RISK PROFILE

Methylsulfonylmethane (MSM)

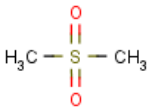
CAS No.67-71-0

Date of reporting 05.06.2012

Content of document

1 Identification of substance ..... p. 1
2 Uses and origin ..... p. 2
3 Regulation ..... p. 3
4 Relevant toxicity studies ..... p. 3
5 Exposure estimates and critical NOAEL/NOEL ..... p. 5
6 Other sources of exposure than cosmetic products ..... p. 6
7 Assessment ..... p. 8
8 Conclusion ..... p. 9
9 References p.10
10 Annexes p.12

1. Identification of substance

Chemical name (IUPAC):	Methylsulfonylmethane (MSM)
INCI	Dimethyl sulphone (DMSO2)
Synonyms	
CAS No.	67-71-0
EINECS No.	200-665-9
Molecular formula	$(CH_3)_2SO_2$
Chemical structure	
Molecular weight	94.13
Contents (if relevant))	
Physiochemical properties	Appearance: white crystalline powder Density: 1.17 g/cm^2 Boiling point: 248 °C Melting point: 109 °C Flash point: 143 °C Vapor pressure: 5.15 mm/Hg @ 25.00 °C. (est) Solubility: completely miscible with water (1,000 g/l). Log P_{OW}: -1.41 References: Gaylord chemical bulletins [online]).

2. Uses and Origin

Uses	➢ **Cosmetic products:** *Functions according to* • CosIng database: "Solvent" – "dissolves other substances" "Viscosity controlling" – "increases or decreases the viscosity of cosmetics" • Other: MSM is found in a wide variety of cosmetic products, including antiperspirant/deodorant, (Annex 4). MSM is claimed to be anti-inflammatory and to moisturize, soften and rejuvenate dry, aging, or damaged skin (Gaylord chemical bulletins [online]). MSM was included in a study conducted by the Danish Technological Institute (Miljøministeriet) that concerned health risk assessment of so-called sports products being used for easing of uncomfortable sensations caused by exercise (Hansen et al., 2006). *Concentrations of MSM being applied* Examples: in the Danish study a maximum content of 8.2 µg MSM /g (i.e. 0.82%, w/w) was found in a sport product sample (Hansen et al., 2006). A lotion marketed on the internet contained 10% MSM (Annex 4). *Frequency of use* The EWG Skin Deep cosmetic database (EWG's Skin Deep [online]) lists 266 cosmetic products containing MSM: – facial moisturizer/ treatment (61 products) – nail polish (58 products) – anti-aging (30 products) – facial cleanser (27 products) – moisturizer (24 products) The German database 'Codecheck' contains 22 products in the same categories as EWG, including sun-creams (Codecheck [online]). ➢ **Food**[1] MSM occurs naturally in small amounts in some green plants, fruits and vegetables, and is an important source for organic sulphur (Parcell, 2002; Annex 3[i]; The MSM miracle [online]). MSM is also frequently used - and is present in larger amounts - in dietary supplements (Annex 3[ii]). ➢ **Medicinal products**

[1] MSM (OptiMSM") is Generally Recognized As Safe (GRAS) as a food ingredient has –see GRAS notice to FDA, 2007. http://www.accessdata.fda.gov/scripts/fcn/gras_notices/grn000229.pdf

	MSM is promoted as having anti-inflammatory and analgesic effects, often in combination with glucosamine and/or chondroitin, but its ability to decrease degenerative processes in joints (e.g. osteoarthritis) is as yet unproven (Gregory et al., 2008). See also Annex 2[iv, v] for summary of preclinical and clinical studies. Some concrete products meant for relief of pain and muscle/joint soreness are mentioned in Annex 4. MSM was included in a publication by the Danish Technological Institute (Miljøministeriet) titled *"Survey and health risk assessment of products for treatment of sports injuries and pains"*, (Hansen et al., 2006). ➢ **Other products**
Origin (natural/synthesis)	MSM is an organic sulphur-containing substance that is an important source for organic/biological sulphur, e.g. cysteine and methionine production, which are important components of proteins, connective tissues, hormones, and enzymes (Parcell, 2002). Available salt forms or related substances for MSM include tablets containing glucosamine with/without sodium chondroitin sulfate and MSM (Helsebiblioteket [online]; UpToDate [online]). MSM is an oxidation product of DMSO (dimethyl sulfoxide). Thus, it is chemically related to DMSO, and has been used similarly as an organic solvent; roughly 15% of DMSO is converted metabolically to MSM. As a food ingredient, MSM is produced from DMSO and hydrogen peroxide, forming a white, odourless, slightly bitter tasting substance. References: Gaylord chemical bulletin [online]. UpToDate [online].

3. Regulations

Norway	No regulation[2]
EU	No regulation
Rest of the world	No regulation

4. Relevant toxicity studies

Absorption Skin GI tractus	No dermal absorption data is available, and a default value of 100 % will therefore be used in calculations of margin of safety (SCCS, 2010).

[2] The Norwegian medicinal products agency considered MSM a medicinal remedy. Because of that up till 2008 topical products containing the substance were considered medicines – meaning a topical product containing it were automatically classified a medicine. This regime has since been lifted.

Distribution **Metabolism**	MSM is found naturally at concentrations about 0.2 mg/kg in the circulation of the human body (adult male).
Excretion	Orally MSM is rapidly absorbed, well distributed, and efficiently excreted from the body (Magnuson et al., 2007). MSM is excreted in human and bovine milk and in human urine (4-11 mg/day of MSM are normally excreted in the urine) (Parcell, 2002 and references therein). When DMSO is applied on the skin or taken orally, about 15% of it breaks down in the body to form MSM.
Local toxic effects Irritation Sensitivity	No adverse effects of MSM such as skin allergy or irritations has been reported (RTECS database, Annex 1; Hansen et al., 2006). Topically applied MSM was judged as "non-irritant" to the skin of New Zealand white rabbits, and there was no evidence for skin sensitization in guinea pigs. References: Gaylord chemical bulletin [online]; Toxnet [online]).
Systemic toxic effects	In humans, no peer-reviewed data was retrieved on the potential adverse effects of long-term use of MSM. Most human studies have been focusing on positive health effects of MSM (e.g. pain relief for arthritis). Orally ingested MSM is believed to be non-toxic in humans in the range of 1 - 3 g/day (Parcell, 2002; Hansen et al., 2006). A laboratory study reported no toxic effects even at oral doses up to 8 g /kg body weight/ day (about 250 times the highest dose normally used by humans) (Morton & Siegel, 1986).
Acute	Annex 2 [i] presents a summary of acute and sub-acute animal toxicity studies on MSM. The acute oral median lethal dose (LD50) of MSM is greater than 17 g /kg bw when administered as a 25 % (w/v) aqueous solution to albino rats. Most studies in rats showed no adverse events following acute exposure of MSM at daily doses of 2 - 5 g /kg bw. See also Toxnet [online]; RTECS- #PB2785000).
Repeated dose	In a 90-day sub-chronic follow-up study, rats receiving orally doses of 1.5 g MSM/kg bw/day showed no adverse effects or increased mortality (Horváth et al., 2002). The NOAEL based on this experiment was determined to be >1500 mg/kg bw/day.
Mutagenicity / genotoxicity	No evidence was found for genotoxicity of MSM *in vitro* and *in vivo* at doses up to 5 mg/ml and 5000 mg/kg, respectively (Lee et al., 2006). (Annex 2, iii).
Carcinogenicity	No data retrieved.
Reprotoxicity / teratogenicity	In a nematode model of developmental and reproductive genetics, MSM was found to cause chromosome abnormalities and a decrease in fertility (Goldstein et al., 1992). The relevance of these results to humans is unclear, and more definitive developmental toxicity studies in animals are required, and has since been performed (Magnuson et al., 2007a). The reproductive toxicity of DMSO was evaluated in an *in vitro* culture of mammalian rodent embryos (Augustine-Rauch et al., 2004, cited in

	Annex 2, [ii]). At a concentration of 0.04% in culture media, DMSO produced significant embryo toxicity, resulting in failure of neural tube closure. However, *in vitro* data is difficult to extrapolate to *in vivo* responses in humans. The first (and only) reported study evaluating maternal or developmental toxicity in rats, found no evidence for reproduction toxicity at doses up to 1000 mg/kg/day The authors reported the NOAEL for maternal and developmental toxicity as ≥ 1000 mg/kg/day, the highest dose tested (Magnuson et al., 2007; Annex 2, ii).
Other effects	DMSO[3] exposure to developing mouse brains can produce brain degeneration (Hanslick et al., 2009). This neurotoxicity could be detected at doses as low as 0.3 ml/kg (DMSO > 99% pure), a level exceeded in children exposed to DMSO during certain medical treatments.

5. Exposure estimate and critical NOAEL / NOEL

NOAEL/NOEL critical	The NOAEL was estimated to be at least 1500 mg/kg/day, based on a 90 day repeated dose toxicity study in rats (Horváth et al., 2002).
Exposure cosmetic products	• **Sports cream** [4] The systemic exposure dose (SED) of MSM is illustrated by a sports cream with a maximum content of 8.2 mg/g (0.82 %) MSM: Total amount applied of product[5]: 5 g Daily exposure (male, 70 kg): 5000 mg/70 kg = 71.43 mg/kg bw/day Frequency of application: 1/day Dermal absorption[6] (SCCS default value): 100% = 1.0 Concentration of ingredient in the product: 0.82% = 0.0082 Retention factor: 1 SED = 71.43 mg/kg bw/day x 1 x 1.0 x 0.0082 x 1 = **0.585 mg/kg bw/day** • **Shaving cream** 10% MSM (cream, **shaving cream**) Amount applied (SCCS default value): 1 mg/cm^2 Surface area (SCCS default value): 305 cm^2 Body weight: 74 kg (men) Total amount applied of product: 1 mg/cm^2 x 305 cm^2 = 305 mg Daily exposure (male, 74 kg): 305 mg/74 kg = 4.1 mg/kg bw/day

[3] The possible relevance for MSM exposure is that approx. 15% of DMSO is converted metabolically to MSM.
[4] Sports creams falling within the scoop of the cosmetic products regulation must not claim pain removal or easing of discomfort in muscles. Such claims will automatically place these products within the scoop of the medicinal products legislation.
[5] The applied amount of sports cream is based on a pilot experiment in which one leg of two persons was exposed to 5 grams of cream. See also Hansen et al. (2006) for method of calculation.
[6] Assumed that the fraction of the absorbed substance is 100 % for log Pow <4

	Frequency of application: 1/day Dermal absorption (SCCS default value): 100% = 1 Concentration of ingredient in the product: 10% = 0.1 Retention factor: 0.01 SED= 4.1 mg/kg bw/day x 1 x 1.0 x 0.1 x 0.01 **= 4.12 µg/kg bw/day** • **Body lotion** 10% MSM (cream, **body lotion**) Calculated relative daily exposure of product: 123.20 mg/kg bw/day Concentration of ingredient in the product: 10% = 0.1 Dermal absorption (SCCS default value): 100% = 1 SED = A (mg/kg bw/day) x C(%)/100 x DA_p (%)/100 = 123.20 mg/kg bw/day x 0.1 x 1 = **12.32 mg/kg bw/day** **Overall SED**: 0.585 + 0.004 + 12.32 = **12.9 mg/kg bw/day**

Margin of Safety (MOS)	NOAEL: 1500 mg/kg bw/day **MoS for sports cream**: SED = 0.585 mg/kg bw/day MoS (NOAEL/SED) =1500/0.6 = 2564 **MoS for shaving cream**: SED = 4.12 µg/kg bw/day MoS = 1500/0.00412 = 364088 **MoS for body lotion**: SED = 12.32 mg/kg bw/day MoS = 1500/12.32 = 121 **MoS for overall exposure of cosmetic products**: 1500/12.9 = **116**

6. Other sources of exposure than cosmetic products

Food and supplements	The main oral intake of MSM is from dietary supplements *('nutraceuticals'),* with typical dosages in the range of 500 – 2500 (up to 8000) mg/day (UpToDate [online]). (-> ca. 8 – 40 mg/kg bw/day). The natural occurrence of MSM in a variety of fruits, vegetables, and grains is much less (e.g. tomatoes, 0.86 ppm). MSM is present in cow milk; 3.3 ppm - equals 3.3 µg /g product (Hansen et al. 2006: pp. 46).
Pharmaceuticals	For clinical trials of osteoarthritis, daily doses of 1500 -6000 mg MSM has been reported (WebMD [online]).
Other sources	
Adverse side effects – from uses other than cosmetics	MSM is believed to be non-toxic. No threshold limit values or restrictions for the substance have been found (Hansen et al., 2006). See also annex 2. MSM has been used for many years (e.g. dietary supplements and in clinical trials) in amounts above 2000 mg/day without reported significant adverse effects. Diarrhea, skin rash, headache, and fatigue may be experienced in less than 20% of people (Relis [online]).

	MSM is capable of crossing the blood brain barrier, and accumulation of MSM in the human brain of a person taking MSM supplements has been reported, but no adverse clinical or neurochemical effects have been observed (Lin et al., 2001). A recent report demonstrating that DMSO produces widespread apoptosis in the developing central nervous system of newborn mice (Hanslick et al., 2009), is of potential relevance also for MSM, since these two substances are closely related (i.e. approximately 15% of DMSO is converted metabolically to MSM). The effect was detectable at doses as low as 0.3 ml/kg (DMSO > 99% pure), a level exceeded in children exposed to DMSO during certain medical treatments (e.g. bone marrow transplantation). Further, DMSO caused neuronal loss at 0.5% and 1.0% concentrations in an *in vitro* rat hippocampal culture. Human bone marrow cells used for transplants are protected from damage by DMSO while being frozen. Acute DMSO toxicity has been reported in very compromised patients that received intravenous infusion (200 ml or 500 ml) of cells suspended in 10% DMSO directly into the bloodstream (Chen-Plotkin et al., 2007). This technique is used routinely in children who receive bone marrow transplantation, and because doses of DMSO are higher than 0.3 ml/kg, there is concern that DMSO might be neurotoxic. Young children who get bone marrow transplants may be at risk for the neurotoxic effects of DMSO. However, there is no data in rodents that examine the cognitive and behavioral effect of neonatal DMSO. Possible drug interactions of concerns have not been reported.

7. Assessment

General toxicity
Long term studies in humans have showed no significant adverse effects of MSM, and no threshold limit values or restrictions for the substance have been found (Hansen et al., 2006; see also annex 2).

A study in 2009 demonstrating that DMSO produces premature death of nerve cells in infant and juvenile mice (Hanslick et al., 2009), gives rise to concerns that young children who get bone marrow transplants may be at risk for the neurotoxic effects of DMSO. Acute DMSO toxicity has been reported in compromised patients that received *intravenous* infusion of cells suspended in 10% DMSO directly into the bloodstream, but there is no data in rodents that examine the cognitive and behavioral effect of neonatal DMSO (Chen-Plotkin et al., 2007).

Cosmetics
Systemic exposure dose (SED) was calculated using cosmetic products with different exposure levels, such as shaving cream (small body surface, rinse-off), sports cream (medium body surface, leave-on), and body lotion (large body surface, leave-on). In sports cream, as part of a survey by the Danish Environmental Protection Agency, Hansen et al. (2006) found that the highest content of MSM was 8.2 mg/g (i.e. 0.82%, w/w), whereas 10% MSM was used as an illustrative example for shaving cream and body lotion. Calculation of the corresponding MoS values, using a NOAEL value of 1500 mg/kg/day (based on long-term toxicity studies in animals), gave MoS values of 364088 (shaving cream), MoS = 2500 (sports cream), and MoS = 121 (body lotion). Because the NOAEL is based on animal data, a MoS of 100 (or more) represents a sufficient safety margin.

Remarks:
Maximum safe doses for young children, pregnant or nursing women, or people with liver or kidney disease are not known.

Food supplements
MSM is a natural component of food, with the main intake being from dietary supplements, with typical use levels in the range of 500 – 2500 mg/day. The corresponding SED (8 – 40 mg/kg bw/day) is similar to or higher than the largest exposure of MSM from cosmetics (SED = 12.3 mg/kg bw/day).

There are no data indicating any negative long-term health effects of MSM ingested as dietary supplement (GRAS Notification of MSM to FDA [online]; see also Annex 2).

Medicinal products
MSM is not accepted for therapeutic use.

Total exposure
We assessed the systemic exposure from cosmetic products containing 10% MSM (shaving cream, body lotion) and 0.82% MSM (sports cream), as an illustration of total body exposure. The corresponding MoS is 116, representing a sufficient safety margin if only cosmetic products are considered. If MSM in dietary supplements is taken into account, a safety margin below 100 must be expected, as the contribution from dietary supplements is generally greater than from cosmetics.

Remarks:
It is presently unknown whether the observation that DMSO produces premature death of nerve cells in infant and juvenile mice (Hanslick et al., 2009) is of relevance to the dermal exposure of MSM from cosmetic products, or from orally ingested MSM in dietary supplements. Further animal studies should examine the safety of MSM as it relates to neurotoxicity, in particular with regard to cognitive and behavioral effects of neonatal dermal and/or oral exposure of MSM.

8. Conclusion

No adverse effects of MSM such as skin allergy or irritations have been reported, and the published toxicity data of MSM indicate that the substance is safe in cosmetic products at indicated usage levels (e.g. up to 10% MSM in body lotion). Because the toxicological and physiological properties of MSM have not been fully explored in humans, care should be used in handling this substance.

For MSM in all cosmetic products, we propose a maximum usage dose of 1.0%.
(This represents a MoS > 1000 for overall exposure of cosmetic products).

9. References

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10. Annexes

Annex 1: RTECS database

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*** CHEMICAL IDENTIFICATION ***

RTECS NUMBER            : PB2785000
CHEMICAL NAME           : Methane, sulfonylbis-
CAS REGISTRY NUMBER     : 67-71-0
LAST UPDATED            : 199710
DATA ITEMS CITED        : 4
MOLECULAR FORMULA       : C2-H6-O2-S
MOLECULAR WEIGHT        : 94.14
SYNONYMS/TRADE NAMES :
   * Dimethyl sulfone
   * Dimethyl sulphone
   * Methyl sulfone
   * Methylsulfonylmethane
   * Sulfonylbismethane

                      *** HEALTH HAZARD DATA ***

                       ** ACUTE TOXICITY DATA **

TYPE OF TEST            : LD50 - Lethal dose, 50 percent kill
ROUTE OF EXPOSURE       : Oral
SPECIES OBSERVED        : Rodent - rat
DOSE/DURATION           : >5 gm/kg
TOXIC EFFECTS :
   Details of toxic effects not reported other than lethal dose value
REFERENCE :
   NTIS** National Technical Information Service.  (Springfield, VA 22161)
   Formerly U.S. Clearinghouse for Scientific & Technical Information.
   Volume(issue)/page/year: OTS0533525

TYPE OF TEST            : LD50 - Lethal dose, 50 percent kill
ROUTE OF EXPOSURE       : Administration onto the skin
SPECIES OBSERVED        : Rodent - rabbit
DOSE/DURATION           : >5 gm/kg
TOXIC EFFECTS :
   Details of toxic effects not reported other than lethal dose value
REFERENCE :
   NTIS** National Technical Information Service.  (Springfield, VA 22161)
   Formerly U.S. Clearinghouse for Scientific & Technical Information.
   Volume(issue)/page/year: OTS0533525

                         *** STATUS IN U.S. ***

   EPA TSCA Section 8(b) CHEMICAL INVENTORY

   EPA TSCA TEST SUBMISSION (TSCATS) DATA BASE, JUNE 1998


                           *** END OF RECORD ***
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Annex 2: Toxicity studies

Excerpts: GRAS Notification MSM [online].

(i) Acute and subacute toxicity

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

Species	Route	Duration of exposure	LD_{50} (mg/kg)	Reference
Mouse	Oral	Acute	>2000	Yu and Peano (2000a)
Mouse	Oral	Acute	>5000	Kocsis *et al* (1975)
Mouse	Intraperitoneal	Acute	>5000	Kocsis *et al*. (1975)
Rat	Oral	Acute	>2000	Horvath *et al*. (2002)
Rat	Oral	Acute	>2000	Yu and Peano (2000b)
Rat	Oral	Acute	>20,000	Hixson (1958)
Rat	Oral	Acute	≥17,020	Schoenig *et al* (1968)
Rat	Oral	Acute	>5000	De Crescente (1981, 2004b)
Rat	Inhalation	Acute	>600	Yu and Peano (2000c)
Rat	Intraperitoneal	Acute	>5000	Kocsis *et al*. (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 *et al* (2001)

*No additional information was stated

(ii) Reproductive toxicity

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 *et al* (2006b)
Rat embryo	0.04% DMSO in culture media	48 hours	Incubated in culture media	Significant embryo toxicity	Augustine-Rauch *et al*. (2004)
Nematode	Five percent MSM concentration *in vitro*	11 days	Grown in media containing MSM	Dose-related decrease in fertility and increased production of abnormal gametes Loss of viability and fertility	Goldstein *et al* (1992)

DMSO = dimethylsulfoxide, MSM = methylsulfonylmethane

(iii) Summary genotoxic effects

Table 10. Summary of the genotoxic effects of MSM

Type of assay	Test organism	Concentration	Results	Reference
		In vitro		
Reverse mutation assay*	*Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, TA1537	50 – 5000 µg/plate	No significant increase in reversions	Fassio and Barone (2000)
Reverse mutation assay*	*S typhimurium* strains TA97A, TA98, TA100, TA102, TA1535	50 – 5000 µg/plate	No significant increase in reversions	Summers (2005)
Reverse mutation assay*	*S typhimurium* strains TA98, TA100, TA1535, TA1537; *Escherichia coli* stram WP2uvrA	312 5 – 5000 µg/plate	No significant increase in reversions	Zheng and Lee (2004d)
Reverse mutation assay*	S. typhimurium strains TA98, TA100, TA1535, TA1538	2500 – 10,000 µg/plate	No significant increase in reversions	Lee *et al* (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)
		In vivo		
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

(iv) Clinical studies – oral administration of MSM

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 *et al* (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 *et al* (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 *et al* (2002)

(v) Summary preclinical and clinical studies

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 90th 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_{50}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 $tk^{+/-}$ mouse lymphoma cells at up to 5000 µg/plate,
- 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.[4] 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.

Annex 3: Food products containing MSM and consumption

(i) Food products containing MSM

9. APPENDIX I

Food products reported to contain MSM

Product	Level (ppm)	Reference
Alfalfa	0.07	Pearson *et al.* (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 *et al.* (1981)
Cucumber	Trace	VCF (1999)
Durian (*Durio zibethinus*)	NR	VCF (1999)
Guava fruit (*Psidium guajava* 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 *et al* (1981)
Mussel	0 29	VCF (1999)
Oatmeal	<0.05	VCF (1999)
Pork liver	NR	VCF (1999)
Raspberry (*Rubus idaeus* L)	Trace	VCF (1999)
Shrimps (cooked)	NR	VCF (1999)
Shrimps (roasted)	NR	VCF (1999)
Swiss chard (*Beta vulgaris*)	0 05-0.18	Pearson *et al* (1981)
Tea, black	0 3	VCF (1999)
Tomato	Trace- 0 86	VCF (1999)
Vitis vinifera L	NR	VCF (1999)
Watercress (*Nasturtium officinale* 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

(ii) Consumption of MSM added to target food

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

Annex 4: Examples of uses for MSM in cosmetic products on the market – retrieved 07.03.2011

Product Name	**Distributor /Manufacturer**	**Markets –retail trade**	**Cosmetic category (intended use)**	**References /internet links**[7]
Mystic Tan Perfect Tan Kit Body	Mystic Tan Inc.	International (www.amazon.com, www.drugstore.com)	Naturally-derived tanning agents and enriched with antioxidant botanicals to create healthy-looking skin and the perfect tan	1)
MSM Natural Pain Relieving Cream Plus Glucosamine Bromelain and Chondroitin	Natural Radiance	International www.amazon.com	Pain Relieving Cream; MSM helps relieve inflammation in the tissues and swelling of muscles and joints	2)
Life-Flo MSM Plus Natural Methylsulfonylmehtane Body Cream, Maximum Strength	Life-Flo Group, The	International www.amazon.com	anti-aging; moisturizer	3)
Laid in Montana Hot Spice & Ice Herbal Pain Reliever with MSM	Laid in Montana by Montana Emu Ranch Company	http://www.ewg.org	muscle / joint soreness; pain relief	4)
MSM Pure & Natural Lotion (10% MSM)	Sunstar Organics	International: sunstarorganics.com		5)

[7] 1) http://www.drugstore.com/mystic-tan-perfect-tan-kit-body-66-value-dollars/qxp194285; http://www.amazon.com/Mystic-Tan-Perfect-Body-Value/dp/B001CE1I5O
2) http://www.excessivesweatingrelief.com/msm-natural-pain-relieving-cream-plus-glucosamine-bromelain-and/
3) http://www.ewg.org/skindeep/product/120941/Life-Flo_MSM_Plus_Natural_Methylsulfonylmehtane_Body_Cream,_Maximum_Strength/
4) http://www.ewg.org/skindeep/product.php?prod_id=181522&remove=1
5) http://tinyurl.com/6wdtssc