DIMETHYL SULFOXIDE (DMSO)

A "NEW" CLEAN, UNIQUE, SUPERIOR SOLVENT

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ABSTRACT

Dimethyl Sulfoxide (DMSO) - A "New" Clean, Unique, Superior Solvent.

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Even though commercialized since the 1950's, DMSO is "New" because it is often not considered as a viable compound in may potential applications and thus is very underutilized in the market place. Several reasons are explained for this. Worldwide production capacity has been steadily increasing over the last 15 years.

DMSO is a unique solvent that is manufactured as a high quality product from a renewable process stream in the paper production industry. It has very low toxicity to humans and the environment, is recyclable after most uses, is present in many foods, and plays a significant role in nature's Global Sulfur Cycle. DMSO is a highly polar, aprotic solvent. Solvency is discussed in terms of the Hansen Solubility Parameters in both the theoretical and practical sense. Several broad based uses in the Paint Stripping, Semiconductor, and Pharmaceutical Industries are shown for pure DMSO and in DMSO based solvent systems. DMSO can meet the ever-increasing safety and environmental demands of the 21st Century. *35 References*

This paper will cover four major aspects of Dimethyl Sulfoxide (DMSO) chemistry. (Figure 1). It will cover DMSO history and how it is manufactured by an environmentally friendly process, DMSO's low toxicity, the outstanding properties of DMSO when compared to competing solvents, and existing and potential applications.

DMSO was first prepared in the laboratory in 1867 (by Saytezff), basically lay dormant for about a century, and commercial production began in the late 1950's with increases ever since. So how can DMSO be a "New" solvent? It is "New" because it is not widely known in terms of its full capabilities, and it is greatly underutilized in industries where there is sizable potential for DMSO use as a clean, non-toxic, superior dipolar aprotic solvent. (Figure 2).

Worldwide shipments of DMSO when compared with several major competing solvents[(1)], show that DMSO is consumed at only 10-20% of the rate of competing solvents and at only 50% of its worldwide capacity. Japan/Korea and North America are the largest consumers of DMSO (Figure 3). The major use of DMSO in Asia is the semiconductor industry and in North America it is the pharmaceutical industry. The use of DMSO has not been high in the rest of the world. There could be significant growth in the use of DMSO if these two uses were spread worldwide.

Why is DMSO that is significantly less toxic, and can be used as a replacement for the other solvents shown, either neat or in safe solvent mixtures, so underutilized? Perhaps DMSO usefulness has not been fully communicated to those in positions able to make decisions on commercial solvent selection, or perhaps it is because of "Safety Myths" that have surrounded DMSO for a number of years. These myths have been debunked in two publications:

1. Paper: Dimethyl Sulfoxide (DMSO: A Superior Solvent Underutilized Because of a Safety Myth, by Robert P. Vignes, Ph.D. of Vignes EHS Consulting; presented at the Semiconductor Safety Association Annual Meeting, April 25-28, 2000, Arlington, VA. Contains 65 References

2. CD Video: DMSO Myth Buster.- 15 Minutes of Facts About DMSO

Both of the above are available from Gaylord Chemical Corporation, 106 Galeria Blvd., Slidell, LA 70458; phone (800) 426-6620 or (504) 649-5464.

The process to make DMSO starts with the black liquor stream from a paper mill. (Figure 4). Black liquor contains lignins which are the "glue" that holds the cellulose together in pine trees. The lignins react with sulfur recovered from hydrocarbon streams in an oil refinery to make dimethyl sulfide (Figure 5). Since the lignins come from a renewable

resource and the sulfur from the reduction of sulfur in fuels, both raw materials can be considered “green” in nature.

Once the DMS has been made and purified, it is reacted with oxygen using dinitrogen tetroxide as an oxygen transfer agent. The nature of NO and NO_2, is such that one molecule of NO_2 can transfer up to 40 oxygen atoms during one pass through the reactor. Exiting the reactor the NO is separated and recycled back for additional passes through the reactor.

The low toxicity of DMSO is very significant (Figure 6). Acute inhalation toxicity for Sprague-Dawley rats was very low when tested at high concentrations in air, which, because of the low vapor pressure of DMSO, cannot be achieved under normal atmospheric conditions. [3] The acute inhalation toxicity is comparable to nail polish and much less toxic than the active ingredient in vinegar --- acetic acid.

The acute oral toxicity of DMSO (Figure 7) in terms of LD_{50} literature averages for three animal species, were converted to human equivalent in pounds with a safety factor or 10 for interspecies extrapolation and other testing uncertainties.[4]. Two conclusions can be drawn: (1) the human oral dose for DMSO required to kill 50% of those ingesting it (LD_{50}) is fairly high and (2) DMSO is approximately five times safer than N-Methylpyrrolidone (NMP) under these circumstances.

DMSO has a proven safety record with humans. There were four, purposely planned, human exposure case studies by various routes of DMSO administration.[5-13] (Figure 8). In Case No. 1, there was no significant short-term effects on the kidneys (no nephrotoxicity) for intravenous injection of up to 40% DMSO in water for seven patients with spinal cord injuries.

In Case No. 2, when DMSO was applied to the skin or taken by mouth in fairly high doses (1 g/kg body weight = 80 g or about 0.2 lb for a 175 lb person) all DMSO was partially metabolized to Dimethyl Sulfone ($DMSO_2$) and DMS and excreted from the body within 24 hours. Thus, No Observable Effects Levels (NOEL) are high also for dermal and oral administration. The oral NOEL of 1,000mg/kg is equal to the tested dose just described (0.2 lb/175 lb human) and the dermal NOEL is 2600 mg/kg is over 2½ times the tested dose in these studies. Case No. 3 (Figure 9) showed that topical (dermal) application of mixtures of DMSO and Penicillin G almost doubles the skin penetration rate of the Penicillin, but did not enhance the penetration rate of higher molecular weight substances such as the "allergic chemicals" associated with house dust, animal hair, and grasses and weeds. Finally, in case No. 4 (Figure 10) direct toxicity testing using 100% DMSO both inside the human body (invivo) and on human organs and tissue outside the body (invitro), showed that the "toxicity of DMSO is exaggerated", it is really quiet low, and in fact it is useful in treating muscle and joint inflammation, as well as other pharmaceutical uses. DMSO is present in many of the foods we eat (Figure 11) [17] and the normal human dietary consumption is about 21 mg/day. In the United States, the average concentration of DMSO in rainwater is between 0.14 and 0.19ppb. This is a segment of the involvement of DMSO in the Global Sulfur Cycle. [18]

The comparative toxicity of several common dipolar aprotic solvents is shown in Figure 12. [16]. DMSO is the only one that does not have a maximum allowed exposure limit assigned to it in the workplace. This is further testament to its low toxicity. The Workplace Environmental Exposure Level (WEEL) for N-methylpyrrolodone (NMP) of 10ppm was set by the American Industrial Hygiene Associateon (AIHA). Threshold Limit Values for

dimethylformamide (DMF) and dimethylacetamide (DMAC) set by the American Conference of Governmental Industrial Hygienist (ACGIH) are quite low at 10ppm for airborne concentrations in an 8-hour workday/40 hour workweek. The NOEL for DMSO is higher than the other solvents by a factor of 4.4 to 22, again indicating relatively low toxicity for DMSO Sleepiness as a side effect of NMP could be a problem in the workplace.

Turning to the environment, approximately 60 billion pounds of DMSO are produced in nature annually as part of the Global Sulfur Cycle (Figure 13). [19] With the appropriate natural enzymes to catalyze the reactions, DMSO is reduced to DMS, which dealkylates in two steps to hydrogen sulfide via methanethiol. H_2S is then realkylated to methanethiol and DMS, much of which evaporates, and is then oxidized in nature to DMSO. The DMSO returns to earth and the cycle begins over again.

The toxicity to fish, aquatic invertebrates, and aquatic plants is very low [14] (Figure 14). The LD_{50}'s range for salmon and trout are 12 to 17 g/kg. The EC_{50}'s for aquatic invertebrates and plants are from 2% to 3%. DMSO is environmentally compatible and the EPA has classified DMSO as "practically non toxic". [15]

The chemical structure and some of the basic physical properties of DMSO[2] are shown in Figure 15. Discussion of structural detail will be given later in this paper. Note the low vapor pressure which means, among other things, that fumes are not an issue from a safety stand point. Both the flash point and auto ignition temperature in air are high. The very small Henry's Law constant indicates that in a mixture of DMSO and water (totally miscible), the

water will evaporate and leave the DMSO behind which is a desirable environmental feature for capture/recovery of DMSO from spills. The very low octonol-water partition coefficient means DMSO certainly does not bioaccumulate. The biodegradation rate in water/soil and the photodegradation rate in air are fairly rapid.

Now let's turn to the fundamental basis for technical design of solvent systems, in this case based on DMSO, for many of the excellent safety, health and environmental reasons just discussed[20,21]. The Hildebrand total solubility (Figure 16) model which is defined as the square root of the cohesive energy density, gives a single number that is directly proportional to the molar heat of vaporization (corrected for energy due to volume expansion to the vapor state, i.e. RT) and inversely proportional to the molar volume. The total solubility parameter is a measure of the energy required to form a cavity in the solvent matrix to accommodate another solvent or a solute at the molecular level. Said another way, the solubility parameter is a measure of the cohesive energy that tends to hold a solvent together and which must be overcome before it will mix freely with another substance. Thus, on an absolute scale, the higher the solubility parameter for a solvent, the more difficult it will be to get another substance to mix with it. Returning to the Hildebrand equation, the higher the heat of vaporization and the smaller the molar volume, the more cohesively a solvent is held together. While true, thinking of solubility parameters in an absolute sense can be somewhat misleading. It is more important to consider Solubility Parameters relative to each other, while remembering a basic principle of solubility chemistry: "Like Dissolves Like". For mixing two or more substances, it is more important that the Solubility Parameters be similar, than whether they are "high" or "low" in an absolute sense.

Hansen [26] divided the Hildebrand Total Solubility Parameter into the energies associated with three modes of interaction among molecules, such that the square of the Total Solubility Parameter ($*_t$) is equal to the sum of the squares of the following:

1) Dispersive Interactions ($*_d$) – due to temporary separation of charges within a molecule and the associated instantaneous interactions with adjacent molecules. It can be viewed as a "transient dipole".
2) Polar Interactions ($*_p$) – due to permanent dipoles in a molecule and associated interactions with adjacent molecules. Polar interactions can induce dipoles in non-polar molecules and also interact in that manner.
3) Hydrogen-bonding Interactions ($*_h$) – due to attraction of hydrogen atoms to atoms with higher electronegivity, such as oxygen, chlorine, etc. In other words, polarized hydrogens, which interact with adjacent molecules.

The Hansen parameters blend linearly on a volume basis. These parameters may be calculated based on known physical properties, determined experimentally (as we will show shortly), or simply looked up in a Table of Hansen Parameters, which can be sparse in data when dealing with a wide variety of substances.

Hansen Parameters for solvents can be determined by calculation (Figure 17). First, the dispersive parameter (δ_d) is approximated by equating it to the total solubility parameter (δ_t) of a homomorph of the solvent under study. A homomorph is a non polar solvent, usually a saturated hydrocarbon that is similar in size and shape to the solvent under study. In a

saturated hydrocarbon, the only solvent forces are dispersive, and hence, while being a good approximation for δ_d for a polar solvent, it is the largest potential source of error in the calculation process. Total solubility parameters ($\delta_{t)}$ are known for a relatively high number of solvents. Next, the polar parameter is calculated by an equation in which δ_p is equal to 18.3 times the dipole moment (μ) in debye units divided by the square root of the molar volume (V) expressed as cubic centimeters per gram mole. The total solubility parameter (δ_t) for the polar solvent under study is then either looked up in a book of predetermined values [22] or calculated using the Hildebrand equation (Figure 16) shown previously in which δ_t is equal to the square root of the molar heat of vaporization (ΔH), corrected for volume expansion (-RT), R=universal gas constant, T= temperature in degrees Kelvin, divided by the molar volume (V). Finally, the hydrogen bonding Hansen Solubility Parameter, δ_h, maybe back calculated by taking the square root of the difference between the square of the total solubility parameter (δ_t^2) minus the squares of the dispersive (δ_d^2) polar (δ_p) parameters determined in the manner just described.

There is a process to determine these same parameters experimentally. (Figure 18). First (Step A) a solute to be dissolved or a solvent to be replaced is selected. Next (Step B) the Hansen Solubility Parameters for the sphere of the solute or solvent are estimated. Finally, (Step C), a solvent mixture with the Hansen Parameters of the solute or solvent near the center of the Hansen Sphere for the mix is determined. Specifically, the procedure used at Gaylord Chemical Corporation, Slidell, LA 70458, the world's largest producer of DMSO is shown in Figure 19.

These specifics of how to experimentally determine Hansen Solubility Parameters of Sample Materials is outlined below, courtesy of Dr. Artie McKim (5/30/00) of Gaylord Chemical Corporation:

HSP Testing of Sample Materials

1. Sample is measured/cut/weighed into even portions (typically 0.5g) and placed into scintillation vials. Each vial contains 5.0 mL of a test solvent. As many as 33 test solvents are used, which are chosen to cover the ranges of the three Hansen Solubility Parameters.

2. The vials are gently swirled on a shaker table for a set amount of time, when the solution phenomenon in each vial is evaluated. For most materials 1, 6, and 24 hour intervals are useful. A rating system is used to describe solution. An example of such a system is:

   3 – Complete solution

   2 – partial solution/swelling

   1 – little solution/swelling

   0 – no effect noted.

3. The solvents that were effective are examined on two-dimensional diagrams, each of which has two of the three HS parameters. Thus, three diagrams are used: $*_p$ vs $*_d$, $*_p$ vs $*_h$, $*_d$ vs $*_h$, (wherein subscripts p, d, and h denote HS Parameters polar,

dispersive, and hydrogen bonding). The points in each of the three plots may be used to estimate a circular relationship in two dimensions, which, when taken together, estimate a sphere in three-dimensional HSP space.

4. This data, when plotted, often suggests a fairly narrow range of values which are an estimate of the HS Parameters of the tested material Formulations which have HS Parameters similar in this range (and which contain DMSO) are good candidates for testing as effective solvent mixtures; because they have solvent profiles similar to solvents (of known HS Parameters) which were proving effective. There are effects not taken into account by this method (molecular volume, acidity, chemical reactivity, etc), but the three component HSP methodology must be tested for efficacy on the substrate.

The results of such testing by Gaylord Chemical Corporation for several solvent mixtures (GCC 6 through GCC 10) are shown in Figure 20. The large circle represents the solubility plot for commercially available paint strippers which contain methylene chloride, a toxic, highly regulated substance. Note that all of the Gaylord Chemical Corporation formulations, which contain DMSO and no methylene chloride fall within the large circle, and can therefore replace the methylene chloride based strippers. Once again the plot is in two dimensions for simplicity, but recognize that the third parameter, the dispersive component ($*_d$) is present but varies to a relatively smaller degree, making all of the circles in Figure 20 actually envelopes in which all of the GCC formulations are fully contained in the larger envelope – i.e. they are not knocked out by variability in the dispersive dimension. A summary

of practical DMSO uses in paint stripping applications include mixtures of 1 to 99% of DMSO with 99 to 1% ether(s), in which the preferred ratios are dependent upon the functionality of the intended use. Such DMSO based mixtures can be used to remove polyurethane paints from metal substances, and gylcero-phthalic or alkyd-urethane based paints from wood. Gaylord Chemical Corporation currently has a patent pending[24] on paint stripping mixtures in which ethers are replaced with esters which have lower flammability, are less toxic and are generally safer with no sacrifice in efficacy (Figure 21).

Some common solvents are plotted in Figure 22 as a two dimensional Hansen Parameter Solubility Map. The third dimension (dispersion parameter, δ_d) is relatively constant for these solvents, so the actual plot would resemble a thin wafer bulged slightly more toward the center. In any case, note that DMSO is fairly close to the center of the plot, which means that it will be compatible with most of the solvents shown. This is demonstrated in Figure 23 in which the solubility circle, i.e. chemicals that will dissolve in DMSO, includes everything except aliphatic hydrocarbons. Figure 24 focuses on the Semiconductor Industry, and depicts the solubility circles (wafers) for an uncured and cured typical polyamide resin. The closer to the center of the circle, the better the solubility (i.e. higher loading) of the resin. DMSO can be blended with some of the other solvents such as Dibasic Esters (DBE), Isopropyl Alcohol (IPA), NMP, Acetone, MEK or amines to move the solubility parameter closer to the center of the circle to obtain optimum resin loading for any specific resin. Some advantages of using DMSO in the manufacture of chips for the semiconductor industry are summarized in Figure 25. The purity, low toxicity, and efficacy over a wide range of photoresist materials are to emphasized.

Some of the unique properties of the DMSO molecule are shown in Figure 26. Unsymmetrical sulfoxides are chiral, [22] and the optical rotation of enantiomerically resolved 1,1,1 trideutro DMSO is –3.8°. DMSO exists, for the most part, as the polar resonance structure in which sulfur has a lone electron pair and a partially positive charge and oxygen has a partially negative charge. It is this thermodynamically stable structure that makes DMSO highly polar, while at the same time reducing the lability of the protons to give DMSO the aprotic characteristic. Note the relatively short distance of the sulfur-oxygen bond (1.48A°) which is about the same length as the sulfur-oxygen soluble bond in sulfone compounds R-$S(O_2)$-R (1.43±0.01A°) and in dichlorsulfoxide Cl-S-Cl (1.45±0.02A°). The sulphur - carbon bonds are over 20% longer.

In reactions, the DMSO molecule has sites available for attack by "hard" (e.g. protonic acids such as HCl, HBr) and "soft" (e.g. Lewis Acids as BF_3) acids and good nucleophilic attack at the sulfur. A comparison of the dielectric constants at 25°C (,) for DMSO and two other common dipolar, aprotic solvents, DMF and acetonitrile shows DMSO to be over 30% higher, which suggests significantly higher polarity for DMSO. The "Donor Number" which is a measure of the election availability on the sulfur atom for donation to other molecules (in this case antimony pentechloride) to form complexes is more than double that for the electron availability in acetonitrile and a little higher than DMF.

One use of DMSO in diastereoselectivity enhancement is shown in Figure 27 for a sodium hydride catalyzed methylation of optically pure N-Sylfinyl phemylamine to give a mixture of N-Sulfinylaziridine epimers from which elimination of the sulfinyl group easily

occurs to give pure phemyl aziridines.[23] Dimethylsulfonium methylide and dimethyloxosulfonium methylide were both used as methylene transfer reagents to form the N-sulfinylazirdine epimers mixture with the former functioning more selectively in polar solvents, (e.g DMSO) and the latter in non polar solvents (e.g. Toluene). Lower optical selectivity was seen in other common dipolar aprotic solvents, as DMF and tetra hydrofuran (THF).

DMSO can increase the chemical reaction rates of addition, displacement, etherification, and solvolysis reactions (Figure 28). Increased selectivity is observed in alkylation reactions, and higher yields in cyclization and condensation reactions. Higher molecular weights are seen using DMSO as the solvent in polymerization reactions. Enhanced reactivity of bases in elimination and isomerization reactions are noted using DMSO.

DMSO can function as a reaction solvent in pharmaceutical, agricultural, and polymer processes and sugar esters (Figure 29). It is a raw material in production of certain dietary supplements. DMSO is commercially utilized in removal of coatings, such as paint and is used in the electronics industry for photorist stripping and solvent rinsing.

Pharmaceuticals manufactured using DMSO, spans the range from antibiotics and antihistamines, to X-ray Contrast Reagents, to psychologically active drugs. (Figure 30)

The International Conference on Harmonization (ICH) of the Pharmaceutical Industry, places compounds in one of three classes (Figure 31). Note DMSO is in Class III, the lowest toxicity class to humans, no health based exposure limits needed (consistent with DMSO having no TLV) and Permissible Daily Exposure of 50 mg/day or more. Recall, the normal

dietary intake of DMSO is about 21 mg/day (Figure 9). Other common polar, aprotic solvents are in Class II, designated as animal carcinogens with possible irreversible neurotoxicity or teratogenicity. Class I designates known human carcinagens, as benzene and carbon tetrachloride.

USP Grade DMSO is recommended for certain medical uses, as in treatment of urinary tract problems, in FDA approved products for internal use (DMSO/water mixtures) neat for human cell and organ preservation. (Figure 32). The topical application of mixtures of DMSO and non-steroid anti-inflammatory drugs (NSAID's) is under study in Canada and is being considered for FDA approval.

The unique properties of sucrose fatty acid esters, commonly known as sugar esters, have been appreciated in Japan for many years. Sucrose esters are white to cream colored free-flowing powders with low taste and odor. They are stable up to 180°C at pH values between 4 and 8. This means the esters can be used as emulsifiers in virtually all foodstuffs[25].

Sucrose esters allow the preparation of low fat foodstuffs, which have the same rheological characteristics as their high fat counterparts. In ice cream, sucrose esters prevent the loss of entrained air and prevent the formation of ice crystals. Sugar esters prevent "fat bloom" in chocolate and retard the spoilage of coffee maintained in vending machines at 50°C for long periods. Other sugar esters find application in personal care products and in agriculture as pesticides with low mammalian toxicity.

The solvent of choice for the sugar ester process is DMSO due to its low toxicity and excellent solvating ability for a vast array of organic chemicals, including sucrose. The solubility of sucrose at 85°C in DMSO is 51.1%. In contrast N, N-Dimethylformamide, DMF dissolves only 23.6%.

In the first step of the sugar ester process, sucrose in DMSO solution is transesterified using potassium carbonate catalyst, at circa 100°C with the ethyl ester of a suitable naturally occurring fatty acid (e.g. palmitic, stearic or oleic). Excess DMSO is vacuum stripped using a wiped film evaporator (Figure 33).

The residual material is poured into water forming an emulsion. The sugar ester is precipitated by breaking the emulsion via the addition of ethanol. The product is filtered and the filtercake is washed with ethyl acetate to remove unreacted fatty acid ester and to facilitate drying.

In the United States domestically produced food grade sugar esters have not reached significant commercial success due to the very tight (and from a toxicity standpoint unreasonable) FDA specification on residual DMSO solvent. It is curious that the FDA spec for residual arsenic, LD50 = 763 mg/kg (rat, oral) is 3 ppm and the spec for residual lead, is 10 ppm while the spec for residual DMSO, LD50 = 14,500 mg/kg (rat, oral) is 2 ppm.

In summary DMSO, is a clean, safe, environmentally friendly, highly polar, aprotic solvent (Figure 34). It is manufactured from trees and from the sulfur by product from fuel purification. It is often recycled after use. DMSO is “New” to the market place because it is

underutilized in spite of the fact that it can be used neat or in safe solvent blends as a direct replacement for more toxic materials. It does not have a TLV assigned, and it is Class III (and preferred most safe) in the Pharmaceutical Industry International Conference on Harmonization (ICH). It is globally accepted by the medical community. DMSO has virtually no environmental impact, does not bioaccumulate and photodegrades fairly rapidly (Figure 35). The Hansen Solubility Parameter model has been used both theoretically and experimentally to define solubility spheres for solvents to be replaced and solutes to be dissolved (Figure 36). Enhancements in diastereoselectivity, reaction rates and yields are noted for DMSO compared to other solvents in certain reactions. Some existing commercial uses that could be readily expanded include Pharmaceutical, coatings removal and photoresist stripping/rinsing.

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REFERENCES

1. Gaylord Chemical Corporation, 106 Galeria Boulevard, Slidell, LA 70458. Phone 1-800-426-6620 or (504) 649-5464. Internal Communication.
2. Dimethyl Sulfoxide (DMSO) Physical Properties, Bulletin # 101, Gaylord Chemical Corporation (12/98)
3. Toxicology and Applied Pharmacology 15,74-82 (1969): Effects of Acute and Repeated Inhalation of DMSO in Rats, Fishman, E.G., et al.
4. References: Brown, VK, et al. A note on the Toxicity and Solvent Properties of DMSO. J. Pharm. Pharmacology, 15,688-692, (1963)
   Canjolle, F., et al. Toxicity and Pharmacologic Properties of DMSO. Compt. Rend. Acad, Sci, Paris, 258 (1964)
   Faurant, J. Pharm. Actions and Toxicity of DMSO and other... J.Pharm., and Pharmacol, 16, (1964)
   Rosenkrantz, H. et al. DMSO: Its Steroid Solubility… Cancer Chemotherap. Rep. No. 31, 7, (1963)
   Sommers, S. et al, Toxicological Investigations of DMSO. Arzeneimittal-Forsch. 14, (1964)
   Urarmura, T, et al. An experimental Study on the Toxicity of DMSO used as a Solvent, Igakukenkyu, 30 (1960)
   Willson, JE. et al. A Toxologic Study of DMSO. Toxicol. And Appl. Pharmacol., 7, (1965)
5. W. M. Bennett, MD and R.S. Muther, MD. Lack of Nephotoxicity by Intravenous Dimethyl sulfoxide, Clinical Toxicology, 181 (5) pp 615-618 (1981).
6. H.B. Hucker, et, al, Mereck, Sharp & Dohme Research Laboratories, West Point, PA. Studies on the Absorption, Excretion and Metabolism of DMSO in Man. The Journal of Pharmacology and Experimental Therapeutics. Vol 155, No 2 pp 309-317, 1967.
7. M.B. Sulzberger, et al, R & D Services, U.S. Army, Letterman----General Hospital, Presidio of San Francisco, CA. Sept. 1, 1966.
8. Biological Actions of Dimethyl Sulfoxide. Annals New York Acad.Sci, 141, 1967
9. Biological actions of dimethyl sulfoxide, Eds, Jacob SW, Herschler R. Annals New York Acad Sci 243, 1975
10. Biological actions and medical applications of dimethyl sulfoxide Ed: de la Torre JC Annals New York Acad Sci 411, 1983
11. Toxicology updates: dimethyl sulfoxide by Willwhite CK and Katz PIJ Appl Toxicol 4, 155-160, 1984.
12. Problem of definition study of DMSO and interactive health effects with other Chemicals. Smith LH et al Oak Ridge National laboratory – NTIS microfiche. 1983
13. DMSO – a review by Brayton CP. Cornell Vet 76, pp 61-90 1986. Elf Aquitaine Lacq.

14. Geiger, Brook, Call, Acute Toxicity of Organic Chemicals to Fathead Minnows. Vol 5: Center of Lake Superior Environmental Studies, University of Wisconsin, Superior (1990)

and

Bienville, P.E., Smith, C.E. Shanks, W.E. Some Toxic Effects of DMSO in Salmon and Trout; Toxical, Appl. Pharmocol. Vol 12, pp 156-178 (1968)

15. Bowman, ML. et al. Stressed Broassay Systems for Rapid Screening of Pesticide Residues, PartI: Evaluation of Bioassay System, Arch, Environ, Contam. Toxicol., 10, 9-24 (1981)
16. DMSO, Gaylord Chemical Corporation, 106 Galeria Boulevard, Slidell, La. 70458 Phone 1-800-426-6620 or (504) 649-5464, Information Bulletin 9-95-1
17. Pearson, T.W., et al. Natural Occurring Levels of Dimethyl Sulfoxide in Selected Fruits, Vegetables, Grains and Beverages, Journal of Agricultural and Food Chemistry, Vol 29, pp 1089-1091, Sept. – Oct., 1981
18. Andreae, M.D. Anal. Chem. 52, 150-153. (1980

and

Harvey, G.R. and Lang, R.G. Geophys, Res. Let., 13,49-51 (1986)

19. Becker, K and Patroescu, J.V., Reactions of Organic Sulfur Compounds in the Atmosphere. Report, Bericht-Bergische Univ., Gesamthoclpscheule Wuppertal, Fachbereich 9 Phy. Chem., 35:1-160 (1996)

and

Oh, Don Jun., Dimethyl Sulfoxide and Organosulfide Cycle Graphical Pathway Map, University of Minnesota, e-mail at: www.labmed.edu/mmbbd/sulf/sulf_image_map.html (2000)

20. Humble Oil and Refining CO., P.O.Box 2180,Houston, TX 77001: Lubetest D – 1P
21. Gaylord Chemical Corporation, 106 Galeria Boulevard, Slidell, LA 70458 Phone 1-800-426-6620 or (504) 649-5464. Using Dimethyl Sulfoxide (DMSO) in Industrial Formulations, Bulletin #102, Sept. 1994
22. Pirkle, W.H. et al, JACS. 90, 6250 (1968)
23. Ruano, et al, Tetrachedron Letters, Vol 36 No. 2, pp 295-298 (1995)
24. Gaylord Chemical Corporation, 106 Galeria Boulevard, Slidell, LA 70458 Phone 1-800-426-6620 or (504) 649-5464, Patent Pending; DMSO containing Paint Stripping Compositions
25. Gaylord Chemical Corporation, 106 Galeria Boulevard, Slidell, LA 70458 Phone 1-800-426-6620 or (504) 649-5464. Memo, Kvakovszky to Zeillmann, Sugar Ester Chemistry, July 2000
26. Hansen Solubility Parameters, A Users Handbook Charles M. Hansen. CRC Press, International Standard Book Number (ISBN) D-8493-1525-5 (2000)

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