eighth Street, Vancouver, WA 98660, a GRAS notification for Methylsulfonylmethane (OptiMSM<sup>®</sup>) for use as a food ingredient, such that the daily consumption of OptiMSM<sup>®</sup> at 4845.6 mg/day is GRAS, under the proposed conditions of use. A GRAS expert panel dossier, setting forth the basis for the GRAS determination, as well as CVs of the members of the GRAS panel, is enclosed.

Best regards,

George A. Burdock, Ph.D., D.A.B.T., F.A.C.N.  
*Diplomate, American Board of Toxicology*  
*Fellow, American College of Nutrition*

## 1. GRAS Exemption Claim

### A. Claim of Exemption from the Requirement for Premarket Approval Pursuant to Proposed 21 CFR § 170.36 (c) (1)

Methylsulfonylmethane (OptiMSM<sup>®</sup>) as a food ingredient has been determined to be Generally Recognized As Safe (GRAS) and; therefore, exempt from the requirement of premarket approval, under the conditions of its intended use as described below. The basis for this finding is described in the following sections.

A. Burdock, Ph.D., D.A.B.T., F.A.C.N.  
*Diplomate, American Board of Toxicology*  
*Fellow, American College of Nutrition*  
Burdock Group  
2001 Ninth Avenue, Suite 301  
Vero Beach, FL 32960

Date 12 July 2007

**000003**

**(i) Name and Address of the Notifier**

Tim Gardner  
Bergstrom Nutrition  
1000 West Eighth Street  
Vancouver, WA 98660

**Agent of Notifier:**

**George A. Burdock, Ph.D., D.A.B.T., F.A.C.N.**

*Diplomate, American Board of Toxicology*

*Fellow, American College of Nutrition*

Burdock Group

2001 Ninth Avenue, Suite 301

Vero Beach, FL 32960

Telephone: 772-562-3900

Facsimile: 772-562-3908

Email: [gburdock@burdockgroup.com](mailto:gburdock@burdockgroup.com)

**(ii) Common Name of the Notified Substance**

The common name of the proprietary formulation of methylsulfonylmethane has been defined as:

OptiMSM<sup>®</sup>

**(iii) Conditions of Use**

OptiMSM<sup>®</sup> may be used as a supplemental source of MSM<sup>1</sup>, at levels up to 4000 ppm in meal supplement and meal replacement foods, fruit smoothie-type drinks, and fruit-flavored thirst quencher-type beverages, and up to 30,000 ppm in food bars, such as granola bars and energy-type bars, provided that food standards of identity do not preclude such use.<sup>2</sup>

**(iv) Basis of GRAS Determination**

Pursuant to 21 CFR § 170.3, methylsulfonylmethane (OptiMSM<sup>®</sup>) has been determined GRAS by scientific procedures for its intended conditions of use. The safety of OptiMSM<sup>®</sup> is supported by preclinical and clinical studies on MSM, and the consumption of MSM in the diet from natural sources. This determination is based on the views of experts who are qualified by scientific training and experience to evaluate the safety of substances used as ingredients in food.

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<sup>1</sup> Methylsulfonylmethane

<sup>2</sup> Title 21 of the US Code of Federal Regulations (CFR), section 170.10, 2006

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## (v) Availability of Information

The data and information that serve as a basis for this GRAS determination are available for the Food and Drug Administration's (FDA) review and copying at a reasonable time at the office of:

**George A. Burdock, Ph.D., D.A.B.T., F.A.C.N.**

*Diplomate, American Board of Toxicology*

*Fellow, American College of Nutrition*

Burdock Group

2001 Ninth Avenue, Suite 301

Vero Beach, FL 32960

Telephone: 772-562-3900

Facsimile: 772-562-3908

E-mail: [gburdock@burdockgroup.com](mailto:gburdock@burdockgroup.com)

Alternatively, copies of data and information can be provided to FDA upon request, by contacting Dr. Burdock.

## 2. Detailed Information On the Identity of the Notified Substance

### A. Identity

MSM is a white, odorless, slightly bitter tasting crystalline substance, which is easily soluble in water. The MSM molecule consists of two methyl groups and two oxygen atoms bound to a sulfur atom, such that sulfur comprises approximately 34% of the elemental weight (Figure 1). The molecular weight of MSM is approximately 94 Daltons. MSM is a metabolite of dimethyl sulfoxide (DMSO) and can be easily prepared through the oxidation of DMSO. Currently, there are two purification methods used in commercial production of MSM as a dietary supplement: crystallization and distillation. The general descriptive characteristics of MSM are presented in Table 1.

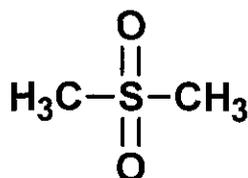


Figure 1. MSM structure

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**Table 1. General description of OptiMSM<sup>®</sup> methylsulfonylmethane**

|                  |  |
|------------------|--|
| Appearance       | White crystalline solid  |
| CAS No.          | 67-71-0  |
| Chemical formula | C <sub>2</sub> H <sub>6</sub> O <sub>2</sub> S   |
| EINECS No        | 200-665-9  |
| Molecular weight | 94.13  |
| Odor             | Odorless   |
| Synonyms         | Dimethyl sulfone, DMSO <sub>2</sub> , Methylsulfonyl methane; MSM, Sulfonylbismethane, Sulfonyl sulfur |

CAS = Chemical Abstracts Service, EINECS = European Inventory of Existing Chemical/Commercial Substances

### Common or Usual Name:

The common name of methylsulfonylmethane (OptiMSM<sup>®</sup>) has been defined as:

OptiMSM<sup>®</sup>

### B. Composition

MSM is produced from a reaction between dimethyl sulfoxide (DMSO) and hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>). In the reaction, the hydrogen peroxide provides an available atom of oxygen to the DMSO, forming MSM. All of the hydrogen peroxide is consumed during the reaction phase of OptiMSM<sup>®</sup> manufacture. Water is formed as a by-product in the reaction. After the reaction, the mixture is sent through a four-stage distillation process, to remove the remaining water and any low-boiling impurities. Controlling the distillation temperatures, vacuum, reflux, and heat input, allows for distillation of pure MSM from any high-boiling impurities or contaminants (*i.e.*, waste). After distillation, the molten product is sent to a prilling chamber to form microprills.<sup>3</sup> Figure 2 illustrates the manufacturing process of OptiMSM<sup>®</sup>. The resulting OptiMSM<sup>®</sup> conforms to the specifications presented in Table 2.

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<sup>3</sup> Microspherical pellet of MSM

### C. Method of Manufacture of OptiMSM®

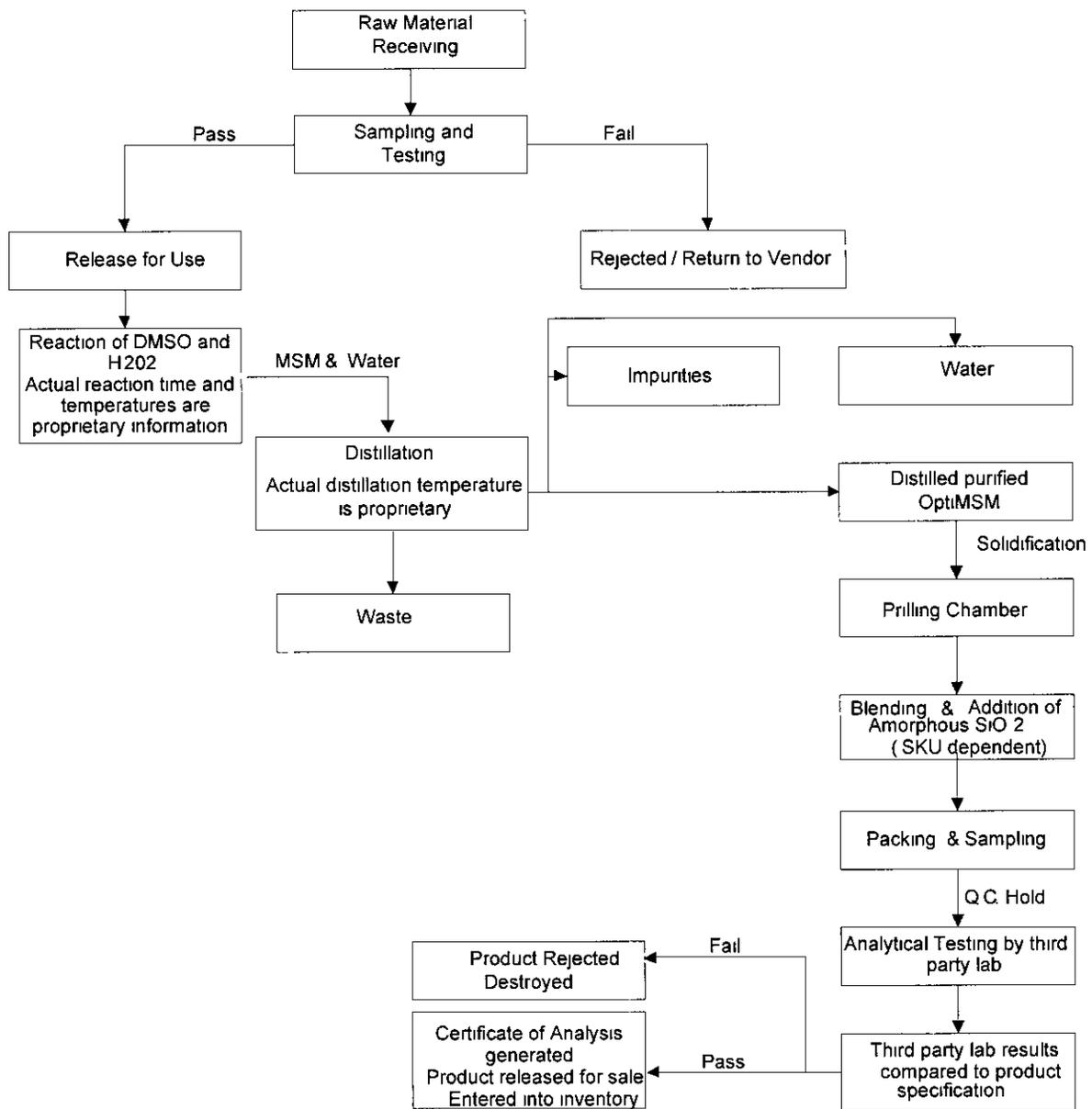


Figure 2. Methysulfonylmethane (OptiMSM®) production scheme

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## D. Specifications for Food Grade OptiMSM®

**Table 2. Specifications of methylsulfonylmethane (OptiMSM®)**

| Analysis                           | Method                            | Specification    | Batch Analysis Results (n = 5) |         |
|------------------------------------|-----------------------------------|------------------|--------------------------------|---------|
|                                    |                                   |                  | Range                          | Average |
| Appearance                         |                                   | White microprill |                                |         |
| MSM (purity)                       | GC-FID*                           | >99.8%           | 99.8 – 100%                    | 99.9%   |
| Melting point                      | USP29/NF24<741>                   | 109.5°C ±1.0°C   | 109.6 – 109.8°C                | 109.7°C |
| Water content                      | USP29/NF24<9211a>                 | <0.1%            | 0.01 – 0.06%                   | 0.034%  |
| Dimethylsulfoxide content          | GC-FID*                           | <0.05%           | <0.05%                         | <0.05%  |
| Amorphous silicon dioxide additive | Added as <i>percent</i> by weight | 0.5%             | 0.5%                           | 0.5%    |
| <b>Heavy metals</b>                |                                   |                  |                                |         |
| Lead                               | EPA 200.8-ICP-MS                  | <0.01 ppm        | <0.01 (BQL)                    | BQL     |
| Arsenic                            | EPA 7060A-GFAA                    | <0.01 ppm        | <0.01 (BQL)                    | BQL     |
| Aluminum                           | EPA 200.8-ICP-MS                  | <1.0 ppm         | <1.0 (BQL)                     | BQL     |
| Mercury                            | EPA 7471A                         | <0.001 ppm       | <0.001 (BQL)                   | BQL     |
| Cadmium                            | EPA 200.8-ICP-MS                  | <0.005 ppm       | <0.005 (BQL)                   | BQL     |
| <b>Microbiological</b>             |                                   |                  |                                |         |
| Aerobic plate count (1 g)**        | AOAC 990.12                       | <10 CFU/g        | <10 CFU/g (BQL)                | BQL     |
| Total Coliforms (1 g)              | AOAC 991.14                       | <10 CFU/g        | <10 CFU/g                      | BQL     |
| Yeasts and molds (1 g)             | AOAC 997.02                       | <10 CFU/g        | <10 CFU/g (BQL)                | BQL     |

AOAC = Association of Official Analytical Chemists, BQL = Below quantifiable limit, CFU = Colony forming units, EPA = Environmental Protection Agency, GC-FID = Gas Chromatography-Flame Ionization Detector, GFAA = Graphite Furnace Atomic Absorption, ICP-MS = Inductively Coupled Plasma Mass Spectrometry, MSM = methylsulfonylmethane, NF = National Formulary, ppm = parts *per* million, USP = United States Pharmacopeia, \*Single third party lab validated, \*\*≥10 CFU/g results will generate microbial ID test *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, with the method limit of quantitation at 0.01%

### 3. Self Limiting Levels of Use

The quantity of OptiMSM® use is self-limited<sup>4</sup> by its bitter taste at high levels.

### 4. Basis of GRAS Determination

The determination that OptiMSM® is GRAS is on the basis of scientific procedures. See attached- DOSSIER IN SUPPORT OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF METHYLSULFONYLMETHANE (OptiMSM®) AS A FOOD INGREDIENT. On the basis of the data and information described in the attached dossier and other publicly available information, there is consensus among experts qualified by scientific training and experience to evaluate the safety of substances added to food, that there is reasonable certainty that OptiMSM® is generally recognized as safe under the intended conditions of use.

<sup>4</sup> The amount consumed limited by unpleasant taste, odor and/or color

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**DOSSIER IN SUPPORT OF THE GENERALLY RECOGNIZED  
AS SAFE (GRAS) STATUS OF OPTIMSM<sup>®</sup>  
(METHYLSULFONYLMETHANE; MSM) AS A FOOD  
INGREDIENT**

**June 20, 2007**

**Panel Members**

Joseph F. Borzelleca, Ph.D., F.A.T.S.

I. Glenn Sipes, Ph.D., F.A.T.S.

Kendall B. Wallace, Ph.D., D.A.B.T., F.A.T.S.

2001 9th Avenue, Suite 301 • Vero Beach, FL 32960 • Phone: 772.562.3900 • Fax: 772.562.3908

1-888-6-BURDOCK

[www.burdockgroup.com](http://www.burdockgroup.com)

**000009**

**DOSSIER IN SUPPORT OF THE GENERALLY RECOGNIZED AS SAFE (GRAS)  
STATUS OF OPTIMSM® (METHYLSULFONYLMETHANE; MSM) AS A FOOD  
INGREDIENT**

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# DOSSIER IN SUPPORT OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF OPTIMSM<sup>®</sup> (METHYLSULFONYLMETHANE; MSM) AS A FOOD INGREDIENT

## 1. INTRODUCTION

The undersigned, an independent panel of recognized experts (hereafter referred to as the Expert Panel)<sup>1</sup>, qualified by their scientific training and relevant national and international experience to evaluate the safety of food and food ingredients, was convened by Bergstrom Nutrition, Vancouver, WA, to determine the Generally Recognized As Safe (GRAS) status of OptiMSM<sup>®</sup> (methylsulfonylmethane; MSM; dimethyl sulfone)<sup>2</sup> as a food ingredient at levels up to 4000 ppm in meal supplement and meal replacement foods, fruit smoothie-type drinks, flavored thirst quencher-type beverages, and up to 30,000 ppm in food bars, such as granola and energy-type bars. A comprehensive search of the scientific literature for safety and toxicity information, specifically on methylsulfonylmethane, and its parent compound, dimethyl sulfoxide (DMSO) in general, was conducted through December 2006, by Burdock Group and made available to the Expert Panel. The Expert Panel independently and critically evaluated materials submitted by Bergstrom Nutrition and other materials deemed appropriate or necessary.

Following an independent, critical evaluation of the data and information, the Expert Panel concluded that methylsulfonylmethane, meeting appropriate food grade specifications and manufactured in compliance with current Good Manufacturing Practices, is Generally Recognized As Safe (GRAS) based on scientific procedures for the conditions of intended use described herein.

### 1.1. Historical perspective

Methylsulfonylmethane (MSM; CAS No. 67-71-0) belongs to a family of organic sulfur-containing compounds that are widely distributed in the food chains of terrestrial and marine life.

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<sup>1</sup>Modeled after that described in section 201(s) of the Federal Food, Drug, and Cosmetic Act, As Amended. See also attachments (*curriculum vitae*) documenting the expertise of the Panel members

<sup>2</sup> OptiMSM<sup>®</sup> is a licensed brand of distilled MSM, produced in the U S A in a National Nutritional Foods Association (NNFA) GMP-certified facility.

MSM is a volatile component in the sulfur cycle (Lovelock *et al* , 1972). A precursor of MSM, dimethyl sulfide (DMS), is formed initially by ocean plankton and released into the atmosphere. Dimethyl sulfide in the atmosphere interacts with ozone and sunlight, leading to the formation of dimethyl sulfoxide (DMSO) and MSM. As DMSO and MSM are soluble in water, they return to earth via rainfall. Central equatorial Pacific rainwater was reported to contain 1 to 10 µg MSM/l, while air samples from various areas in Miami, FL contained approximately 2 to 6 ng MSM/m<sup>3</sup> (Harvey and Lang, 1986). MSM can be taken up by plants and incorporated into their structure, and occurs naturally in a variety of fruits, vegetables, grains, animals and humans, in at least trace amounts (Pearson *et al* , 1981). MSM is also found at high levels in nonedible plants such as horsetail and certain species of algae. MSM is considered a source of sulfur for the formation of the amino acids, cysteine and methionine. The biological role of MSM, if any, remains to be fully explored (Hendler and Rorvik, 2001).

## 1.2. Description, occurrence, manufacturing and specifications

MSM is a white, odorless, slightly bitter tasting crystalline substance, and it is easily soluble in water. The MSM molecule consists of two methyl groups and two oxygen atoms bound to a sulfur atom, such that sulfur comprises approximately 34% of the elemental weight (Figure 1). The molecular weight of MSM is approximately 94 Daltons. MSM is a metabolite of DMSO and can be easily prepared through the oxidation of DMSO. Currently, there are two purification methods used in commercial production of MSM as a dietary supplement: crystallization and distillation. The general descriptive characteristics of MSM are presented in Table 1.

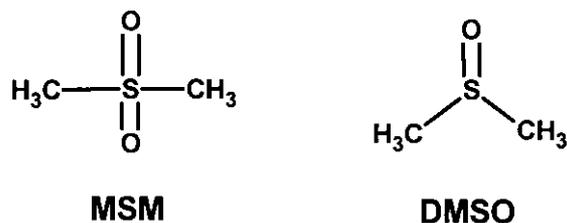


Figure 1. Chemical structure of MSM and DMSO

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**Table 1. General description of OptiMSM® MSM**

|                  |   |
|------------------|---|
| Appearance       | White crystalline solid   |
| CAS No           | 67-71-0   |
| Chemical formula | C <sub>2</sub> H <sub>6</sub> O <sub>2</sub> S  |
| EINECS No.       | 200-665-9   |
| Molecular weight | 94.13   |
| Odor             | Odorless  |
| Synonyms         | Dimethyl sulfone, DMSO <sub>2</sub> ,<br>Methylsulfonyl methane; MSM;<br>Sulfonylbismethane, Sulfonyl<br>sulfur |

CAS = Chemical Abstracts Service, EINECS = European Inventory of Existing Chemical/Commercial Substances

### 1.3. Occurrence

Sulfur is the third most abundant mineral in the human body and the sixth most abundant mineral in breast milk, based on a *percentage-of-body-weight* basis. The most abundant source of MSM in the human diet is cow's milk, which contains approximately 3.3 to 8.2 ppm MSM (Williams *et al* , 1966a). MSM is found in small amounts in meats and dairy, fruits (apples and raspberries), vegetables (tomatoes, Swiss chard, asparagus, beets, cabbage, and cucumbers), grains (corn, alfalfa and oats), and beverages (coffee, tea and beer). MSM is found at higher levels in non-edible plants, such as horsetail. By employing GC-MS,<sup>3</sup> Imanaka *et al* (1985) identified presence of MSM in cow's milk, and chicken meat and liver. Foods containing MSM are presented in APPENDIX I.

MSM is also endogenous to humans, with a circulating plasma concentration of MSM in adult human subjects that may range from 0.2 to 0.5 ppm (Engelke *et al* , 2005). <sup>1</sup>H-NMR<sup>4</sup> spectroscopy was utilized to confirm the presence of MSM in cerebrospinal fluid and plasma samples at concentrations that ranged between 0 and 25 μmol/l (2.4 μg/ml) in healthy subjects, and approximately 50 μmol/l in patients with severe methionine adenosyltransferase I/III (MAT I/III) deficiency (Engelke *et al.*, 2005). Engelke *et al.* (2005) concluded that MSM is commonly present in human blood and cerebrospinal fluid, and is derived from dietary sources, bacterial metabolism, and endogenous human methanethiol metabolism. Other research found MSM to be one of approximately 300 substances in the volatile fraction of human urine (Zlatkis and Liebich,

<sup>3</sup> Gas Chromatography Coupled Mass Spectroscopy

<sup>4</sup> Hydrogen Nuclear magnetic Resonance

1971). Approximately 4-11 mg of MSM is normally excreted daily in urine (Williams *et al* , 1966a).

#### 1.4. Manufacturing process

MSM is produced from a reaction between dimethyl sulfoxide (DMSO) and hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>). In the reaction, the hydrogen peroxide provides an available atom of oxygen to the DMSO, forming MSM. All of the hydrogen peroxide is consumed during the reaction phase of OptiMSM<sup>®</sup> manufacture. Water is formed as a by-product in the reaction. After the reaction, the mixture is sent through a four-stage distillation process, to remove the remaining water and any low-boiling impurities. Controlling the distillation temperatures, vacuum, reflux, and heat input, allows for distillation of pure MSM from any high-boiling impurities or contaminants (i.e., waste). After distillation, the molten product is sent to a prilling chamber to form microprills.<sup>5</sup> The final product is packaged in fiber boxes and fiber drums, each with a food grade 4-mil polyethylene liner or super sacks with a 3-mil polyethylene liner. A sample of the finished product is taken during the packaging process. A portion of this sample is kept as a historical retain and a portion is sent to an independent third party analytical laboratory for testing. Each lot is subjected to rigorous physiochemical, microbiological, and metals analysis. The third party laboratory issues an analytical report to Bergstrom Nutrition that is compared to pre-established specifications (Table 2). If the analytical results fall within the specifications, a certificate of analysis is generated and the lot of OptiMSM<sup>®</sup> is released by Quality Control and entered into inventory. If the analytical results fail to fall within the pre-established specifications, the lot of OptiMSM<sup>®</sup> is rejected and destroyed. Figure 2 illustrates the manufacturing process of OptiMSM<sup>®</sup>.

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<sup>5</sup> Microspherical pellet of MSM

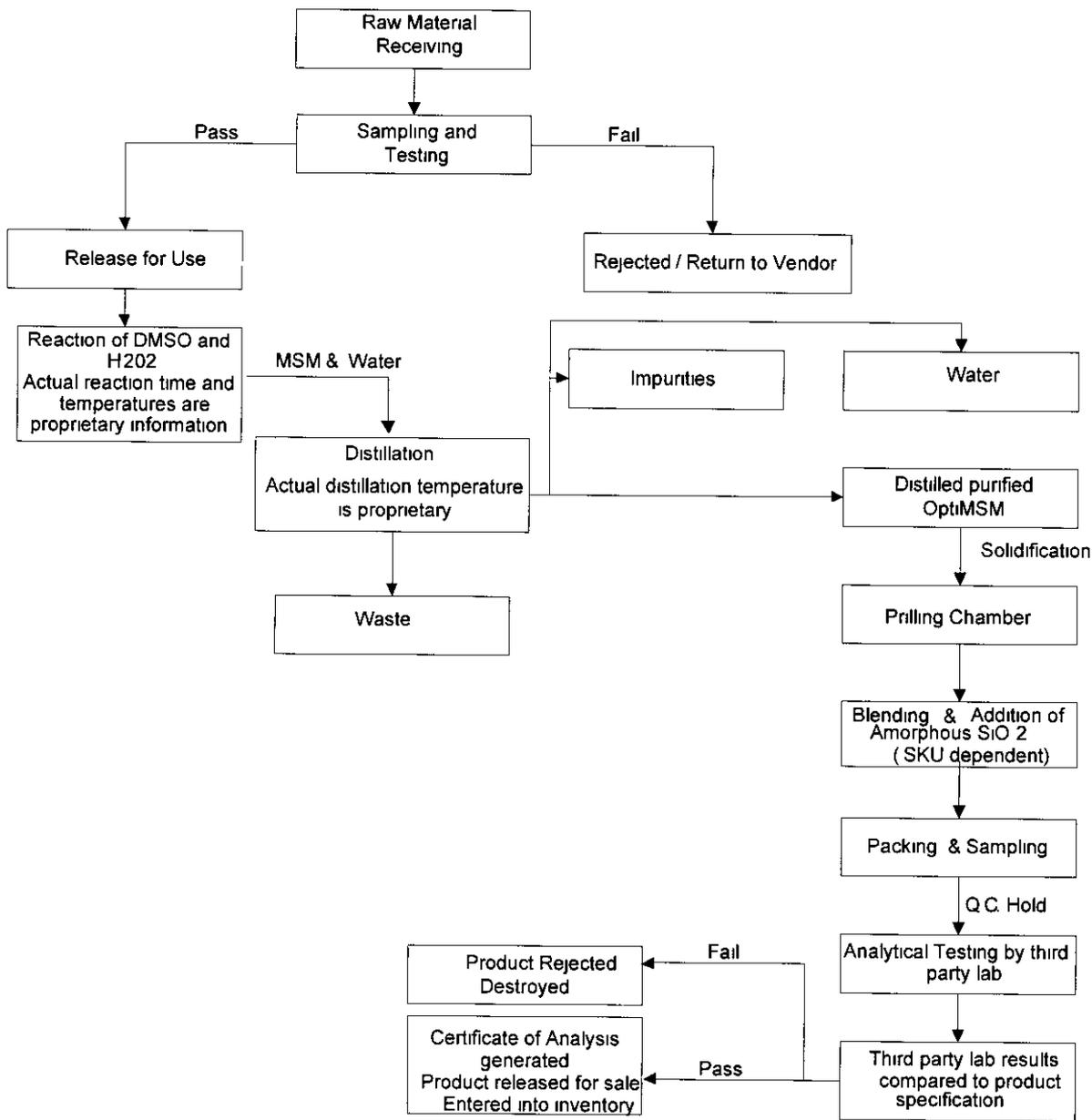


Figure 2. OptiMSM<sup>®</sup> manufacturing process (Bergstrom Nutrition, 2006a)

### 1.5. Specifications

The specifications provided by Bergstrom Nutrition for OptiMSM<sup>®</sup> are presented in Table 2.

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**Table 2. Specifications of OptiMSM® (Bergstrom Nutrition, 2006)**

| Analysis                           | Method                            | Specification    | Batch Analysis Results (n = 5) |         |
|------------------------------------|-----------------------------------|------------------|--------------------------------|---------|
|                                    |                                   |                  | Range                          | Average |
| Appearance                         |                                   | White microprill |                                |         |
| MSM (purity)                       | GC-FID*                           | >99.8%           | 99.8 – 100%                    | 99.9%   |
| Melting point                      | USP29/NF24<741>                   | 109.5°C ±1.0°C   | 109.6 – 109.8°C                | 109.7°C |
| Water content                      | USP29/NF24<9211a>                 | <0.1%            | 0.01 – 0.06%                   | 0.034%  |
| Dimethylsulfoxide content          | GC-FID*                           | <0.05%           | <0.05%                         | <0.05%  |
| Amorphous silicon dioxide additive | Added as <i>percent</i> by weight | 0.5%             | 0.5%                           | 0.5%    |
| <b>Heavy metals</b>                |                                   |                  |                                |         |
| Lead                               | EPA 200.8-ICP-MS                  | <0.01 ppm        | <0.01 (BQL)                    | BQL     |
| Arsenic                            | EPA 7060A-GFAA                    | <0.01 ppm        | <0.01 (BQL)                    | BQL     |
| Aluminum                           | EPA 200.8-ICP-MS                  | <1.0 ppm         | <1.0 (BQL)                     | BQL     |
| Mercury                            | EPA 7471A                         | <0.001 ppm       | <0.001 (BQL)                   | BQL     |
| Cadmium                            | EPA 200.8-ICP-MS                  | <0.005 ppm       | <0.005 (BQL)                   | BQL     |
| <b>Microbiological</b>             |                                   |                  |                                |         |
| Aerobic plate count (1 g)**        | AOAC 990.12                       | <10 CFU/g        | <10 CFU/g (BQL)                | BQL     |
| Total Coliforms (1 g)              | AOAC 991.14                       | <10 CFU/g        | <10 CFU/g                      | BQL     |
| Yeasts and molds (1 g)             | AOAC 997.02                       | <10 CFU/g        | <10 CFU/g (BQL)                | BQL     |

AOAC = Association of Official Analytical Chemists, BQL = Below quantifiable limit, CFU = Colony forming units, EPA = Environmental Protection Agency, GC-FID = Gas Chromatography-Flame Ionization Detector, GFAA = Graphite Furnace Atomic Absorption, ICP-MS = Inductively Coupled Plasma Mass Spectrometry, MSM = methylsulfonylmethane, ppm = parts per million, USP = United States Pharmacopeia, \*Single third party lab validated, \*\*≥10 CFU/g results will generate microbial ID test *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, with the method limit of quantitation at 0.01%

## 1.6. Approved and other Uses

MSM has been marketed as a dietary supplement worldwide. In the USA, MSM is regulated under the Dietary Supplement Health and Education Act (DSHEA) of 1994. Currently, addition of MSM to food is not regulated by FDA as a food additive (i.e., it is not presented as such in the Code of Federal Regulations), nor has it been the subject of any GRAS notifications received by the Agency as evidenced by the current ‘Summary of all GRAS Notices’ List.<sup>6</sup>

## 1.7. Proposed uses

Bergstrom Nutrition proposes to use OptiMSM® as a food ingredient, at levels up to 4,000 ppm in meal supplement and meal replacement foods, fruit smoothie-type drinks, and fruit-flavored thirst quencher-type beverages, and up to 30,000 ppm in food bars, such as granola

<sup>6</sup> <http://www.cfsan.fda.gov/~rdb/opa-gras.html>, site visited January 8, 2007

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bars and energy-type bars (Table 3). OptiMSM<sup>®</sup> will be added to foods for those individuals that want additional MSM in their diet. The bitter taste of OptiMSM<sup>®</sup> makes its use self-limiting. The proposed use levels of OptiMSM<sup>®</sup> are presented in Table 3.

**Table 3. Proposed use levels of MSM**

| Description  | Concentration<br>(mg/g) |
|--|-------------------------|
| FRUIT SMOOTHIE DRINK, W/ FRUIT AND DAIRY PRODUCTS      | 4                       |
| MEAL SUPPLEMENT / REPLACEMENT, PREPARED, RTD           | 4                       |
| MEAL REPLACEMENT, PROTEIN, MILK BASED, FRUIT JUICE MIX | 4                       |
| MEAL REPLACEMENT, PROTEIN TYPE, MILK-BASE, POWDER      | 4                       |
| HIGH PROTEIN BAR, CANDY-LIKE, SOY & MILK BASE          | 4                       |
| MEAL REPLACEMENT/SUPPLEMENT, LIQUID, HI PROTEIN        | 4                       |
| GRANOLA BAR W/ OATS, SUGAR, RAISINS, COCONUT           | 30                      |
| GRANOLA BAR, OATS, FRUIT, NUTS, LOWFAT                 | 30                      |
| GRANOLA BAR, NONFAT                                    | 30                      |
| GRANOLA BAR W/ PEANUTS, OATS, SUGAR, WHEAT GERM        | 30                      |
| GRANOLA BAR, HIGH FIBER, YOGURT COATING, NOT CHOC      | 30                      |
| POWERBAR (FORTIFIED HIGH ENERGY BAR)                   | 30                      |
| FRUIT-FLAVORED THIRST QUENCHER BEVERAGE, LOW CAL       | 4                       |
| FRUIT-FLAVORED THIRST QUENCHER BEVERAGE                | 4                       |

### 1.8. Estimated daily intake from the proposed use

A consumption analysis database<sup>7</sup> was analyzed to determine a hypothetical maximum daily ingestion of OptiMSM<sup>®</sup> when added to specific foods (Table 3). This nationwide dietary intake survey was conducted during 2001-2002, and was comprised of two days of data that was collected for all respondents in the food survey ( $n = 9,701$  individuals). Comprehensive and detailed questions were posed to the participants, and the results were used to code individual foods and portion sizes consumed. The results were weighted to place more strength on foods that were consumed by more individuals, and extrapolated to the US population. Food and beverage categories for the addition of OptiMSM<sup>®</sup> were designated by Bergstrom Nutrition, and are identified in Table 3 and in APPENDIX II. All categories designated by Bergstrom Nutrition have been utilized in the calculations as appropriate; however, certain categories designated by

<sup>7</sup> HHS What We Eat in America, National Health and Nutrition Examination Survey (NHANES) 2001-2002. *US Department of Agriculture, US Department of Health and Human Services*  
[http://www.ars.usda.gov/Services/docs.htm?docid=7674&pf=1&cg\\_id=0](http://www.ars.usda.gov/Services/docs.htm?docid=7674&pf=1&cg_id=0), site visited January 9, 2007

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Bergstrom Nutrition may contain foods or beverages under which a standard of identity exists, prohibiting the addition of ingredients (i.e., OptiMSM<sup>®</sup>) not identified under statutes for the standard of identity for that food.

The maximum concentration of OptiMSM<sup>®</sup> suggested was utilized in the consumption analysis, to ensure that the estimate includes any individuals who consume larger amounts of the foods. Although the ingredient may be added to only one part of a complex food mixture (i.e., “beef with barbeque sauce”), the consumption of the total food was utilized in the consumption analysis calculations. Currently, there is not a method to determine the *percentage* of a single component of a complex food mixture, as several foods are made in the home and components are added in various ratios. Therefore, complex food mixtures were not utilized in this consumption analysis. The resulting mean consumption (eater’s only) of OptiMSM<sup>®</sup> in the selected food codes (APPENDIX III) is 1935.7 mg/day (29.6 mg/kg/day),<sup>8</sup> and the 90<sup>th</sup> percentile consumption (eater’s only) is 3840 mg/day (57.2 mg/kg/day).

### 1.9. Other production and exposure reports

MSM is found in small amounts in various foods, although not all sources have been quantified. Foods containing MSM are presented in APPENDIX I. The consumption of MSM occurring naturally was determined utilizing a consumption analysis database<sup>9</sup> and the concentrations noted in APPENDIX I, with a mean consumption of MSM from natural sources at 2.3 mg/day, and a 90<sup>th</sup> percentile consumption at 5.6 mg/day (Table 4).

A possible source of MSM in the diet also comes from consumption of dietary supplements. MSM consumption from dietary supplements is difficult to determine from currently available data. The 1987 National Health Interview Survey identified that 51.1% of the adults aged 19-99 years in the US consumed a vitamin/mineral supplement in the past year, but that only 23.1% did so daily (Subar and Block, 1990). Multivitamins were the most commonly

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<sup>8</sup> Age-specific body weight distributions were utilized in the determination of the mg/kg/day value, based on those respondents that consumed the food, and therefore the average body weight used in the calculations was not a single, standard value (Portier *et al* , 2007).

<sup>9</sup> Source. HHS What We Eat in America, National Health and Nutrition Examination Survey (NHANES) 2001-2002. *US Department of Agriculture, US Department of Health and Human Services.*  
[http://www.ars.usda.gov/Services/docs.htm?docid=7674&pf=1&cg\\_id=0](http://www.ars.usda.gov/Services/docs.htm?docid=7674&pf=1&cg_id=0), site visited January 9, 2007

consumed supplement at that time. MSM is available from many different companies as a dietary supplement. An average daily consumption of MSM from dietary supplements is typically found at 1000 mg MSM/capsule, with the suggested daily intake at one capsule per day. Since there are no available statistical data on consumption of dietary supplements that are a source of MSM, we have used the levels reported in labeling as a basis for estimating consumption ranges.<sup>7</sup> Thus, the typical potential theoretical MSM consumption from dietary supplements is likely to be equal to 1000 mg. This estimate is added to those in Table 4 to arrive at the total potential theoretical background consumption of MSM from both conventional food and dietary supplements.

**Table 4. Potential total MSM intake for individuals consuming selected supplemented foods and dietary supplements**

| MSM Intake from:   | Per User (mg/day) |                             |
|--|-------------------|-----------------------------|
|  | Mean              | 90 <sup>th</sup> Percentile |
| Natural sources  | 2.3               | 5.6                         |
| Possible maximum consumption with OptiMSM <sup>®</sup> as an added food ingredient | 1935.7            | 3840.0                      |
| Potential dietary supplement use*  | 1000              | 1000                        |
| <b>Potential total MSM from all sources (food + dietary supplements)</b>           | <b>2938.0</b>     | <b>4845.6</b>               |

\*Recommended daily dose per label suggestion from the typical maximum intake via dietary supplement use

## 2. BIOLOGICAL DATA

### 2.1. Absorption, metabolism and excretion

Otsuki *et al.* (2002) investigated the metabolism of MSM in rats using a <sup>35</sup>S radioisotope tracer method. Five week old, male Wistar rats (*n* = four per group) were fed standardized diets for 2, 43, 83, and 96 days (Groups: G1, G2, G3, and G4, respectively) followed by a seven-day oral gavage administration (once per day) of <sup>35</sup>S-MSM at a dose level of 470 mg/kg/day. Urine and feces were collected daily for seven days and processed for radioactivity levels. At the end of seven days, tissues were collected for the determination of radioactivity, and included blood, bone, brain, fat, GI tract, hair, heart, kidney, liver, muscle, nail, pancreas, skin, spleen, and testis. The total radioactivity yield in urine, feces, and tissues for the groups G1, G2, G3, and G4 were 100.6, 94.9, 89.4 and 68.5% of the administered <sup>35</sup>S, respectively. The *percentage* of administered <sup>35</sup>S radioactivity in tissues was greater in younger rats, or the group fed the standardized diet for shorter periods of time, compared to those fed for longer periods. In the

animals fed for longer periods and treated with  $^{35}\text{S}$ -MSM, the total amount of radioactivity was not accounted for, and investigators did not comment on this inconsistency. The majority of the  $^{35}\text{S}$  radioactivity administered daily was excreted into the urine (~70%) and feces (~10%). Daily total urinary and fecal excretion of  $^{35}\text{S}$  radioactivity in each group was similar during the seven-day administration period, indicating that the rate of MSM metabolism was relatively high. The  $^{35}\text{S}$  concentrations in the blood, spleen and hair tended to be the highest, but the radioactivity per gram of tissue was similar in other tissues. The *percent* incorporation of  $^{35}\text{S}$  into tissues was much lower in rats treated with  $^{35}\text{S}$ -MSM, as compared to rats treated with  $^{35}\text{S}$ –methionine using an identical protocol. Results from this study demonstrate that over 80% of the daily administered  $^{35}\text{S}$ -MSM was excreted within the same day (Otsuki *et al.*, 2002).

Pratt *et al.* (2001) investigated absorption of MSM in horses. In this study, six horses were used (two control and four treated). In the treatment group, on Days 1 to 5 of the trial, each horse received 0.5 mCi (18,500 kBq) of radiolabeled  $^{35}\text{S}$ -MSM (applied on a piece of bread and fed with molasses). On Days 6 to 9, 20 g of “cold”, i.e., unlabeled MSM was given to the four treatment horses. Urine and feces were collected twice daily throughout the trial. On Days 0, 5 and 9, blood and synovial fluids were collected. The investigators were not able to obtain sufficient amount of synovial fluid from some horses. In the treatment group, radiolabeled sulfur was detected in both urine and feces by Day 1, with peak excretion around Day 5. A decreased level of radioactivity was noted on Day 9. The investigators determined that approximately 55% of the radiolabeled sulfur from MSM was absorbed by the horses.

In a preliminary study, Wilcox (2005) determined the pharmacokinetics of MSM in rats following oral and intravenous administration. Sprague-Dawley male rats ( $n =$  five per group) were administered a single oral or intravenous dose of 500 mg MSM/kg. Following administration of MSM, blood was collected at 0, 0.08, 0.25, 0.5, 1, 2, 4, 6, 8, 24, 48, and 72 hours and processed for determination of MSM levels by gas chromatography. The results indicated the calculated bioavailability of MSM as being greater than 100%, with pharmacokinetic data from this study presented in Table 5. Data analysis indicated that the maximum plasma MSM concentration from oral administration was higher than the maximum plasma concentration immediately following the i.v. bolus dose. This is contrary to classical

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pharmacokinetic analysis, and placed the data in suspect. In addition, the animals in the orally-dosed group showed greater variability in the calculated area under curve from zero time to infinity ( $AUC_{0-inf}$ ), when compared to animals receiving intravenous MSM. Finally, in the orally dosed MSM group, two of the five rats showed half-lives of 16 and 18 hours, while the other three showed an approximate half-life of seven hours, and therefore, a reliable half-life from this study could not be reported.

Due to the limitations noted in the study by Wilcox (2005), an additional pharmacokinetic profile and distribution of radiolabeled MSM was evaluated in rats (Magnuson *et al.*, 2006a). Male Sprague-Dawley rats were administered a single oral dose of  $^{35}\text{S}$ -MSM (500 mg/kg), with blood radioactivity levels determined at 0, 0.25, 0.5, 1, 2, 4, 8, 12, 24, and 48 hours post ingestion. In addition, tissue radioactivity levels were measured at 48 and 120 hours, and urine and fecal  $^{35}\text{S}$  levels measured for the -24 to 0 time period (predose period), and every 24-hour time period after  $^{35}\text{S}$ -MSM administration, for up to 120 hours.

Oral  $^{35}\text{S}$ -MSM was rapidly and efficiently absorbed, with a mean time to peak concentration ( $T_{max}$ ) of 2.1 hour, a peak concentration ( $C_{max}$ ) of 622  $\mu\text{g/ml}$ , and a calculated area under the curve from zero to infinity ( $AUC_{0-inf}$ ) of 15,124  $\mu\text{g/ml/hr}$ , as indicated in Table 5 (Magnuson *et al.*, 2006a). The half-life of MSM was calculated at 12.2 hours. Soft tissue radioactivity distribution indicated a homogeneous distribution throughout the body, with lower  $^{35}\text{S}$  concentrations in the skin and bone. Approximately 85.5% of  $^{35}\text{S}$  was recovered in the urine after 120 hours, while only 3% was located in the feces. No quantifiable levels of radioactivity were found in any tissues 120 hours after  $^{35}\text{S}$ -MSM administration, indicating complete elimination. These results indicate that MSM is rapidly absorbed, well distributed, and completely excreted.

**Table 5. Pharmacokinetic parameters following oral administration of 500 mg/kg MSM**

| Parameter     | Wilcox (2005)              | Magnuson <i>et al.</i> (2006a) |
|---------------|----------------------------|--------------------------------|
| Half-life     | 11.4 hours                 | 12.2 hours                     |
| $T_{max}$     | 1.9 hours                  | 2.1 hours                      |
| $C_{max}$     | 635.9 $\mu\text{g/ml}$     | 622 $\mu\text{g/ml}$           |
| $AUC_{0-inf}$ | 11,893 $\mu\text{g/ml/hr}$ | 15,124 $\mu\text{g/ml/hr}$     |

$AUC_{0-inf}$  = calculated area under the curve from time zero to infinity,  $C_{max}$  = peak concentration,  $T_{max}$  = time to peak concentration

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Richmond (1986) investigated the incorporation of sulfur from MSM into guinea pig serum proteins as peptidyl methionine and cysteine. Male guinea pigs (3/group) were gavaged with 0.0075, 0.075 and 0.75  $\mu\text{Ci } ^{35}\text{S-MSM/g}$  (1.73, 17.3 and 173  $\mu\text{moles of MSM/g of guinea pig}$ ). Six hours after administration of the radioactive compound, a single intraperitoneal injection of unlabeled MSM (corresponding to ten times the micromole radioactivity of MSM) was administered. Blood, urine and fecal samples were collected for radioactivity determinations and incorporations in serum proteins. The majority of the radioactivity was excreted in the urine (chemical species not reported). No radioactivity was detected in feces. For the respective dose groups, approximately 1.9, 1.3 and 2.8% of the  $^{35}\text{S}$  given was found in serum and 0.74, 0.14 and 0.022% was incorporated into serum proteins. Serum methionine and cysteine residues were found to be radiolabeled, suggesting that sulfur from  $^{35}\text{S-MSM}$  was incorporated in these amino acids. The authors speculated that there was rate limiting step in incorporation but did not elaborate on this.

MSM has been reported as an oxidized metabolite of DMSO *in vivo*. Pharmacokinetic analyses of DMSO have been studied in humans and animals after a variety of dosing routes. DMSO is rapidly absorbed and there appears to be general distribution of DMSO and/or its metabolites in all tissues, reaching peak levels within two to six hours. Serum levels were lower following cutaneous administration compared to oral or intravenous routes. Available evidence suggests that DMSO is metabolized by a simple oxidation-reduction system (Wood and Jacob, 1968). DMSO via subcutaneous, intravenous, or oral administration is metabolized to MSM and DMS. Approximately 3 to 6% of DMSO is exhaled as DMS. In humans, approximately 71% of DMSO was recovered in urine following oral administration. In human urinary excretion studies, administered DMSO followed a linear excretion rate, while urinary excretion of the metabolite MSM was delayed after DMSO dosing, but followed an exponential rate thereafter. This may be related to the differences in renal clearance of these two moieties or that MSM was bound to tissues and slowly liberated (Hucker *et al* , 1967; Wood, 1971).

In a human clinical study, Egorin *et al* (1998) investigated plasma concentrations and pharmacokinetics of DMSO and its metabolites that result from delivery of cryopreserved myeloid stem-cell preparations. In this study, ten patients (sex or age not given) underwent autologous transplants with stem cells, cryopreserved in 10% DMSO. The infused DMSO

concentration in stem cells ranged between 254 to 824 mmol. The infusion lasted for 20 and 120 minutes. Plasma concentrations of MSM increased during the first 24 hours, plateaued at 4.4 mmol/l and remained there for 48 hours (last sample drawn). Urinary excretion of MSM accounted for 4% of the administered dose.

Layman and Jacob (1985) investigated the absorption and excretion of DMSO in Rhesus monkeys given daily oral doses of 3 g DMSO/kg for 14 days. MSM, as a major metabolite of DMSO, appeared in blood within two hours of the first oral dose and reached a steady state after four days of administration. Following the last dose, MSM was cleared from blood within approximately 120 hours. The half-life of MSM was determined as 38 hours. Approximately 16% of the administered DMSO was excreted as MSM. Urinary elimination of unmetabolized DMSO was approximately 60%.

Ogata *et al* (1979) reported that intraperitoneal administration of DMSO at a dose level of 0.55 g/kg to female Wistar rats resulted in urinary excretion of approximately 75% as DMSO and 14% as MSM during eight days. The combined excretion of DMSO and MSM for Day one was ~78%. On Day 2, the combined excretion was ~9% and thereafter the excretion was below 1%.

Williams *et al.* (1966b) investigated the excretion and metabolism of dimethyl sulfide (DMS), DMSO and MSM in rabbits, by chromatographic determinations of urine samples. Female New Zealand rabbits (number not specified) were subcutaneously administered <sup>14</sup>C-MSM at a dose of 1.1 g/day (3 ml of a 0.364 g/ml aqueous solution) for four days. In additional investigations, 1 ml of DMSO (50% solution) was administered subcutaneously to rabbits for five days. On the second day, <sup>14</sup>C-DMSO was substituted for the non-radioactive material. The dose of DMS could not be quantified. In the <sup>14</sup>C-MSM study, 76% of the dose was recovered as MSM over a collection period of 20 days. On Days 6, 9 and 12 approximately 42, 44 and 9% of the radioactivity was recovered in the urine, respectively, indicating that most of the injected MSM (i.e., 95%) was excreted by Day 12. The radioactivity excreted in the urine was all accounted for as MSM and no DMSO was detected. MSM was also found in the urine of the untreated rabbit. In rabbits administered DMSO, the urine was collected for six days, pooled, extracted, and analyzed for DMSO and MSM concentrations. Radiolabeled DMSO

(approximately 35% of the initial DMSO dose) and MSM (at approximately 10% of the DMSO dose) were detected in the pooled urine samples. The results of this study suggest that subcutaneously administered MSM is absorbed into the blood and excreted in urine, and administered DMSO is metabolized in the body to form MSM.

Hucker *et al.* (1966) investigated excretion of DMSO and MSM in rats. In the MSM investigations, rats (sex, strain, number not specified) were intraperitoneally injected with 21 mg/kg of <sup>35</sup>S-MSM and urinary excretion of MSM was determined; 64% of the dose was excreted as MSM within 24 hours. Additional details of the study were not given. In the DMSO investigations, a single intraperitoneal administration of 0.5 mg <sup>35</sup>S-DMSO/kg to 24 rats (sex, strain not specified) resulted in urinary excretion of 15% of the dose as MSM. In this same report, results of human excretion of MSM following DMSO administration were described. One human subject (sex, age not mentioned) given 21 g of DMSO by the oral route excreted approximately 3% of the dose in urine (24 hours) as MSM.

In another study, oral administration of DMSO at a dose of 1 g/kg to six human subjects resulted in peak serum concentrations of MSM after 72-96 hours (Hucker *et al.*, 1967). Approximately 51% of the DMSO was excreted in the urine unchanged over the first 120 hours, and up to 22% was excreted as MSM. Hucker *et al.* (1967) also reported results of two male subjects treated with a single dermal application of <sup>35</sup>S-DMSO at a dose of 1 g/kg (70% DMSO in water; 125 µCi total dose). Following DMSO application, serum levels of MSM peaked at 36-72 hours, with a half-life of 60-70 hours. At the end of 13 days, MSM was marginally detectable in the serum. Urinary excretion of MSM was noted at eight hours and continued for 19 days. Approximately 13% of the administered dose was excreted as DMSO and 19% as MSM.

In summary, the pharmacokinetics of MSM and DMSO, the parent compound of MSM, have been extensively studied. Gavage administration of radiolabeled <sup>35</sup>S-MSM to rats resulted in rapid absorption into blood and subsequent excretion in urine. Radioactivity was noted in serum proteins, particularly in the amino acids, cysteine and methionine. These observations suggest that the sulfur moiety from MSM can enter the amino acid pool. In another study, subcutaneous administration of <sup>35</sup>S-MSM (1.1 g/day for four days) resulted in slow excretion of the radioactivity over a period of 20 days with the majority excreted by the 12<sup>th</sup> day. Studies with

dimethyl sulfoxide in Rhesus monkeys suggest that DMSO is rapidly metabolized to MSM, with a blood half-life for MSM of 38 hours. The blood half-life of MSM following DMSO administration appears different from that of following direct MSM administration. The half-life of MSM following direct MSM administration to rats is approximately twelve hours. The available studies indicate that a fraction of DMSO is metabolized to MSM in the body and then excreted.

### **3. TOXICOLOGICAL STUDIES**

#### **3.1. Acute and short-term studies**

In an acute toxicity study, Sprague-Dawley rats (10 per sex) were administered a single dose of 2000 mg MSM/kg by gavage (Horváth *et al.*, 2002). Rats were observed twice daily for clinical signs and mortality. On Day 15, all surviving rats were euthanized. Necropsy examination included a thorough inspection of all external surfaces, organs and orifices. No mortality, adverse effects, clinical signs of toxicity, or differences in weight gain were noted. This study suggests that the LD<sub>50</sub> of MSM in rats is greater than 2000 mg/kg body weight.

Yu and Peano (2000a; 2000b) investigated the acute toxicity of MSM in rats and mice.<sup>10</sup> In these studies, Crl:CD(SD)BR rats and CD1(ICR)BR mice (five/sex/group) were administered a single oral dose of 2000 mg MSM/kg. No deaths or signs of toxicity were observed in rats or mice. The results of these studies suggest that the LD<sub>50</sub> of MSM in rats and mice is greater than 2000 mg/kg.

Hixson (1958) administered MSM by gavage to rats (sex and strain not specified, ten per group) at doses of 2000 to 20,000 mg per kilogram body weight and observed for six days for signs of toxicity. There were no deaths at any dose. Histopathological analysis of one animal from the high dose and control groups did not find any significant treatment-related changes.

Schoenig *et al.* (1968) administered a single oral (gavage) dose of 10,300 or 15,400 mg MSM/kg body weight to albino Charles River rats (two males and two females in each group).

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<sup>10</sup> The full reports for the acute toxicity studies conducted by Yu and Peano (2000a; 2000b) were not available for review and the data has not gone under peer review (Bergstrom Nutrition, Personal Communication).

The test material was administered in the form of a 25% aqueous solution. One animal died at the 15,400 mg/kg dose. The LD<sub>50</sub> was reported as  $\geq 17,020$  mg/kg (Moving Average Method). Necropsy of the animal that died during the study and animals euthanized at the end of the 14-day observation period did not reveal any gross pathological alterations in tissues and organs examined. De Crescente (1981a) utilized male Sprague-Dawley rats to evaluate the toxicity of an acute oral dose of 5000 mg/kg MSM, and reported that the rat oral LD<sub>50</sub> was estimated to be greater than 5000 mg/kg.

In a single dose toxicity study, Crl:CD(SD)BR rats (five/sex) were given a 16% solution of MSM in water by the intranasal route at a dose of 0.6 ml/kg (approximately equivalent to 600 mg/kg) (Yu and Peano, 2000c). The administration frequency was six administrations within a 24 hour period at 1.5-hour intervals (0.1 ml/kg/time). Clinical observations, body weight determinations and gross pathology examinations were conducted. No mortality, clinical or body weight changes were observed. MSM given to rats by intranasal route did not induce mortality or clinical signs of toxicity.

Based on a summary report in a U.S. patent, rats (strain and sex not stated) were administered a 40% aqueous solution of MSM at a dose of 20,000 mg MSM/kg body weight/day by gavage daily for six weeks (Herschler, 1981). It was stated in the summary report that no mortality occurred and none of the rats displayed any signs of unusual symptoms or behavior. No data on clinical chemistry findings or changes in body weight were reported in the summary report, and therefore the data could not be verified. This study suggests a low order of MSM toxicity; however, the details of the evaluation were not available. In the same patent, the safety of intravenously administered MSM (compositions for blood dilution and/or systemic treatment of collagen-related diseases) was determined in a dog. MSM (20% aqueous solution) was administered to a dog at a dose level of 2000 mg/kg/day for “several weeks.” It was stated in the patent that the dog “did not react adversely to MSM and did not require physical restraint.” No other information was stated.

Kocsis *et al.* (1975) reported that intraperitoneal administration of MSM (5000 mg/kg) to rats (sex, strain not specified;  $n = 24$ ) resulted in drop in body temperature by about 10°C during the first hour, when the rats were exposed to 5°C, although there was a large variation in the

results and significance was not reached. In additional experiments, Kocsis *et al.* (1975) also studied changes in motor activity in mice following administration of 5000 mg/kg of MSM by the oral and intraperitoneal routes. Compared to a saline-treated control group, intraperitoneal administration of MSM significantly reduced motor activity as measured by number of revolutions on an activity wheel. Oral administration of MSM did not produce significant changes.

Zheng and Lee (2004c),<sup>11</sup> reported that a single oral dose of 2000 mg MSM/kg body weight to two male and two female Beagle dogs did not produce any fatalities, symptoms or weight change. The duration of the observation period was not provided in the study summary. The conclusion of the study was that the approximate LD<sub>50</sub> of MSM for Beagle dogs is greater than 2000 mg/kg.

In a repeat dose study, Schmoling *et al.* (2001; 2004a) administered 50 g (1200 mg/kg/day; delivered in two portions) of MSM to two male Holstein calves (5 days old; 41-43 kg) for 30 days. No apparent changes were noted in overall health, digestive intolerance or discomfort. Milk consumption was not altered by supplemented formula. During Days 3-8 of the study loose stools occurred and was not considered as pathological diarrhea by the investigators.

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<sup>11</sup> OptiMSM® was utilized in the studies conducted by Zheng and Lee. (2004d), Bergstrom Nutrition, personal communication.

**Table 6. Summary of acute and subacute toxicity studies on MSM**

| Species | Route           | Duration of exposure | LD <sub>50</sub> (mg/kg) | Reference                      |
|---------|-----------------|----------------------|--------------------------|--------------------------------|
| Mouse   | Oral            | Acute                | >2000                    | Yu and Peano (2000a)           |
| Mouse   | Oral            | Acute                | >5000                    | Kocsis <i>et al.</i> (1975)    |
| Mouse   | Intraperitoneal | Acute                | >5000                    | Kocsis <i>et al.</i> (1975)    |
| Rat     | Oral            | Acute                | >2000                    | Horvath <i>et al.</i> (2002)   |
| Rat     | Oral            | Acute                | >2000                    | Yu and Peano (2000b)           |
| Rat     | Oral            | Acute                | >20,000                  | Hixson (1958)                  |
| Rat     | Oral            | Acute                | ≥17,020                  | Schoenig <i>et al.</i> (1968)  |
| Rat     | Oral            | Acute                | >5000                    | De Crescente (1981, 2004b)     |
| Rat     | Inhalation      | Acute                | >600                     | Yu and Peano (2000c)           |
| Rat     | Intraperitoneal | Acute                | >5000                    | Kocsis <i>et al.</i> (1975)    |
| Rat     | Oral            | 42 days              | >20,000                  | Herschler (1981, 2004c)        |
| Dog     | Oral            | Acute                | >2000                    | Zheng and Lee (2004c)          |
| Dog     | Intravenous     | Several weeks*       | >2000                    | Herschler (1981)               |
| Cow     | Oral            | 30 days              | >1200                    | Schmoling <i>et al.</i> (2001) |

\*No additional information was stated

In summary, acute oral studies in rats, mice and dogs indicate that the LD<sub>50</sub> for MSM is greater than 2000 mg/kg; some studies suggest that the LD<sub>50</sub> may be greater than 20,000 mg/kg.

### 3.2. Subchronic studies

In a subchronic toxicity study, Wistar rats [CrI:(WI)BR] (20/sex) were given 1500 mg of OptiMSM<sup>®</sup> /kg/day by gavage for 90 days (Horváth *et al.*, 2002). The study was conducted under good laboratory practice (GLP) guidelines, but did not conform to FDA Redbook guidelines, as only one OptiMSM<sup>®</sup> dose was administered. The dose of 1500 mg/kg/day was reported as the upper limit of solubility of OptiMSM<sup>®</sup> in water. Rats in the control group (20/sex) received distilled water. Animals were observed twice daily for clinical signs and mortality. Food consumption and body weight was measured weekly. Before the initiation of treatment and once at Week 7 of treatment, blood was drawn from the retro-orbital sinuses of five male and five female rats. On day 91, prior to necropsy, blood samples were collected from all animals. The hematological parameters examined included erythrocyte (RBC), leukocyte (WBC), platelet counts, hematocrit and mean corpuscular hemoglobin. Clinical chemistry parameters included serum enzymes, lipid profile, serum proteins, albumin and blood chemistries. Urinalysis was carried out on five male and five female rats prior to treatment and on Week 7. Urinalysis parameters included appearance, volume, specific gravity, pH, protein,

glucose, and blood. The following organs were weighed and fixed in formaldehyde for histopathological observations: liver, kidneys, adrenals, left testicle, brain, thymus, heart, mesenteric lymph nodes, submandibular lymph nodes, stomach, duodenum, pancreas, lungs, pituitary, trachea, esophagus, thyroids, parathyroids, left epididymis, prostate, uterus and ovaries.

Administration of OptiMSM<sup>®</sup> for 90 days did not cause any mortality. Similarly, no treatment-related changes in clinical signs of toxicity, body weight or food consumption were noted. At autopsy, no gross pathological changes or any differences in organ weights were noted, except a significant increase in kidney weights of treated male rats. However, histopathological examination of kidneys in both males and females did not reveal any treatment-related lesions. The slight but statistically significant kidney weight difference was considered due to low within-group deviations rather than a toxicological effect. All hematology and blood chemistry data were reported as normal. Urinalysis parameters were normal. In a follow-up investigation (Financsek, 2003), histopathological evaluation of organs and tissues from the 90-day MSM study (Horváth *et al* , 2002) were performed. No treatment-related histopathological lesions were found in any of the organs and tissues of male and female rats treated with 1500 mg/kg/day OptiMSM<sup>®</sup> daily for 90 days. Based on the above described and follow up study, the NOAEL for OptiMSM<sup>®</sup> is 1500 mg/kg/day, the only dose tested.

Riegel (1999) investigated the effects of MSM on the musculature of Standardbred horses. Thirty horses were randomly divided into three groups of ten animals each. Each horse was three to four years old and weighed approximately 500 kg. The first group served as control while Group 2 and 3 were treated orally with 10 and 20 g MSM/day (20 and 40 mg/kg/day), respectively for twelve weeks. Each animal was thermographed at several pre-selected times for determination of body temperature variations. Blood samples were drawn initially and at weekly intervals for hematology (RBC, WBC, packed cell volume, and the types of WBC's) and serum chemistry analysis (albumin levels, alkaline phosphatase, BUN, calcium, creatinine, glucose, magnesium, phosphorus, aspartate aminotransferase, serum protein, total bilirubin, sodium, potassium, chloride, *gamma*-glutamyl transpeptidase, creatine kinase, albumin/globulin ratio, globulin, lipemic index, hemolytic index, and icteric index). In the treatment groups, reductions in thermal gradients were noted. No adverse effects of MSM were noted in the treatment groups.

The hematological examination did not reveal any significant variations in the parameters studied that would indicate anemia, electrolyte imbalances, hepatotoxicity or renal damage. As this was not a toxicological study, toxicological parameters were not evaluated and a NOAEL was not reported, but no treatment-related effects were noted. On the basis of the parameters examined, the NOAEL was 40 mg/kg body weight, the highest dose tested. A summary of the subchronic studies is presented in Table 7.

**Table 7. Summary of the effects of subchronic administration of MSM**

| Species | Route             | Duration of exposure | NOAEL (mg/kg/day) | Reference                    |
|---------|-------------------|----------------------|-------------------|------------------------------|
| Rat     | Gavage            | 90 days              | 1500*#            | Horváth <i>et al.</i> (2002) |
| Horse   | Oral dose syringe | 84 days              | 40*               | Riegel (1999)                |

\*Only dose administered, #No Observable Effect Level

### 3.3. Anticarcinogenicity studies

McCabe *et al.* (1986) investigated the chemopreventive effects of MSM in female Sprague-Dawley rats treated with dimethylbenzanthracene (DMBA).<sup>12</sup> Rats were maintained on feed containing 1 and 4% (1000 and 4000 mg/kg/day<sup>13</sup>) MSM for up to 300 days. One week after the administration of MSM, all animals including the control group, received 15 mg DMBA by gastric intubation. The animals were examined weekly for mammary tumor incidence and size. Tumor incidence was not affected by MSM administration. Time to appearance (latency period) of both tumors and cancer was prolonged by administration of 4% MSM. Administration of MSM did not affect body weight changes. The authors stated that no “toxic” reactions to MSM were observed. Critical toxicological parameters were not evaluated, as this was not a toxicological study, and the NOAEL for MSM for this study could not be determined.

In another anti-carcinogenicity study, O’Dwyer *et al.* (1988) investigated the effects of MSM on 1,2-dimethylhydrazine (DMH)-induced colon cancer in male Sprague-Dawley rats. MSM was administered to rats ( $n = 20$ ) via drinking water as a 1% solution (1000 mg/kg/day<sup>14</sup>) for 36 weeks. One week after the initiation of MSM treatment, all animals including the control

<sup>12</sup>A complete carcinogen, covalently binding to DNA and causing the formation of neoplasms

<sup>13</sup> Dose in mg/kg/day unit is based on a conversion factor of 1000 (PAFA, 1993)

<sup>14</sup> Dose in mg/kg/day unit is based on a conversion factor of 1000 (PAFA, 1993)

**000031**

group, were injected subcutaneously with DMH (20 mg/kg). The DMH treatment was repeated at weekly intervals for 20 weeks. Primary tumors were detected by serial laparotomy at two-month intervals following completion of carcinogen injections for 20 weeks. MSM administration significantly delayed the average time to tumor onset. Additionally in the animals receiving MSM, fewer poorly differentiated tumors were noted. No weight loss or toxicity was observed. Results from this study suggest that MSM inhibits DMH-induced colon cancer in rats. Critical toxicological parameters were not evaluated, as this was not a toxicological study, and the NOAEL for MSM for this study could not be determined.

In two separate abstract reports, Wang *et al.* (2003a; 2003b) reported that OptiMSM<sup>®</sup> administration to female Sprague Dawley rats via drinking water at a 5% concentration (5000 mg/kg/day) prevented the DMBA-induced mammary carcinogenesis at the initiation stage. In both studies, the rats were treated with MSM for 15 days prior to, and for 90 days after a single treatment with DMBA (25 mg/kg). All animals were sacrificed at approximately the ninth month after DMBA treatment, and examined by light microscopy for pathological changes in the mammary glands. The authors of these abstracts reported that MSM inhibited the formation of DMBA-induced tumor formation. No benign tumor or carcinoma was observed in the DMBA plus MSM and age-matched control groups, which only showed normal histology or mild hyperplasia (Wang *et al.*, 2003a; 2003b).

In summary, MSM administration in rats significantly delayed the average time to tumor onset in DMH-induced colon cancer, and prolonged the latency period of both tumor and cancer formation induced by DMBA. MSM administration during the initiation stage also prevented DMBA-induced mammary carcinogenesis. Administration of MSM did not affect body weight, and not toxic reactions were noted in any of the studies. A summary of these studies is presented in Table 8.

**000032**

**Table 8. Anticarcinogenicity studies in rats administered MSM in drinking water**

| Species | MSM (mg/kg/day) | Duration of MSM exposure | Carcinogen | Outcome  | Reference                         |
|---------|-----------------|--------------------------|------------|--|-----------------------------------|
| Rat     | 1000 and 4000   | 300 days                 | DMBA       | Latency period of both tumors and cancer were prolonged by 4000 mg/kg/day oral MSM | McCabe <i>et al.</i> (1986)       |
| Rat     | 1000            | 252 days                 | DMH        | MSM administration significantly delayed average time to tumor onset               | O'Dwyer <i>et al.</i> (1988)      |
| Rat     | 5000            | 105 days                 | DMBA       | MSM inhibited tumor formation  | Wang <i>et al.</i> (2003a, 2003b) |

DMH = 1,2-dimethylhydrazine, DMBA = dimethylbenzanthracene

### 3.4. Reproduction studies

Magnuson *et al.* (2006b) evaluated the developmental toxicity potential of OptiMSM<sup>®</sup> when administered orally to pregnant rats during the period of major organogenesis and histogenesis.<sup>15</sup> A preliminary range-finding study was first conducted, in which OptiMSM<sup>®</sup> microprill was administered via oral gavage at 0, 50, 250, 500, and 1000 mg/kg/day to 8-9 sperm-positive female Sprague-Dawley rats/group/day on gestation Days 6 through 20. Maternal or fetal toxicity was not observed in these animals. Thus, four groups of 24-25 time-bred primiparous female rats were administered 0, 50, 500, or 1000 mg/kg/day via gavage on gestation Days 6 through 20. Maternal body weight, body weight gain, corrected body weight/body weight gain, feed consumption, and uterus weight were unaffected by treatment with OptiMSM<sup>®</sup>. No evidence of maternal toxicity, and no significant differences in litter viability, litter size, or litter body weight were detected. Fetal analyses failed to show any biologically significant increases in the incidence of anomalies or malformations in the OptiMSM<sup>®</sup>-treated groups. No incidence of increased fetal mortality, altered growth, or structural alterations was observed in the fetuses of dams administered 50 to 1000 mg/kg/day OptiMSM<sup>®</sup>. The authors reported the NOAEL for maternal and developmental toxicity as 1000 mg/kg/day, the highest dose tested. This study did not evaluate the effect of OptiMSM<sup>®</sup> on the libido, fecundity or implantation in rats.

<sup>15</sup> The origin of a tissue; the formation and development of the tissues of the body  
<http://216.251.232.159/sendweb/internetsomd/ASP/1525674.asp>, site visited February 13, 2007.  
Bergstrom OptiMSM<sup>®</sup> GRAS-Draft  
June 20, 2007  
05.CARD001 00

The reproductive toxicity of DMSO was evaluated in an *in vitro* culture of mammalian rodent embryos (Augustine-Rauch *et al* , 2004). At a concentration of 0.04% in culture media, DMSO produced significant embryo toxicity, resulting in failure of neural tube closure (Augustine-Rauch *et al* , 2004). *In vitro* data is difficult to extrapolate to *in vivo* responses in humans, but the data presented by Magnuson *et al.* (2006b) indicate that OptiMSM<sup>®</sup> is not toxic to the reproductive system of rats at up to 1000 mg/kg/day. A summary of the reproductive effects of MSM is presented in Table 9.

In a gametogenesis study, Goldstein *et al.* (1992) investigated the effects of MSM in *Caenorhabditis elegans* (nematodes). In this *in vitro* study, *C. elegans* were exposed to MSM at concentrations of 0.5, 1, 2, and 5% for eleven days, and compared to *C. elegans* exposed to DMSO at the same concentrations. Differential effects on X-chromosome nondisjunction, loss of viability and fertility were noted. The observed decrease in life span of the nematodes was associated with senescent morphology of meiotic prophase nuclei, such that nuclei from young and old specimens were indistinguishable. A dose-related decrease in fertility and increased production of abnormal gametes were noted. At MSM concentrations >1%, synaptonemal complexes were absent from pachytene nuclei, prohibiting the effective pairing and segregation of homologous chromosomes. The results of this *in vitro* investigation in nematodes raised questions regarding the teratogenic potential of MSM. As the results from this nematode study cannot be meaningfully extrapolated to humans, more definitive developmental toxicity research in animals was required, and has since been performed (Magnuson *et al.* , 2006b).

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**000034**

**Table 9. Summary of the reproductive toxic effects of MSM or DMSO**

| Species    | Dose   | Duration              | Route                         | Outcome  | Reference                            |
|------------|--|-----------------------|-------------------------------|--|--------------------------------------|
| Rat        | 0, 50, 250, 500, and 1000 mg/kg/day MSM        | Gestation days 6 – 20 | Oral gavage                   | No significant differences in litter viability, fetal mortality, altered growth, or structural alterations, compare to control. NOEL for maternal and developmental toxicity at highest dose tested (1000 mg/kg/day) | Magnuson <i>et al</i> (2006b)        |
| Rat embryo | 0.04% DMSO in culture media                    | 48 hours              | Incubated in culture media    | Significant embryo toxicity  | Augustine-Rauch <i>et al.</i> (2004) |
| Nematode   | Five percent MSM concentration <i>in vitro</i> | 11 days               | Grown in media containing MSM | Dose-related decrease in fertility and increased production of abnormal gametes Loss of viability and fertility  | Goldstein <i>et al</i> (1992)        |

DMSO = dimethylsulfoxide, MSM = methylsulfonylmethane

### 3.5. Genotoxicity

The potential mutagenic effects of MSM in the reverse mutation assay are summarized in Table 10. Fassio and Barone (2000) investigated the mutagenic potential of MSM in a reverse mutation assay in *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 in the presence and absence of S9 liver homogenate fraction.<sup>16</sup> Two independent experiments were conducted. The first trial was conducted using the plate incorporation assay with and without metabolic activation, while the second one was conducted without metabolic activation and the preincubation method with metabolic activation. In both experiments, five concentrations of MSM ranging from 50 to 5000 µg/plate were tested. No significant cytotoxic effects of MSM were noted. MSM did not induce any significant increase in the number of reversions, either in the presence or absence of metabolic activation. This was substantiated by the work of Summers (2005), who evaluated the potential mutagenicity of OptiMSM<sup>®</sup> in the Ames assay utilizing the

<sup>16</sup> The full report for this genotoxicity study was not available for review; the information was obtained from the study summary statement and could not be verified with the study data.

reverse mutation assay in *S. typhimurium* strains TA97A, TA98, TA100, TA102, and TA1535 (with and without metabolic activation). OptiMSM<sup>®</sup> was analyzed for potential mutagenicity at 50, 160, 500, 1600, and 5000 µg/plate in the five tester strains, and none of the strains produce a two-fold increase in the number of spontaneous revertants or demonstrated a concentration-related response. Therefore, OptiMSM<sup>®</sup> did not meet the criteria for a potential mutagen, at concentrations up to 5000 µg/plate.

In another report of reverse mutation, Zheng and Lee (2004d) investigated mutagenicity of MSM in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and in a tryptophan-dependent strain of *Escherichia coli* WP2uvrA (pKM101) in the presence and absence of metabolic activation.<sup>17</sup> The MSM concentrations used were 312.5, 625, 1250, 2500 and 5000 µg/plate. Compared to negative control, the number of reverse colonies of each test strain for the test material did not increase more than two-fold in the presence or absence of metabolic activation. In these assays, MSM did not cause growth inhibition or precipitation even at 5000 µg/plate. The investigators concluded that MSM was not mutagenic in these reverse mutation assays. Recent work by Lee *et al.* (2006c) evaluated MSM for genotoxicity in the reverse mutation tests using *S. typhimurium* strains TA98, TA100, TA1535, and TA1538 at MSM concentrations of 2500, 5000, and 10,000 µg/plate MSM, both in the presence and absence of a metabolizing enzyme system (S9). MSM was found to be nonmutagenic in this test system.

In a L5178Y tk<sup>+/-</sup> mouse lymphoma forward mutation assay, Hall (2005) evaluated the ability of OptiMSM<sup>®</sup> to induce mutations at the thymidine kinase (TK) locus of L5178Y tk<sup>+/-</sup> mouse lymphoma cells at up to 5000 µg/ml. Treatment of the cell cultures with OptiMSM<sup>®</sup> at up to 5000 µg/ml, in the presence and absence of S9 metabolic activation for three hours failed to induce mutations. Treatment at the same OptiMSM<sup>®</sup> concentration for 24 hours without S9 metabolic activation also failed to induce mutations in this mouse lymphoma cell line (24 hour treatment of the test article in the presence of S9 metabolic activation is not required by OECD<sup>18</sup> guidelines). These studies indicate that MSM does not induce forward or reverse mutations in bacterial or mammalian cells *in vitro*.

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<sup>17</sup> The full reports for the genotoxicity studies conducted by Zheng and Lee (2004a; 2004b; 2004d) were not available for review, therefore, the data was not available for review.

<sup>18</sup> Organization for economic cooperation and development

Zheng and Lee (2004a) also investigated potential effects of MSM on chromosome aberrations in Chinese hamster lung (CHL) culture cells. Effects of MSM were studied at concentrations of 1250, 2500 and 5000 µg/ml. Cells samples were prepared following 24 hours of MSM exposure and chromosome aberrations were counted. Exposure to MSM did not increase chromosome aberrations in the absence or presence of metabolic activation. The investigators concluded that MSM did not induce chromosome aberrations in Chinese hamster lung cells. Lee *et al.* (2006c) also found that MSM (1.25, 2.5, and 5 mg/ml) treatment failed to significantly increase the number of aberrant cells, either in the presence or absence of metabolic activation, using the *in vitro* chromosome aberration assay using a CHL cell line.

In an *in vivo* study, Zheng and Lee (2004b) evaluated micronucleation effects of MSM on mouse myelocytes. Eight week old male mice were administered a single oral dose of 0, 500, 1000 or 2000 mg MSM/kg. The positive control group received mitomycin C (MMC, 2 mg/kg, intraperitoneal). Animals were killed 24 hours following treatment and myelocytes were collected from femur bone. Bone marrow cells were stained with a Giemsa solution to examine the presence of micronucleation. MSM administration did not result in any significant increase in micronucleated polychromatic erythrocytes. No cytotoxicity or hematogenesis was noted at any of the MSM doses. A significant increase in the frequency of micronucleation was noted in animals administered with mitomycin C (positive control). The investigators concluded that MSM did not cause micronucleation of mouse myelocytes.

In summary, MSM failed to produce genotoxicity in reverse mutation assays in *S. typhimurium* or *E. coli* at up to 5000 µg/plate, did not induce chromosome aberrations in CHL cells at up to 5000 µg/ml, and did not significantly increase micronucleation in mouse myelocytes when acutely administered to mice at up to 2000 mg MSM/kg (Table 10).

**000037**

**Table 10. Summary of the genotoxic effects of MSM**

| Type of assay                          | Test organism   | Concentration               | Results  | Reference                |
|--|---|-----------------------------|--|--------------------------|
| <i>In vitro</i>                        |   |                             |  |                          |
| Reverse mutation assay*                | <i>Salmonella typhimurium</i> strains TA98, TA100, TA102, TA1535, TA1537                          | 50 – 5000 µg/plate          | No significant increase in reversions                                | Fassio and Barone (2000) |
| Reverse mutation assay*                | <i>S. typhimurium</i> strains TA97A, TA98, TA100, TA102, TA1535                                   | 50 – 5000 µg/plate          | No significant increase in reversions                                | Summers (2005)           |
| Reverse mutation assay*                | <i>S. typhimurium</i> strains TA98, TA100, TA1535, TA1537; <i>Escherichia coli</i> strain WP2uvrA | 312.5 – 5000 µg/plate       | No significant increase in reversions                                | Zheng and Lee (2004d)    |
| Reverse mutation assay*                | <i>S. typhimurium</i> strains TA98, TA100, TA1535, TA1538   | 2500 – 10,000 µg/plate      | No significant increase in reversions                                | Lee <i>et al</i> (2006)  |
| Mouse lymphoma forward mutation assay* | L5178Y tk+/- mouse lymphoma cells   |                             | No significant increase in forward mutations                         | Hall (2005)              |
| Chromosome aberration assay*           | Chinese hamster lung cells  | 1250 – 5000 µg/ml           | No significant induction of chromosomal aberrations                  | Zheng and Lee (2004a)    |
| <i>In vivo</i>                         |   |                             |  |                          |
| Mouse micronucleation assay            | Mouse   | 500 – 2000 mg/kg acute dose | No significant increase in micronucleated polychromatic erythrocytes | Zheng and Lee (2004b)    |

\* With and without metabolic activation

### 3.6. Irritation studies

Skin irritation potentials of MSM were investigated in rabbits using the standard OECD<sup>19</sup> protocol (Renoldi and Peano, 2000a).<sup>20</sup> In this study, single 500 mg doses of the test material were applied under semi-occlusive dressing to the skin of the trunk of three New Zealand albino rabbits for three minutes and one hour. No clinical signs, either general or local (at the application sites), were noted in any rabbit. The test article was classified as non-irritating to skin.

<sup>19</sup> OECD (404) Acute dermal irritation/corrosion assay. Adopted July 17, 1992.

<sup>20</sup> This summary is based on the results section of an unpublished report, in which the actual data was not available for review; therefore, the accuracy of the report summary can not be verified, and its relevance to oral intake is marginal (Bergstrom Nutrition, personal communication).

Yu and Peano (2000c)<sup>21</sup> studied local intranasal irritation of MSM in CrI:CD(SD)BR rats (*n* = five per sex). MSM was administered as a 16% solution in water by the intranasal route at a dose of 0.6 ml/kg to six male rats, a species not typically utilized for irritation studies. Clinical observations, body weight determinations and gross pathology examinations were conducted. A detailed post-mortem examination, including gross pathology and histology was performed on nasal turbinates. No deaths or general/local clinical changes or body weight growth abnormalities were noted. At the post-mortem examinations, no treatment-related changes were noted. The investigators concluded that intranasal administration of MSM did not induce mortality, signs of toxicity or local irritation reactions.

### **3.7. Eye irritation studies**

In an eye irritation study, the primary ocular irritation potential of MSM was tested by instilling single 100 mg doses of the test material into the eye of three (two males and one female) albino New Zealand rabbits (Renoldi and Peano, 2000b).<sup>22</sup> Slight redness of the conjunctivae and very slight chemosis were detected in all rabbits. At 24 hours, only slight conjunctival redness was noted, which persisted in only one rabbit at the 48 hour reading. At 72 hours following MSM instillation, no ocular changes were noted. Fluorescein staining performed at 24 hours following MSM instillation did not reveal any foreign body in the eye. The test article was considered as a non-irritant to the eye.

### **3.8. Sensitization studies**

In a guinea pig maximization test, the cutaneous allergic potential of MSM was tested (Vigna and Peano, 2000).<sup>23</sup> Dunkin Hartley albino guinea pigs were sensitized by intradermal injection of a 4% solution of MSM. The injection of the test article at 4% caused slight irritation

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<sup>21</sup> This summary is based on the results section of an unpublished report, in which the actual data was not available for review, therefore, the accuracy of the report summary can not be verified, and it's relevance to oral intake is marginal (Bergstrom Nutrition, personal communication).

<sup>22</sup> This summary is based on the results section of an unpublished report, in which the actual data was not available for review, therefore, the accuracy of the report summary can not be verified, and it's relevance to oral intake is marginal (Bergstrom Nutrition, personal communication).

<sup>23</sup> This summary is based on the results section of an unpublished report, in which the actual data was not available for review, therefore, the accuracy of the report summary can not be verified, and it's relevance to oral intake is marginal (Bergstrom Nutrition, personal communication).

(erythema). Two weeks after the epidermal induction application, the challenge was completed by epicutaneous application of the test article (16%) under occlusive dressing. No animals showed positive reactions at the challenge. The investigators concluded that under the experimental conditions applied, MSM did not appear to possess sensitizing potential.

### 3.9. Miscellaneous studies

In an *in vitro* study, Alam and Layman (1983) investigated the effects of DMSO and MSM on the release of labeled arachidonic acid from phosphatidyl choline and phosphatidyl ethanolamine in bovine aortic endothelial cells. Radiolabeled  $^{14}\text{C}$ -arachidonic acid was added to endothelial cell cultures prepared from intact bovine aortas treated with 2% DMSO or MSM for 24 hours. A decrease in production of the prostaglandin 6-keto-PGF $_{1\alpha}$  by 73 and 49% with DMSO and MSM, respectively, was noted. Similarly, production of prostacyclin (PGI $_2$ ) was inhibited by 72 and 50% by DMSO and MSM, respectively. In another study, Layman (1987) investigated the effects of MSM on bovine aortic smooth muscle and endothelial cells. Approximate concentration range was 1-4% DMSO or MSM, and the cells were harvested on 1, 2, 3, 4, 7, 10, and 14 days of culture. MSM caused a dose-dependent inhibition of cell growth. The IC $_{50}$  of MSM was reported as 1% for smooth muscle cells and 2.9% for endothelial cells. After four days of incubation of cells with MSM, the growth inhibition of smooth muscle cells was completely reversible at 1% MSM concentration, partially reversible at 2 and 3%, and completely irreversible at 4%. For the endothelial cells the growth was completely reversible at all of the concentrations. These *in vitro* studies indicate that the growth of smooth muscle cell was more susceptible to MSM compared to endothelial cells.

Spilker (1970) investigated the *in vitro* inotropic<sup>24</sup> effects of MSM on the left atria of male guinea pigs. The concentration of MSM employed was 0.001-0.02 g/ml. In six of the twelve atria no response to MSM was seen at any of the concentrations. However, the other six atria showed an increase in contractile force with increasing concentrations. The peak contractile effect was noted between 0.015 and 0.02 g/ml (15,000 and 20,000  $\mu\text{g/ml}$ , respectively) and

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<sup>24</sup> Increasing strength of cardiac contraction.

declined gradually. This MSM concentration is over 300-fold greater than plasma concentrations of MSM found in an MSM-supplemented individual (58.74 µg/ml) (Engelke *et al* , 2005).

Morton and Siegel (1986) examined the effects of DMSO and MSM in mice with autoimmune lymphoproliferative disease. In this study, male autoimmune strain MRL/lpr<sup>25</sup> and male BXSB mice were exposed to 3% DMSO (8-10 g/kg/day) or 3% MSM (6-8 g/kg/day) in their drinking water for approximately four months, commencing at one to two months of age, before spontaneous disease development could be detected. Life spans of control, DMSO and MSM treated MRL/lpr mice were 39, 43 and 46 weeks, respectively. Compared to controls, both substances showed significantly higher hematocrit, lower spleen and node weight and lower serum IgG in both mouse strains. All strains treated with either DMSO or MSM had decreases in antinuclear antibody responses and significant diminution of lymphadenopathy, splenomegaly and anemia development was observed. Mice of both strains treated with either DMSO or MSM appeared “healthy and vigorous” with no signs of toxicity.

Abstracts of additional studies in MRL/lpr mice or “B/W” mice<sup>26</sup> reported that administration of MSM at 3% in the drinking water (approximately 6-8 g/kg/day) for three months increased the life span of both strains of mice (Bergstrom Nutrition, 2006c). The authors indicated that there was no indication of any toxic side effects or of generalized suppression of the immune response.

Hasegawa *et al* (2004f) investigated the effects of MSM<sup>27</sup> on type II collagen-induced murine arthritis, a model of human rheumatoid arthritis. Male DBA/1J mice (*n* = eight per group) were administered 2.5% MSM in the drinking water (approximately equal to 3750 mg/kg bw/day) one week prior to primary immunization with type II collagen. Three weeks after the primary immunization, the mice were administered a booster shot again with type II collagen. Eight weeks after the collagen and adjuvant booster, the mouse spleen and inguinal lymph nodes

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<sup>25</sup> A strain of mouse that spontaneously develops joint lesions similar to those appearing in humans with rheumatoid arthritis.

<sup>26</sup> A strain of mouse that develops symptoms similar to Coomb’s positive hemolytic anemia and systemic lupus erythematosus.

<sup>27</sup> OptiMSM® was utilized in the studies conducted by Hasegawa *et al* (2004; 2005), Bergstrom Nutrition, personal communication

were removed and the number of leukocytes measured. Therefore, MSM was administered for a total of twelve weeks at approximately 3750 mg/kg bw/day. Compared to controls, the arthritic score (deformation and swelling) in the MSM-drinking mice was significantly decreased ( $P < 0.05$ ). The total number of leukocytes and B220+ cells (B cells) in the lymph nodes was significantly reduced in the MSM-drinking mice compared to the number found in control mice. No adverse effects by MSM administration were noted by the authors. The authors concluded that MSM administration modified the immune responses to type II collagen, lessening the development of collagen-induced arthritis in DBA/1J mice.

Expanding on this work, Hasegawa *et al.* (2005) investigated the effect of MSM ointment on skin inflammation in male hairless (Hos:HR-1) mice subjected to UV rays, MSM via drinking water (2.5%, approximately equal to 3750 mg/kg bw/day) on ovalbumin-induced immediate-type swelling in male Cg7BL/6 mice, and 2.5% MSM via drinking water on scratching behavior induced with histamine injections in ICR mice. MSM was administered for two weeks prior to the ovalbumin-induced immediate-type swelling, and one week prior to the histamine injections to assess scratching behavior. MSM ointment alleviated UV-induced inflammation, suppressed the immediate-phase reaction (but not the late-phase reaction) in ovalbumin-injected mice, and significantly inhibited the scratching behavior induced by histamine injections. The authors did not report any adverse effects due to MSM administration in these studies, either topically or via the drinking water.

In an *in vitro* study, Beilke *et al.* (1987) investigated effects of DMSO and MSM on oxidative function of human neutrophils. In this study, human neutrophils were artificially stimulated to produce oxidative entities such as hydrogen peroxide, superoxide and hypochlorous acid. A decrease in production of these superoxide radicals was noted following treatment with either MSM or DMSO.

### **3.10. Observations in humans**

Several human studies reported distribution of MSM in brain tissues. These studies suggest that MSM can cross the blood brain barrier. Cecil *et al.* (2002) investigated brain distribution of MSM in a five-year-old autistic boy. Following consumption of 1250 mg/day (62.5 mg/kg/day) for one year, magnetic resonance imaging and scanning of the brain indicated

deposition of MSM in basal ganglia (caudate, putamen, internal capsule) and parietal matter. The MSM levels in basal ganglia and white matter were determined as 0.93 and 1.24 mM, respectively. MSM administration did not result in any adverse clinical, structural, or neurochemical effects, although Cecil *et al.* (2002) did not conduct a full toxicity assessment.

Lin *et al.* (2001) investigated levels of MSM in brains of individuals (both healthy and with memory loss) following daily administration of 1-3 g MSM for various periods of time. Magnetic resonance spectroscopy was used to detect brain levels of MSM. In this study, four patients (two male, two female) and three controls (two male, one female) participated. The details of volunteers are summarized in Table 11. MSM was detected in brains of all subjects. In the treated subjects, intra-cerebral steady state levels of MSM were reported at 1.67 mM. In Patient 3, who received MSM for only one day prior to magnetic resonance scanning, levels of MSM were lowest. Highest levels of MSM were noted in Patient 4, who received MSM for over two years and also had evidence of a prior stroke. The imaging results revealed an even distribution of MSM throughout the brain, including brainstem, with similar concentrations in gray and white matter. Among the control volunteers, the highest concentration of MSM was noted in Subject 1, while concentrations were similar in the remaining two subjects. No systematic effects of MSM on brain metabolites were observed. No adverse clinical or neurochemical effects of MSM were observed. The results of this study suggest that MSM crosses the blood brain barrier.

**Table 11. Protocol details of *in vivo* MSM determination study (Lin *et al.* (2001))**

| Subject number | Sex    | Age (years) | MSM Dose (mg/kg) | Duration  | Cerebral area evaluated | Cerebral MSM (mM) |
|----------------|--------|-------------|------------------|-----------|-------------------------|-------------------|
| Patient 1      | Female | 64          | 40               | 2 years   | MB, PCG, WM             | 4.32              |
| Patient 2      | Female | 40          | 100              | 2 years   | PCG, WM                 | 2.69              |
| Patient 3      | Male   | 79          | 30               | 1 day     | PCG, Frontal CG         | 0.67              |
| Patient 4      | Male   | 79          | 40               | > 2 years | PCG, WM                 | 6.78              |
| Control 1      | Female | 51          | 50               | 7 weeks   | PCG                     | 2.33              |
| Control 2      | Male   | 48*         | 30               | 5 weeks   | PCG                     | 0.7               |
| Control 3      | Male   | 48*         | 30               | 1 year    | PCG                     | 0.7               |

MB = Midbrain, PCG = posterior cingulated gyrus (grey matter), WM = parietal white matter, \*The age of the individual was not stated. The mean age of the volunteers was 48 years.

Rose *et al.* (2000) quantified MSM levels in a 62-year-old male subject with Alzheimer's disease. The subject received 'MSM complex' at a dose of 182 mg/kg for seven days.

(approximately 10,900 mg/day), and 2000 mg/day for the remaining 23 days of the 30-day study. The subject also received a pre-study dose, which was not specified. MSM was detected in the brain and a small amount in cerebrospinal fluid. Washout half-life of MSM was reported as approximately 7.5 days. No adverse effects were stated in the publication.

In summary, the presence of MSM was detected in basal ganglia and white matter in one subject consuming ~1250 mg MSM/day for one year. In another study, MSM was detected in brain tissue of an Alzheimer's patient. In four patients with memory loss and three control subjects ingesting MSM at doses of 30 to 100 mg/kg/day, MSM (~1.67 mM *intra-cerebral* steady state levels) was distributed throughout the brain. In this study, one patient suffering from stroke and taking MSM for two years showed the highest concentrations of MSM in brain. The half-life of MSM in one subject was found to be 7.5 days, with MSM detected in the brain and cerebrospinal fluid.

In a multi centered, open label clinical trial on safety and efficacy of MSM, 50 volunteers (15 male, 35 female; age 21-60 years) with seasonal allergic response consumed 2,600 mg of MSM orally per day for 30 days (Barrager *et al*, 2002). Clinical respiratory symptoms and energy levels were evaluated at baseline and on Days 7, 14, 21, and 30 of treatment. Immune and inflammatory reactions were measured by plasma IgE and C-reactive protein at baseline and on Day 30. Plasma histamine levels were determined in five subjects. Improvements in respiratory symptoms and increase in energy levels were noted as a result of MSM treatment. No significant changes were observed in plasma IgE or histamine levels. Five subjects dropped out of the study. Of the five subjects, three dropped due to time constraints, one developed urticaria after Day 2, and one reported an increase in allergy symptoms. In this same study, a subset of 16 subjects that were either non-responders or showed mild response at the initial dose continued treatment for an additional 14 days with a higher dose. In these subjects the MSM dose was increased to 5200 mg/day. All subjects completed the study. No difference in plasma IgE or histamine levels was reported. No adverse effects were reported in the report, and a comprehensive toxicity assessment was not conducted in this study.

In a randomized, double-blind, placebo-controlled study, Lawrence (1998) investigated the effects of MSM on degenerative arthritis.<sup>28</sup> A total of 16 subjects (age 55-78; ten treatment, six placebo) were studied over a period of four months. Subjects in the treatment group received 2250 mg MSM per day. An improvement in control of pain was noted. No dropouts were reported. In addition, as part of a randomized, double-blind, parallel, placebo-controlled study on osteoarthritis of the knee, 30 subjects (age 40 – 70) received 1500 mg MSM per day for a total of twelve weeks, and was compared to the placebo group ( $n = 28$ ) (Usha and Naidu, 2004). MSM significantly decreased the mean pain index from  $1.53 \pm 0.51$  to  $0.74 \pm 0.65$  ( $P < 0.001$ ). All the treatments were well tolerated (Usha and Naidu, 2004). Lawrence (1998) also summarized a double-blind study that evaluated the effects of daily MSM administration, in which eight patients were treated with 2250 mg MSM per day for at least six weeks, while six subjects received placebo. No adverse effects were noted in the abstract, but a detailed analysis of the results was not available. The effect of a combination of glucosamine, chondroitin sulfate and MSM on osteoarthritis has also been evaluated in an open label study with 32 patients (Vidyasagar *et al* , 2004). Two tablets containing a total of 500 mg glucosamine, 400 mg chondroitin sodium sulfate and 250 mg MSM were administered three times per day (resulting in a total daily dose of 1500 mg glucosamine, 1200 mg chondroitin sodium sulfate, and 750 mg MSM) for twelve weeks to 32 patients with osteoarthritis. Two patients complained of diarrhea initially during the treatment, and the authors could not establish the cause. Hematological and biochemical parameters (i.e., blood glucose, blood urea, alanine aminotransferase, aspartate aminotransferase, erythrocyte sedimentation rate, hemoglobin, creatinine, and total white blood cell count) were evaluated at baseline and after twelve weeks on the supplement, and only hemoglobin levels were significantly different ( $P < 0.05$ ) from baseline levels ( $12.72 \pm 1.40$  vs.  $12.00 \pm 1.39$  Gm%, respectively). However, as a combination of substances was administered, it is difficult from this study to determine if this effect was from MSM administration (Vidyasagar *et al* , 2004).

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<sup>28</sup> The abstract of this study was published in 1998 under the citation. Lawrence RM Methylsulfonylmethane (MSM): a double-blind study of its use in degenerative arthritis. *International Journal of Anti-Aging Medicine* 1998; 1(1):50 The complete study was never peer-reviewed or published (Bergstrom Nutrition, personal communication).

More recently, Kim *et al.* (2006) conducted a randomized, double-blind, placebo-controlled clinical trial to assess the effects of OptiMSM<sup>®</sup> on osteoarthritis knee pain. Fifty arthritic patients (men and women aged 40-76) were randomly assigned to receive either the placebo ( $n = 25$ ) or 6000 mg OptiMSM<sup>®</sup> ( $n = 25$ ) orally/day for twelve weeks. A one-week, stepwise approach to the full dose was undertaken, in which the subjects were initially administered 2000 mg/day in two divided doses for three days, and then increased to 4000 mg/day for four days. The dose was increased to 6000 mg/day from the start of Week 2 until the end of the study.

Laboratory tests, questionnaires, blood pressure, weight, Body Mass Index (BMI), and other vitals were collected at baseline and at twelve weeks. Laboratory tests included clinical chemistry (hepatic and renal functions), hematology (complete blood counts and differential white blood cells), fasting lipid profile, stool occult blood tests, and urinalysis. Questionnaires included statements on standard gastrointestinal symptoms and modified neurotoxic symptoms using a four-point Likert scale ranging from 0 to 3 (0 = no, 1 = mild, 2 = moderate, 3 = severe). Questions related to blood clotting changes were also included. Questions related to cognitive function (fatigue, concentration, slowing, memory, motor coordination and language), peripheral neurological symptoms (sensory disturbance and muscle weakness), and other symptoms (insomnia, headache and blurred vision), were also included in the questionnaire.

No abnormal changes were noted in the clinical chemistry, hematology, and urinalysis parameters. No major changes were detected in the complete blood counts, differential white blood cell counts, hepatic and renal functions, lipid profiles, BMI, vitals, stool occult test, or swelling or tenderness of the target knee joints. Decreases in homocysteine ( $P=0.004$ ) and urine malondialdehyde (MDA) ( $P=0.01$ ) were the only two laboratory markers significantly different between OptiMSM<sup>®</sup> and placebo treatment groups. Kim *et al.* (2006) suggested that reduced MDA is a reflection of a reduction in lipid peroxidation, and the decrease in homocysteine may be due to the donation of OptiMSM<sup>®</sup>'s two methyl groups, with the decreases in homocysteine and MDA suggesting a potential role of OptiMSM<sup>®</sup> in supporting metabolic processes requiring methylation, such as antioxidant capacities.

Similar incidences of minor adverse effects were reported for both groups. The incidences of adverse GI and other side effects included bloating, constipation, indigestion, fatigue, concentration issues, insomnia, and headache, and were reported with comparable frequency between the OptiMSM<sup>®</sup> and placebo groups. Forty subjects completed the study: 21 (84%) in the OptiMSM<sup>®</sup> group and 19 (76%) in the placebo group. The majority of patient withdrawals were reportedly due to a lack of perceived response to therapy, two in the OptiMSM<sup>®</sup> group and five in the placebo. One subject from each group was removed due to lack of study follow-up. One OptiMSM<sup>®</sup> subject discontinued due to an adverse effect (neck and back pain) similar in symptoms to a previous kidney infection. The results of this clinical study indicate that OptiMSM<sup>®</sup> may be consumed at doses up to 6000 mg/day with no significant adverse effects (Kim *et al.*, 2006).

In summary, MSM administration resulted in increased concentrations of MSM in both the white and grey areas of the brain, and was well tolerated when consumed at up to 100 mg/kg/day for twelve weeks (Table 12).

**Table 12. Summary of clinical studies evaluating oral administration of MSM**

| MSM Dose and Duration                                       | Number of subjects | Outcome   | Reference                     |
|---|--------------------|---|-------------------------------|
| 37.5 mg/kg/day for 16 weeks                                 | 16                 | Improvement in pain control was noted. No dropouts were reported  | Lawrence (1998)               |
| 37.5 mg/kg/day for six weeks                                | 8                  | No adverse effects were noted from daily intake of MSM  | Lawrence (1998)               |
| 182 mg/kg/day for seven days, then 34 mg/kg/day for 23 days | 1                  | Brain concentrations of MSM were assayed. Washout half-life of MSM at approximately 7.5 days. MSM detected in the brain and cerebrospinal fluid.                      | Rose <i>et al.</i> (2000)     |
| 43.3 mg/kg/day for 30 days                                  | 50                 | Inflammatory reactions were assayed. Improvements in respiratory symptoms and increased energy levels were noted, with no significant plasma IgE or histamine levels. | Barrager <i>et al.</i> (2002) |
| 62.5 mg/kg/day for 1 year                                   | 1                  | Brain concentrations of MSM were assayed. 0.93 and 1.24 mM MSM in basal ganglia, respectively, with no noted adverse clinical, structural, or neurochemical effects   | Cecil <i>et al.</i> (2002)    |

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| MSM Dose and Duration   | Number of subjects | Outcome  | Reference                |
|---|--------------------|--|--------------------------|
| 30 – 100 mg/kg/day ranging from 1 day to greater than 2 years | 7                  | Brain concentrations of MSM were assayed. Even distribution of MSM throughout the brain, with similar concentrations in white and grey matter. No adverse clinical or neurochemical effects of MSM were observed.  | Lin <i>et al.</i> (2001) |
| 25 mg/kg/day for 12 weeks                                     | 30                 | MSM was well tolerated, and decreased the mean pain index in joint function.   | Usha and Naidu (2004)    |
| 100 mg/kg/day for 12 weeks                                    | 50                 | No abnormal changes in clinical chemistry, hematology, and urinalysis parameters from MSM ingestion. No changes in complete blood counts, differential white blood cell counts, hepatic and renal functions, lipid profiles, BMI, vitals, stool occult test, or swelling or tenderness in knees. | Kim <i>et al.</i> (2006) |

BMI = Body Mass Index; IgE = Immunoglobulin E

#### 4. DISCUSSION

Methylsulfonylmethane (MSM) is an organic sulfur-containing substance that occurs naturally in a variety of fruits, vegetables, grains, animals and humans. As a food ingredient, MSM is produced from dimethyl sulfoxide and hydrogen peroxide, forming a white, odorless, slightly bitter tasting substance. Although MSM is not currently regulated for use in food by the FDA, MSM is regulated under DSHEA as a dietary supplement.

MSM is rapidly and efficiently absorbed, with a half-life calculated from rat studies at 12.2 hours, is well distributed, and excreted mainly via the urine. In acute toxicity studies in rats, an LD<sub>50</sub> was reported at greater than 2000 mg/kg MSM. In short-term studies in rats, MSM was administered at doses up to 8000 mg/kg/day for six weeks, with no mortality. A 90-day subchronic study in rats identified the NOAEL from oral exposure to OptiMSM<sup>®</sup> at the highest dose tested, 1500 mg/kg/day (equivalent to 90,000 mg/day in a 60 kg human). In anti-carcinogenicity studies, MSM administered to rats at up to 4000 mg/kg/day for 240-300 days inhibited the formation, delayed the onset, or prolonged the latency period of carcinogen-induced tumor formation. OptiMSM<sup>®</sup> administered to pregnant rats on gestation Days 6 through 20 at up to 1000 mg/kg/day did not increase the incidence of fetal mortality, altered growth, or structural alterations. In addition, OptiMSM<sup>®</sup> lacked genotoxicity potential when evaluated in *in vitro* reverse mutation assays, chromosome aberration assays, and in an *in vivo* mouse myelocyte

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micronucleation assay. MSM has been evaluated for irritancy effects, and was determined as a non-irritant in ocular and dermal irritancy tests in New Zealand rabbits, and a non-irritant in dermal studies in rats. MSM was also found to lack sensitizing capability, when tested in the guinea pig maximization test. To summarize, OptiMSM<sup>®</sup> lacked *in vivo* toxicity in several species at any dose administered, in both short- and long-term studies. MSM also lacked genotoxicity in various *in vitro* and *in vivo* assays.

Human clinical intervention studies indicate that consumption of OptiMSM<sup>®</sup> at doses up to 6000 mg/day for twelve weeks was well tolerated, with no clinically significant toxicity reported. The incidences of adverse gastrointestinal and other side effects with MSM administration were comparable to placebo controls.

Bergstrom Nutrition is proposing the addition of OptiMSM<sup>®</sup> to meal supplement and replacement foods, fruit smoothie-type drinks, flavored thirst quencher-type beverages, and food bars such as granola and energy-type bars, which would result in a mean and 90<sup>th</sup> percentile consumption of OptiMSM<sup>®</sup> at 1935.7 mg/day (32.9 mg/kg/day) and 3840 mg/day (66.9 mg/kg/day), respectively. In addition, OptiMSM<sup>®</sup> is sold as a dietary supplement at recommended daily doses typically at 1000 mg/day (approximately 17 mg/kg/day). Thus, the potential theoretical maximum aggregate OptiMSM<sup>®</sup> consumption at the 90<sup>th</sup> percentile from food and dietary supplement consumption may reach 4845.6 mg/day (approximately 80.7 mg/kg/day). The Expert Panel has critically evaluated the available information on MSM and concluded that consumption of OptiMSM<sup>®</sup> at 4845.6 mg/day is safe and is Generally Recognized As Safe (GRAS), under the proposed conditions of use.

## 5. CERTIFICATION

The undersigned authors of this document—a dossier in support of GRAS status determination for food ingredient use of OptiMSM<sup>®</sup>—hereby certify that, to the best of their knowledge and belief, this document is a complete and balanced representation of available information, favorable as well as unfavorable, known by the authors to be relevant to evaluation of the substance described herein.

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**Ray A. Matulka, Ph.D.**  
*Toxicologist*  
*Burdock Group*

05 JUL 2007

\_\_\_\_\_  
**Date**

\_\_\_\_\_  
**George A. Burdock, Ph.D., D.A.B.T., F.A.C.N.**  
*Diplomate, American Board of Toxicology*  
*Fellow, American College of Nutrition*  
*President, Burdock Group*

5 July 2007

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**Date**

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## 6. CONCLUSION

Based on critical, independent and collective evaluation of the available data and information summarized herein, the Expert Panel has determined that, based on common knowledge throughout the scientific community knowledgeable about the safety of substances added to food, OptiMSM<sup>®</sup> (methylsulfonylmethane; MSM), meeting appropriate food grade specifications, when produced in accordance with current Good Manufacturing Practice (cGMP), is Generally Recognized As Safe (GRAS), by scientific procedures, when used as a food ingredient under the intended conditions of use described herein.

## 7 SIGNATURES

**Joseph E. Borzelleca, Ph.D., F.A.T.S.**  
Medical College of Virginia

*21 June 2007*  
Date

**I. Glenn Sipes, Ph.D., F.A.T.S.**  
University of Arizona, College of Medicine

*03 July 2007*  
Date

**Kendall B. Wallace, Ph.D., D.A.B.T., F.A.T.S.**  
University of Minnesota Medical School

*02 July 07*  
Date

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- Zheng, M. S. and Lee, J. S. (2004d) Bacterial reverse mutation study of dimethylsulfone. Final Report. Study No: B04231. Biototech, Inc., North Chungchung Province, Korea.
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## 9. APPENDIX I

### Food products reported to contain MSM

| Product   | Level (ppm) | Reference                    |
|---|-------------|------------------------------|
| Alfalfa   | 0.07        | Pearson <i>et al.</i> (1981) |
| Apple fresh                                       | NR          | VCF (1999)                   |
| Asparagus (cooked)                                | 0.03        | VCF (1999)                   |
| Asparagus (raw)                                   | NR          | VCF (1999)                   |
| Beef (boiled, cooked)                             | NR          | VCF (1999)                   |
| Beef (grilled, roasted)                           | 0.032       | VCF (1999)                   |
| Beer  | 0.1         | VCF (1999)                   |
| Beetroot (cooked)                                 | Trace       | VCF (1999)                   |
| Butter  | NR          | VCF (1999)                   |
| Cabbage (raw)                                     | Trace       | VCF (1999)                   |
| Cheese, Mozzarella                                | 0.004-0.006 | VCF (1999)                   |
| Chinese quince fruit                              | NR          | VCF (1999)                   |
| Coffee  | 1.6         | VCF (1999)                   |
| Corn, sweet                                       | Trace-0.11  | Pearson <i>et al.</i> (1981) |
| Cucumber  | Trace       | VCF (1999)                   |
| Durian ( <i>Durio zibethinus</i> )                | NR          | VCF (1999)                   |
| Guava fruit ( <i>Psidium guajava</i> L.)          | NR          | VCF (1999)                   |
| Milk, goat's                                      | NR          | VCF (1999)                   |
| Milk, sheep's                                     | NR          | VCF (1999)                   |
| Milk, water buffalo                               | 0.04        | VCF (1999)                   |
| Milk  | 8.2         | Pearson <i>et al.</i> (1981) |
| Mussel  | 0.29        | VCF (1999)                   |
| Oatmeal   | <0.05       | VCF (1999)                   |
| Pork liver  | NR          | VCF (1999)                   |
| Raspberry ( <i>Rubus idaeus</i> L.)               | Trace       | VCF (1999)                   |
| Shrimps (cooked)                                  | NR          | VCF (1999)                   |
| Shrimps (roasted)                                 | NR          | VCF (1999)                   |
| Swiss chard ( <i>Beta vulgaris</i> )              | 0.05-0.18   | Pearson <i>et al.</i> (1981) |
| Tea, black  | 0.3         | VCF (1999)                   |
| Tomato  | Trace-0.86  | VCF (1999)                   |
| <i>Vitis vinifera</i> L                           | NR          | VCF (1999)                   |
| Watercress ( <i>Nasturtium officinale</i> R. Br.) | NR          | VCF (1999)                   |
| Yogurt  | NR          | VCF (1999)                   |

NR= Not Reported, constituent was detected but not quantified, ppm = parts per million, Trace = compound present, concentration at the level of detection limit

## 10. APPENDIX II

### Foods selected for the addition of MSM

| Food Code | Food Description                                    | Concentration (mg/g) |
|-----------|---|----------------------|
| 11553000  | FRUIT SMOOTHIE DRINK, W/ FRUIT AND DAIRY PRODUCTS   | 4                    |
| 11623000  | MEAL SUPPLEMENT / REPLACEMENT,PREPARED,RTD          | 4                    |
| 11830940  | MEAL REPLACEMENT,PROTEIN,MILK BASED,FRUIT JUICE MIX | 4                    |
| 11830970  | MEAL REPLACEMENT, PROTEIN TYPE, MILK-BASE, POWDER   | 4                    |
| 41435110  | HIGH PROTEIN BAR, CANDY-LIKE, SOY & MILK BASE       | 4                    |
| 41440010  | MEAL REPLACEMENT/SUPPLEMENT, LIQUID, HI PROTEIN     | 4                    |
| 53542100  | GRANOLA BAR W/ OATS, SUGAR, RAISINS, COCONUT        | 30                   |
| 53542200  | GRANOLA BAR, OATS, FRUIT, NUTS, LOWFAT              | 30                   |
| 53542210  | GRANOLA BAR, NONFAT                                 | 30                   |
| 53543100  | GRANOLA BAR W/ PEANUTS, OATS, SUGAR, WHEAT GERM     | 30                   |
| 53544300  | GRANOLA BAR, HIGH FIBER, YOGURT COATING, NOT CHOC   | 30                   |
| 53544450  | POWERBAR (FORTIFIED HIGH ENERGY BAR)                | 30                   |
| 92553000  | FRUIT-FLAVORED THIRST QUENCHER BEVERAGE, LOW CAL    | 4                    |
| 92560000  | FRUIT-FLAVORED THIRST QUENCHER BEVERAGE             | 4                    |

## 11. APPENDIX III

### Consumption of MSM added to target foods

| Foodcode | Description   | mg/day | mg/kg/day |
|----------|---|--------|-----------|
| 11553000 | FRUIT SMOOTHIE DRINK, W/ FRUIT AND DAIRY PRODUCTS   | 1530.0 | 21.3      |
| 11623000 | MEAL SUPPLEMENT / REPLACEMENT,PREPARED,RTD          | 1558.3 | 19.9      |
| 11830940 | MEAL REPLACEMENT,PROTEIN,MILK BASED,FRUIT JUICE MIX | 155.8  | 2.1       |
| 11830970 | MEAL REPLACEMENT, PROTEIN TYPE, MILK-BASE, POWDER   | 261.7  | 3.3       |
| 41435110 | HIGH PROTEIN BAR, CANDY-LIKE, SOY & MILK BASE       | 259.9  | 3.3       |
| 41440010 | MEAL REPLACEMENT/SUPPLEMENT, LIQUID, HI PROTEIN     | 1118.4 | 20.2      |
| 53542100 | GRANOLA BAR W/ OATS, SUGAR, RAISINS, COCONUT        | 1220.3 | 20.3      |
| 53542200 | GRANOLA BAR, OATS, FRUIT, NUTS, LOWFAT              | 1016.0 | 18.4      |
| 53542210 | GRANOLA BAR, NONFAT                                 | 1290   | 16.8      |
| 53544450 | POWERBAR (FORTIFIED HIGH ENERGY BAR)                | 2321.3 | 28.9      |
| 92553000 | FRUIT-FLAVORED THIRST QUENCHER BEVERAGE, LOW CAL    | 2700   | 40.0      |
| 92560000 | FRUIT-FLAVORED THIRST QUENCHER BEVERAGE             | 2653.5 | 41.8      |

Note: Not all foods suggested in APPENDIX II may have been consumed by the sample population, therefore, a consumption analysis for only those foods consumed by the sample population (i.e., "eater's only") could be conducted.

Pages 000060-000156 removed under Freedom of Information Act  
Exemption 6.

**SUBMISSION END**

**000157**

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2001 9<sup>th</sup> AVENUE  
SUITE 301  
VERO BEACH, FL 32960  
p•772.562.3900 / f•772.562.3908  
e•gburdock@burdockgroup.com

September 28, 2007

RECEIVED  
OCT 03 2007

BY: (b)(6)

Dr. Marcella Fruchter  
US Food and Drug Administration  
Center for Food Safety and Applied Nutrition  
Harvey W. Wiley Federal Building, HFS – 565  
5100 Paint Branch Parkway  
College Park, MD 20740-3835  
Phone: 301-436-1729

cc: Dr. Laura Tarantino

RE GRN Notice #000229 – Clarification Letter

Drs Fruchter,

Enclosed you should find a letter addressing questions made by FDA in a conference call on September 17,2007, concerning GRN 000229,<sup>1</sup> as well as a clarification statement by the Expert Panel, as requested. Although all of the Expert Panel members have agreed to sign the clarification statement, Dr. Wallace has been inexplicably out of contact with everyone (including his University department and laboratory), and we have not yet received his signature We will forward his signature to you early next week.

If you have any further questions regarding GRN 000229, please contact me.

Sincerely,

(b)(6)

George A. Burdock, Ph.D  
Diplomate, American Board of Toxicology  
Fellow, American College of Nutrition

<sup>1</sup> DOSSIER IN SUPPORT OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF OPTIMISM® (METHYLSULFONYLMETHANE; MSM) AS A FOOD INGREDIENT," notified to the FDA on July 11, 2007



2001 9<sup>th</sup> AVENUE  
SUITE 301  
VERO BEACH, FL 32960  
p•772.562.3900 / f•772.562.3908  
e•gburdock@burdockgroup.com

September 27, 2007

RECEIVED  
OCT 03 2007  
BY: (b)(6)

Dr. Marcella Fruchter  
US Food and Drug Administration  
Center for Food Safety and Applied Nutrition  
Harvey W. Wiley Federal Building, HFS – 565  
5100 Paint Branch Parkway  
College Park, MD 20740-3835  
Phone: 301-436-1729

RE: GRN Notice #000229 – Clarification Letter

Dr. Fruchter:

This letter is in response to your request for clarification on issues you raised in the telephone conversation of September 17, 2007, regarding the GRAS dossier entitled “DOSSIER IN SUPPORT OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF OPTIMISM<sup>®</sup> (METHYLSULFONYLMETHANE; MSM) AS A FOOD INGREDIENT,” notified to the FDA on July 11, 2007.<sup>1</sup> We respectfully submit the following in response to your request for clarification to the pending GRAS Notification (GRN 000229).

---

<sup>1</sup> GRN 000229, filed with FDA on July 25, 2007, in accordance with proposed 21 CFR 170.36

1. *FDA raised a question concerning the context in which the Expert Panel determined OptiMSM® to be Generally Recognized As Safe.*

Please refer to Expert Panel statement (enclosed). Also, please note that this statement has been signed by all members of the Expert Panel, although time constraints precluded all Panelists from signing the same copy.

2. *FDA indicated the Estimated Daily Intake (EDI) levels of MSM from the mean and 90<sup>th</sup> percentile consumption (eater's only) of OptiMSM® in the selected food codes, as stated on page 11 of the GRAS dossier (29.6 mg/kg/day and 57.2 mg/kg/day, respectively), were not in agreement with the same values stated in the Discussion section (page 41) of the same GRAS dossier (32.9 mg/kg/day and 66.9 mg/kg/day, respectively). Please reconcile these two sets of numbers.*

Thank you for bringing this to our attention. The Estimated Daily Intake (EDI) of OptiMSM® in the selected foods at the mean and 90<sup>th</sup> percentile (1935.7 and 3840 mg/day, respectively), on a "mg/kg/day" basis, is correctly stated on page 11 as 29.6 and 57.2 mg/kg/day. The calculation, on a "per body weight" basis, was completed using (the current) body weight distribution data published by Portier et al. (2007).<sup>2</sup> The values stated on page 41 of the GRAS dossier (32.9 and 66.9 mg/kg/day for the mean and 90<sup>th</sup> percentile consumption of OptiMSM®, respectively) were based on body weight data compiled by the EPA in 1985 (EPA's Technical Report Data, "Development of statistical distributions or ranges of standard factors used in exposure assessments") are in error and should be ignored.

3. *APPENDIX I of the GRAS dossier contains a table entitled "Food products reported to contain MSM." One of the food products, milk, was stated to contain MSM at 8.2 ppm, with reference to Pearson et al., 1981.<sup>3</sup> However, the Pearson et al., 1981 document indicates that milk contains levels of MSM at 3.2 ppm. Please clarify the level stated, or the reference utilized.*

Thank you for bringing this to our attention. In this table (APPENDIX I), milk was stated to contain up to 8.2 ppm MSM, as referenced by Pearson et al., 1981. The appropriate reference for this level of MSM in milk is

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<sup>2</sup> Portier, K., Tolson, J.K., and Roberts, S.M. (2007) Body weight distributions for risk assessment. *Risk Analysis* 27:11-26.

<sup>3</sup> Pearson, T W., Dawson, H J, and Lackey, H B (1981) Natural occurring levels of dimethyl sulfoxide in selected fruits, vegetables, grains, and beverages. *Journal of Agricultural and Food Chemistry* 29 1089-1091.

Williams *et al*, 1966a “Dimethyl sulfone: isolation from cows’ milk.”<sup>4</sup>  
Tabular data in this reference indicate that dimethyl sulfone (*i.e.*, MSM) was isolated from pasteurized cows’ milk, with levels ranging from 6.1 – 8.2 ppm. The Williams *et al* (1966) reference therefore is the appropriate citation for this data point.

Thank you for the opportunity to clarify the issues described above. If additional information is required or you have any further questions regarding the GRAS dossier on addition of OptiMSM<sup>®</sup> to the foods and drinks stated, please do not hesitate to contact us. If additional information is required from the Expert Panel, I am sure we can schedule a conference call.

Sincerely,

(b)(6)

George A. Burdock, Ph.D.  
Diplomate, American Board of Toxicology  
Fellow, American College of Nutrition

cc: Dr. Laura Tarantino

---

<sup>4</sup>Williams, K I H., Burstein, S H., and Layne, D S (1966a) Dimethyl sulfone: isolation from cows’ milk. *Proceedings of the Society for Experimental Biology and Medicine* 122 865-866



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**CLARIFICATION TO THE DOSSIER IN SUPPORT OF THE  
GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF  
OPTIMSM® (METHYLSULFONYLMETHANE; MSM) AS A  
FOOD INGREDIENT**

**September 24, 2007**

**Panel Members**

**Joseph F. Borzelleca, Ph.D., F.A.T.S.**

**I. Glenn Sipes, Ph.D., F.A.T.S.**

**Kendall B. Wallace, Ph.D., D.A.B.T., F.A.T.S.**

**000167**

**CLARIFICATION TO THE DOSSIER IN SUPPORT OF THE GENERALLY  
RECOGNIZED AS SAFE (GRAS) STATUS OF OPTIMSM®  
(METHYLSULFONYLMETHANE; MSM) AS A FOOD INGREDIENT**

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**CLARIFICATION TO THE DOSSIER IN SUPPORT OF THE GENERALLY  
RECOGNIZED AS SAFE (GRAS) STATUS OF OPTIMSM®  
(METHYLSULFONYLMETHANE; MSM) AS A FOOD INGREDIENT**

**1. EXECUTIVE SUMMARY**

On a prior occasion, this independent panel of recognized experts (hereafter also referred to as the “Expert Panel”)<sup>1</sup> critically evaluated the available information on OptiMSM®<sup>2</sup> meeting appropriate food grade specifications and manufactured in compliance with current Good Manufacturing Practices (cGMP), and determined that it was GRAS by scientific procedures. The GRAS determination was requested by Bergstrom Nutrition, 1000 West Eighth Street, Vancouver, WA 98660, and notified to the FDA (GRN 000229).<sup>3</sup> In the GRAS determination, the literature through December of 2006 was evaluated for relevant information. The Expert Panel was requested by FDA to amplify the context of Panel’s decision regarding the safe use of OptiMSM® in food at 3840 mg/day (90<sup>th</sup> percentile), in recognition of a possible aggregate 90<sup>th</sup> percentile (including natural sources and via dietary supplements) Estimated Daily Intake of 4845.6 mg/day. The Expert Panel members independently and collectively critically evaluated the statements presented herein and confirmed the GRAS status of OptiMSM® on the basis of the information provided in the original GRAS dossier.

**2. INTRODUCTION**

Bergstrom Nutrition proposes to use OptiMSM® as a food ingredient, at levels up to 4000 ppm in meal supplement and meal replacement foods, fruit smoothie-type drinks, and flavored thirst quencher-type beverages, and up to 30,000 ppm in food bars, such as granola and energy-type bars.

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<sup>1</sup> As defined by §201(s) of the Federal Food Drug and Cosmetic Act

<sup>2</sup> Dossier in support of the Generally Recognized As Safe (GRAS) status of OptiMSM® (methylsulfonylmethane; MSM) as a food ingredient

<sup>3</sup> GRN 000229, please see attached letter from FDA to Dr. Burdock dated August 7, 2007

September 24, 2007

OptiMSM® GRAS Clarification  
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Page 3 of 8

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**000169**

### 3. ESTIMATED DAILY INTAKE

Methylsulfonylmethane (MSM) is a natural constituent of the typical U.S. diet (*i.e.*, vegetables, grain and meat), resulting in a mean MSM consumption at approximately 2.3 mg/day (0.04 mg/kg/day for a 60 kg human). MSM is considered a source of sulfur for the formation of the amino acids cysteine and methionine. OptiMSM® will be incorporated into specific food products as a food ingredient, and these foods are identified in the original GRAS dossier, according to food codes given in the Health and Human Services (HHS) What We Eat in America, National Health and Nutrition Examination Survey (NHANES), 2001-2002, and these codes have been used to calculate the Estimated Daily Intake (EDI) values for OptiMSM® consumption (Table 1). The addition of OptiMSM® to foods previously stated in the GRAS dossier, which included meal supplement and meal replacement foods, fruit smoothie-type drinks, flavored thirst quencher-type beverages, and food bars, such as granola and energy-type bars, results in a 90<sup>th</sup> percentile consumption of OptiMSM® at 3840 mg/day (64 mg/kg for a 60 kg human). OptiMSM® is also available as a dietary supplement, the estimated consumption of which is approximately 1000 mg/day (16.6 mg/kg/day for a 60 kg human).

**Table 1. Current MSM intake from foods, possible MSM intake following supplementation of selected foods with OptiMSM® at the maximum levels indicated in the GRAS dossier, potential OptiMSM® intake from dietary supplement usage, and total MSM intake (predicted + current**

| MSM intake from:  | Per User (mg/day) |                             |
|---|-------------------|-----------------------------|
|   | Mean              | 90 <sup>th</sup> Percentile |
| A. Current consumption from food  | 2.3               | 5.6                         |
| B. Possible maximum consumption with OptiMSM® as an added food ingredient       | 1935.7            | 3840.0                      |
| E. Potential OptiMSM® consumption from dietary supplement use <sup>a</sup>      | 1000.0            | 1000.0                      |
| F. Total consumption from all sources (food + dietary supplements) <sup>b</sup> | 2938.0            | 4845.6                      |

<sup>a</sup>Recommended daily dose *per* label suggestion from the typical maximum intake *via* dietary supplement use

<sup>b</sup>GRN 000229

The GRAS dossier for OptiMSM® indicated that consumption of OptiMSM® at 3840 mg/day (at the 90<sup>th</sup> percentile) is Generally Recognized As Safe (GRAS), under the proposed conditions of use. The estimated aggregate consumption of MSM, through natural sources,

dietary supplement intake, and as OptiMSM® added to food at the 90<sup>th</sup> percentile, is 4845.6 mg/day (80.75 mg/kg for a 60 kg human).

#### 4. PRECLINICAL AND CLINICAL STUDIES

The following is a summary of the preclinical and clinical studies discussed in detail in the GRAS determination that were considered in the context of determining the safety-in-use of OptiMSM®, when added to foods at the 90<sup>th</sup> percentile level of 3840 mg/day (64 mg/kg/day for a 60 kg human). This is not an exhaustive list of all the information considered in this decision.

- ADME data demonstrate that MSM is rapidly absorbed, with a mean time to peak concentration of 2.1 hours, and that five oral studies have shown that MSM is metabolized and efficiently excreted via the urine, with no accumulation as MSM.
- Animal safety testing has repeatedly demonstrated safety:
  - Acute oral LD<sub>50</sub>s show no adverse effects at doses ranging from 2000 to 20,000 mg MSM/kg in several species.
  - Repeated dose studies show no observed adverse effects of MSM. For example, MSM at 1500 mg/kg/day (the only dose tested) when administered to rats for 90 days showed no adverse effects, and a 90-day study in horses had no adverse effects at 40 mg/kg/day MSM.
  - Repeated dose anti-carcinogenicity studies in rats showed no adverse effects of MSM at 4000 mg/kg/day (the highest dose tested) for 300 days.
  - A teratology study in rats showed no adverse effects of MSM at 1000 mg/kg/day, the highest dose tested, when administered at Days 6 through 20 of gestation.
  - MSM failed to produce genotoxicity in reverse or forward mutation assays in bacteria or L5178Y tk<sup>+/-</sup> mouse lymphoma cells at up to 5000 µg/plate,

did not induce chromosome aberrations *in vitro*, and did not increase micronucleation in myelocytes *in vivo* at up to 2000 mg MSM/kg.

- Several additional *in vivo* preclinical studies indicate that MSM was non-irritating when administered topically, intranasally, or to the eye, and was non-sensitizing in the guinea pig maximization test. Administration of MSM at 6000 – 8000 mg/kg/day for approximately four months to a mouse model for autoimmune disease showed no adverse effects, and MSM also had no adverse effects in a murine arthritic model when administered orally for 12 weeks at 3750 mg/kg/day. No effects were noted at the highest doses tested in any of these assays.
- Human studies indicate no adverse effects of MSM consumption:
  - A randomized, double-blind, placebo-controlled clinical trial with 25 subjects that received 100 mg/kg/day OptiMSM® orally for twelve weeks was conducted, with laboratory tests that included clinical chemistry (hepatic and renal function), hematology, lipid profiles, stool occult blood tests, and urinalysis. Questionnaires covering gastrointestinal, peripheral and cognitive neurological symptoms, blood clotting changes, and other symptoms (insomnia, headache and blurred vision) were also conducted. Administration of MSM showed no adverse effects.
  - A five-year-old boy under medical supervision dosed at 62.5 mg/kg/day MSM for one year did not have any adverse clinical, structural, or neurochemical effects.
  - A controlled clinical investigation with controls and three patients (40 – 79 years of age) receiving 40 – 100 mg MSM/kg/day for at least two years showed no adverse effects.
  - An open-label clinical trial in 50 volunteers receiving 43.3 mg/kg/day for 30 days, with a subset of 16 volunteers administered MSM for an

additional 14 days at 86.7 mg/kg/day showed no adverse effects to MSM consumption.

- Two double-blind, placebo-controlled studies with 10 and 8 subjects that received MSM at 37.5 mg/kg/day for four months and six weeks, respectively, showed no adverse effects.
- A double-blind, placebo-controlled study with 30 subjects receiving MSM at 25 mg/kg/day for twelve weeks showed no adverse effects.

On the basis of the data summarized above, MSM or OptiMSM® was consistently shown to be safe at the highest dose administered in animals and humans and, as such, a specific safety factor was not identified.<sup>4</sup> On the basis of the totality (or weight) of the evidence of the safety of MSM, as demonstrated in animal and human studies and, on the basis of the relevant expertise of the members of the Expert Panel, whose training and experience qualifies them to make such determinations, the Expert Panel has determined the safety-in-use of OptiMSM® in the food categories cited in the GRAS dossier, on the basis of scientific procedures. Further, it is the opinion of the Expert Panel that other experts qualified by scientific training and experience to evaluate the safety of food and food ingredients would concur with these conclusions.

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**000173**

## 5. CONCLUSION

We, the Expert Panel, have individually and collectively critically evaluated the information summarized in this clarification to the Dossier in support of the Generally Recognized As Safe (GRAS) status of OptiMSM® (methylsulfonylmethane; MSM) as a food ingredient. This information is consistent with that provided in the initial GRAS determination and fully supports the GRAS status of OptiMSM® at the levels of use stated in the GRAS dossier. We conclude that the use of OptiMSM® as an ingredient under the intended conditions of use described herein is safe and is Generally Recognized As Safe by scientific procedures. It is our opinion that other experts, qualified by scientific training and experience to evaluate the safety of food and food ingredients would concur with these conclusions.

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Joseph F. Borzelleca, Ph.D., F.A.T.S.  
Medical College of Virginia

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Date

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I. Glenn Sipes, Ph.D., F.A.T.S.  
University of Arizona, College of Medicine

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Date

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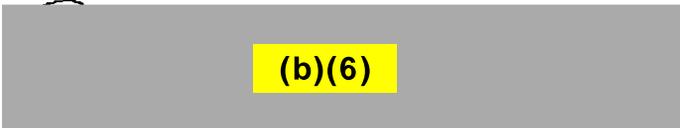
Kendall B. Wallace, Ph.D., D.A.B.T., F.A.T.S.  
University of Minnesota Medical School

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Date

**5. CONCLUSION**

We, the Expert Panel, have individually and collectively critically evaluated the information summarized in this clarification to the Dossier in support of the Generally Recognized As Safe (GRAS) status of OptiMSM® (methylsulfonylmethane, MSM) as a food ingredient. This information is consistent with that provided in the initial GRAS determination and fully supports the GRAS status of OptiMSM® at the levels of use stated in the GRAS dossier. We conclude that the use of OptiMSM® as an ingredient under the intended conditions of use described herein is safe and is Generally Recognized As Safe by scientific procedures. It is our opinion that other experts, qualified by scientific training and experience to evaluate the safety of food and food ingredients would concur with these conclusions.



Joseph F. Borzelleca, Ph.D., F.A.T.S.  
Medical College of Virginia

*26 September 2007*  
Date

I. Glenn Sipes, Ph.D., F.A.T.S.  
University of Arizona, College of Medicine

\_\_\_\_\_  
Date

Kendall B. Wallace, Ph.D., D.A.B.T., F.A.T.S.  
University of Minnesota Medical School

\_\_\_\_\_  
Date

DUPLICATE



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**CLARIFICATION TO THE DOSSIER IN SUPPORT OF THE  
GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF  
OPTIMSM® (METHYLSULFONYLMETHANE; MSM) AS A  
FOOD INGREDIENT**

**September 24, 2007**

**Panel Members**

**Joseph F. Borzelleca, Ph.D., F.A.T.S.**

**I. Glenn Sipes, Ph.D., F.A.T.S.**

**Kendall B. Wallace, Ph.D., D.A.B.T., F.A.T.S.**

DUPLICATE

**CLARIFICATION TO THE DOSSIER IN SUPPORT OF THE GENERALLY  
RECOGNIZED AS SAFE (GRAS) STATUS OF OPTIMSM®  
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DUPLICATE

**CLARIFICATION TO THE DOSSIER IN SUPPORT OF THE GENERALLY  
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(METHYLSULFONYLMETHANE; MSM) AS A FOOD INGREDIENT**

### 1. EXECUTIVE SUMMARY

On a prior occasion, this independent panel of recognized experts (hereafter also referred to as the "Expert Panel")<sup>1</sup> critically evaluated the available information on OptiMSM®<sup>2</sup> meeting appropriate food grade specifications and manufactured in compliance with current Good Manufacturing Practices (cGMP), and determined that it was GRAS by scientific procedures. The GRAS determination was requested by Bergstrom Nutrition, 1000 West Eighth Street, Vancouver, WA 98660, and notified to the FDA (GRN 000229).<sup>3</sup> In the GRAS determination, the literature through December of 2006 was evaluated for relevant information. The Expert Panel was requested by FDA to amplify the context of Panel's decision regarding the safe use of OptiMSM® in food at 3840 mg/day (90<sup>th</sup> percentile), in recognition of a possible aggregate 90<sup>th</sup> percentile (including natural sources and via dietary supplements) Estimated Daily Intake of 4845.6 mg/day. The Expert Panel members independently and collectively critically evaluated the statements presented herein and confirmed the GRAS status of OptiMSM® on the basis of the information provided in the original GRAS dossier.

### 2. INTRODUCTION

Bergstrom Nutrition proposes to use OptiMSM® as a food ingredient, at levels up to 4000 ppm in meal supplement and meal replacement foods, fruit smoothie-type drinks, and flavored thirst quencher-type beverages, and up to 30,000 ppm in food bars, such as granola and energy-type bars.

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<sup>1</sup> As defined by §201(s) of the Federal Food Drug and Cosmetic Act

<sup>2</sup> Dossier in support of the Generally Recognized As Safe (GRAS) status of OptiMSM® (methylsulfonylmethane, MSM) as a food ingredient

<sup>3</sup> GRN 000229, please see attached letter from FDA to Dr. Burdock dated August 7, 2007

September 24, 2007

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### 3. ESTIMATED DAILY INTAKE

Methylsulfonylmethane (MSM) is a natural constituent of the typical U.S. diet (*i.e.*, vegetables, grain and meat), resulting in a mean MSM consumption at approximately 2.3 mg/day (0.04 mg/kg/day for a 60 kg human). MSM is considered a source of sulfur for the formation of the amino acids cysteine and methionine. OptiMSM® will be incorporated into specific food products as a food ingredient, and these foods are identified in the original GRAS dossier, according to food codes given in the Health and Human Services (HHS) What We Eat in America, National Health and Nutrition Examination Survey (NHANES), 2001-2002, and these codes have been used to calculate the Estimated Daily Intake (EDI) values for OptiMSM® consumption (Table 1). The addition of OptiMSM® to foods previously stated in the GRAS dossier, which included meat supplement and meal replacement foods, fruit smoothie-type drinks, flavored thirst quencher-type beverages, and food bars, such as granola and energy-type bars, results in a 90<sup>th</sup> percentile consumption of OptiMSM® at 3840 mg/day (64 mg/kg for a 60 kg human). OptiMSM® is also available as a dietary supplement, the estimated consumption of which is approximately 1000 mg/day (16.6 mg/kg/day for a 60 kg human).

**Table 1. Current MSM intake from foods, possible MSM intake following supplementation of selected foods with OptiMSM® at the maximum levels indicated in the GRAS dossier, potential OptiMSM® intake from dietary supplement usage, and total MSM intake (predicted + current)**

| MSM Intake from:  | Per User (mg/day) |                             |
|---|-------------------|-----------------------------|
|   | Mean              | 90 <sup>th</sup> Percentile |
| A. Current consumption from food  | 2.3               | 5.6                         |
| B. Possible maximum consumption with OptiMSM® as an added food ingredient       | 1935.7            | 3840.0                      |
| E. Potential OptiMSM® consumption from dietary supplement use <sup>a</sup>      | 1000.0            | 1000.0                      |
| F. Total consumption from all sources (food + dietary supplements) <sup>b</sup> | 2938.0            | 4845.6                      |

<sup>a</sup>Recommended daily dose per label suggestion from the typical maximum intake via dietary supplement use.

<sup>b</sup>GRN 000229

The GRAS dossier for OptiMSM® indicated that consumption of OptiMSM® at 3840 mg/day (at the 90<sup>th</sup> percentile) is Generally Recognized As Safe (GRAS), under the proposed conditions of use. The estimated aggregate consumption of MSM, through natural sources,

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dietary supplement intake, and as OptiMSM® added to food at the 90<sup>th</sup> percentile, is 4845.6 mg/day (80 75 mg/kg for a 60 kg human).

#### 4. PRECLINICAL AND CLINICAL STUDIES

The following is a summary of the preclinical and clinical studies discussed in detail in the GRAS determination that were considered in the context of determining the safety-in-use of OptiMSM®, when added to foods at the 90<sup>th</sup> percentile level of 3840 mg/day (64 mg/kg/day for a 60 kg human). This is not an exhaustive list of all the information considered in this decision.

- ADME data demonstrate that MSM is rapidly absorbed, with a mean time to peak concentration of 2.1 hours, and that five oral studies have shown that MSM is metabolized and efficiently excreted via the urine, with no accumulation as MSM.
- Animal safety testing has repeatedly demonstrated safety:
  - Acute oral LD<sub>50</sub>s show no adverse effects at doses ranging from 2000 to 20,000 mg MSM/kg in several species.
  - Repeated dose studies show no observed adverse effects of MSM. For example, MSM at 1500 mg/kg/day (the only dose tested) when administered to rats for 90 days showed no adverse effects, and a 90-day study in horses had no adverse effects at 40 mg/kg/day MSM
  - Repeated dose anti-carcinogenicity studies in rats showed no adverse effects of MSM at 4000 mg/kg/day (the highest dose tested) for 300 days
  - A teratology study in rats showed no adverse effects of MSM at 1000 mg/kg/day, the highest dose tested, when administered at Days 6 through 20 of gestation.
  - MSM failed to produce genotoxicity in reverse or forward mutation assays in bacteria or L5178Y tk<sup>+/+</sup> mouse lymphoma cells at up to 5000 µg/plate,

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did not induce chromosome aberrations *in vitro*, and did not increase micronucleation in myelocytes *in vivo* at up to 2000 mg MSM/kg.

- Several additional *in vivo* preclinical studies indicate that MSM was non-irritating when administered topically, intranasally, or to the eye, and was non-sensitizing in the guinea pig maximization test. Administration of MSM at 6000 – 8000 mg/kg/day for approximately four months to a mouse model for autoimmune disease showed no adverse effects, and MSM also had no adverse effects in a murine arthritic model when administered orally for 12 weeks at 3750 mg/kg/day. No effects were noted at the highest doses tested in any of these assays.
- Human studies indicate no adverse effects of MSM consumption:
  - A randomized, double-blind, placebo-controlled clinical trial with 25 subjects that received 100 mg/kg/day OptiMSM® orally for twelve weeks was conducted, with laboratory tests that included clinical chemistry (hepatic and renal function), hematology, lipid profiles, stool occult blood tests, and urinalysis. Questionnaires covering gastrointestinal, peripheral and cognitive neurological symptoms, blood clotting changes, and other symptoms (insomnia, headache and blurred vision) were also conducted. Administration of MSM showed no adverse effects.
  - A five-year-old boy under medical supervision dosed at 62.5 mg/kg/day MSM for one year did not have any adverse clinical, structural, or neurochemical effects.
  - A controlled clinical investigation with controls and three patients (40 – 79 years of age) receiving 40 – 100 mg MSM/kg/day for at least two years showed no adverse effects.
  - An open-label clinical trial in 50 volunteers receiving 433 mg/kg/day for 30 days, with a subset of 16 volunteers administered MSM for an

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additional 14 days at 86.7 mg/kg/day showed no adverse effects to MSM consumption

- o Two double-blind, placebo-controlled studies with 10 and 8 subjects that received MSM at 37.5 mg/kg/day for four months and six weeks, respectively, showed no adverse effects
- o A double-blind, placebo-controlled study with 30 subjects receiving MSM at 25 mg/kg/day for twelve weeks showed no adverse effects

On the basis of the data summarized above, MSM or OptiMSM® was consistently shown to be safe at the highest dose administered in animals and humans and, as such, a specific safety factor was not identified.<sup>4</sup> On the basis of the totality (or weight) of the evidence of the safety of MSM, as demonstrated in animal and human studies and, on the basis of the relevant expertise of the members of the Expert Panel, whose training and experience qualifies them to make such determinations, the Expert Panel has determined the safety-in-use of OptiMSM® in the food categories cited in the GRAS dossier, on the basis of scientific procedures. Further, it is the opinion of the Expert Panel that other experts qualified by scientific training and experience to evaluate the safety of food and food ingredients would concur with these conclusions.

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<sup>4</sup>The Federal Food Drug and Cosmetic Act does not specify that a safety factor is required in a GRAS determination  
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**5. CONCLUSION**

We, the Expert Panel, have individually and collectively critically evaluated the information summarized in this clarification to the Dossier in support of the Generally Recognized As Safe (GRAS) status of OptiMSM® (methylsulfonylmethane; MSM) as a food ingredient. This information is consistent with that provided in the initial GRAS determination and fully supports the GRAS status of OptiMSM® at the levels of use stated in the GRAS dossier. We conclude that the use of OptiMSM® as an ingredient under the intended conditions of use described herein is safe and is Generally Recognized As Safe by scientific procedures. It is our opinion that other experts, qualified by scientific training and experience to evaluate the safety of food and food ingredients would concur with these conclusions.

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Joseph F. Borzelleca, Ph.D., F.A.T.S.  
Medical College of Virginia

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Date

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I Glenn Sipes, Ph.D., F.A.T.S.  
University of Arizona, College of Medicine

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Date 27 Sept 07

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Kendall B. Wallace, Ph D., D A.B.T., F A.T.S.  
University of Minnesota Medical School

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Date



2001 9<sup>th</sup> AVENUE  
SUITE 301  
VERO BEACH, FL 32960  
p•772.562.3900 / f•772.562.3908  
e•gburdock@burdockgroup.com

October 2, 2007

AM



Dr. Marcella Fruchter  
US Food and Drug Administration  
Center for Food Safety and Applied Nutrition  
Harvey W. Wiley Federal Building, HFS – 565  
5100 Paint Branch Parkway  
College Park, MD 20740-3835  
Phone 301-436-1729

cc: Dr. Laura Tarantino

RE: GRN Notice #000229 – Clarification Letter

Dr. Fruchter,

Attached is a copy of the remaining expert panel member signature for the letter to clarify the GRAS dossier entitled “DOSSIER IN SUPPORT OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF OPTIMSM<sup>®</sup> (METHYLSULFONYLMETHANE; MSM) AS A FOOD INGREDIENT,” notified to the FDA on July 11, 2007.<sup>1</sup> GRN 000229.

If you have any further questions regarding these or any other topics concerning the GRAS dossier of the addition of OptiMSM<sup>®</sup> to the foods and drinks described herein (GRN 000229), please contact me

Sincerely,

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Melinda Swetz  
Project Manager

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<sup>1</sup> GRN 000229, filed with FDA on July 25, 2007, in accordance with 21 CFR 170.36.

5. CONCLUSION

We, the Expert Panel, have individually and collectively critically evaluated the information summarized in this clarification to the Dossier in support of the Generally Recognized As Safe (GRAS) status of OptiMSM® (methylsulfonylmethane; MSM) as a food ingredient. This information is consistent with that provided in the initial GRAS determination and fully supports the GRAS status of OptiMSM® at the levels of use stated in the GRAS dossier. We conclude that the use of OptiMSM® as an ingredient under the intended conditions of use described herein is safe and is Generally Recognized As Safe by scientific procedures. It is our opinion that other experts, qualified by scientific training and experience to evaluate the safety of food and food ingredients would concur with these conclusions.

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Joseph F. Borzelleca, Ph.D., F.A.T.S.  
Medical College of Virginia

\_\_\_\_\_  
Date

\_\_\_\_\_  
I Glenn Sipes, Ph.D., F.A.T.S.  
University of Arizona, College of Medicine

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Date

(b)(6)

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Keridall B. Wallace, Ph.D., D.A.B.T., F.A.T.S.  
University of Minnesota Medical School

2 Oct 2007  
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Date