DIMETHYL SULFOXIDE

Document History
Published: 2003
Rebranded: 2025

I. IDENTIFICATION

Chemical Name: Dimethyl Sulfoxide
Synonyms: DMSO, Methylsulfoxide, Sufinyl bis [methane]
CAS Number: 67–68–5
Molecular Formula: C_2H_6SO
Structural Formula: $(CH_3)_2$ SO

II. CHEMICAL AND PHYSICAL PROPERTIES[1-6]

Physical State: Colorless liquid
Molecular Weight: 78.13
Conversion Factors: 1.0 ppm = 3.20 mg/M^3
1.0 mg/M^3 = 0.31 ppm
Melting Point: 18.5°C (65°F)
Boiling Point: 189°C (372°F)
Vapor Pressure: 0.37–0.42 mmHg at 20°C (68°F)
Saturated Vapor Concentration: 490–550 ppm at 20°C (68°F)
Odor Description and Threshold: Mild garlic odor (threshold not reported), odor apparently decreases with increasing purity
Flammability Limits: LEL: 2.6%; UEL: 42%
Flash Point: 95°C (203°F) Open Cup; 89°C (192°F) Closed Cup
Autoignition Temperature: 215°C (419°F)
Specific Gravity: 1.10 at 20°C (68°F)
Solubility: Soluble in water, and most organic solvents
Stability: Stable, but hygroscopic
Reactivity and Incompatibilities: Reacts violently with strong oxidizers, many acyl halides, boron hydrides, and alkali metals. May form explosive mixtures with metal salts of oxoacids. Releases sulfur dioxide when heated above 100°C

III. USES

The primary use of dimethyl sulfoxide is as an industrial solvent. It is also used as a laboratory analytical reagent, pesticide additive, antifreeze, hydraulic fluid, additive for topical medical formulations, and has limited human and veterinary medical applications.[3,7]

IV. TOXICOLOGICAL DATA

A. Acute Toxicity and Irritancy:

1. *Oral*[5,8-11]

Rat: LD_{50}: 14.5–22 g/kg
Mouse: LD_{50}: 17–22 g/kg
Guinea Pig: LD_{50}: >11 g/kg

2. *Eye*

Six rabbits had undiluted DMSO introduced into the conjunctival sac, amount not specified. Of these, two were irrigated immediately, two after 2–3 minutes, and two were not irrigated. The authors stated that, "No ill effects were noted in any of the treated eyes."[8]

Twenty rabbits had DMSO introduced into the eyes using the Draize method; concentration and volume not specified. The authors stated that, "Slight conjunctivitis...was noted at the 24-hour observation period...[which] had disappeared by 48 hours."[11]

Tests performed in rabbits following the OECD guidelines induced a very slight conjunctival irritation, which cleared in 3 days.[12]

3. *Skin*

a. Absorption

Tests in which mice and rats were dipped up to their necks, "until thoroughly wetted," in 100% or 80% DMSO resulted in an estimated Dermal LD_{50} of approximately, 50 and 40 g/kg, respectively.[13]

b. Irritation

Rabbit: Undiluted DMSO was applied and occluded with a patch. The amount applied was not specified. Slight erythema was observed upon removal of the patch, which cleared rapidly. The authors conclude that DMSO was not irritating.[11]

Guinea pig: Undiluted DMSO was applied to hairless guinea pigs and occluded with cotton gauze for 4 hours. The authors conclude that DMSO was mildly irritating when scored according to the Draize methodology.[14]

c. Sensitization

Guinea Pig: Undiluted DMSO did not cause sensitization using a maximization test methodology.[8]

Mouse: DMSO was negative when tested in the Mouse Ear Swelling Test.[15]

4. Inhalation[11]

Rats: All animals (8 per group) survived exposure to nominal concentrations as follows (LC_0's):

2900 mg/M^3 — 24 hours
1600 mg/M^3 — 4 hours
2000 mg/M^3 — 40 hours

The authors report observing localized areas of pulmonary edema in "some" of the animals from each exposure group, whether sacrificed immediately after exposure or after 2 weeks of observation. It should also be noted that these concentrations would have consisted of both vapor and mist, since these are at or above the saturated vapor concentration for DMSO. No other adverse effects were reported.

5. Other

a. Intraperitoneal[8-10,16]

Rat:	LD_{50}	10.9–13.7 g/kg
Mouse:	LD_{50}	13.9–20.1 g/kg
Guinea Pig:	LD_{50}	>5.5 g/kg

b. Subcutaneous[16]

Rat:	LD_{50}	13.7 g/kg
Mouse:	LD_{50}	16.0 g/kg

c. Intravenous[9,11,16,17]

Rat:	LD_{50}	5.4–8.1 g/kg
Mouse:	LD_{50}	3.1–11 g/kg

B. Genotoxicity:

DMSO has been subjected to a very large number of genotoxicity and mutagenicity tests, since it is commonly used as a solvent in the testing of substances otherwise insoluble in water. Besides references to the more common test methodologies, DMSO also appears as either a test or control material in numerous publications regarding experimental methodologies.

DMSO has been generally found to be non-genotoxic in any of the usual battery of tests. Some of the published results include:

- Chinese Hamster Ovary Cell assay[18-19]
- *Drosophila melanogaster* aneuploidy test[20]
- *S. typhimurium* strains TA97, TA98, TA100, TA1535, TA1537, TA1538 (with and without S-9 activation)[21-23]
- *S. cerevisiae* assay[22]
- *E. coli* WP2 and PQ37 assay[23]
- Rat hepatocyte DNA repair test[24]
- RK Bacterial test[25]
- Mouse lymphoma TK assay[26]

Some published studies indicate positive results for potential genotoxicity, such as:

- Prophage lambda *E. coli* WP2s(λ) Microscreen Assay[27]
- Modified Ames Assay with *S. typhimuriam* strains TA1537 and TA2637[28]
- *E. coli* strain WP2uvrA[28]

The weight of the evidence is that DMSO is not genotoxic.

C. Metabolism and Pharmacokinetics:

Tests in humans, rats, rabbits, and guinea pigs all indicate that DMSO is very rapidly absorbed through the intact skin. DMSO can be measured in circulating blood within minutes of its being injected or applied dermally and can be found throughout the body within a few minutes more. Most of an experimentally applied dose of DMSO was found to be excreted, unmodified, in the urine. A significant portion of absorbed DMSO is metabolized to dimethyl sulfone, which is also excreted in the urine. The estimated half life of DMSO in the body of humans is 11–14 hours, while that of the dimethyl sulfone metabolite is about 60–70 hours. A small proportion of absorbed DMSO is converted *in vivo*, in a reversible reaction, to dimethyl sulfide. The dimethyl sulfide present in exhaled breath is responsible for the characteristic halitosis associated with DMSO exposure, although less than 3% of the absorbed dose is exhaled. Human studies note that application of even a 10% solution of DMSO (although total dose is not specified) results in the persistent, characteristic halitosis. No other metabolic pathways are apparent.[29-33]

D. Developmental/Reproductive Toxicity

Tests performed on rats, mice and rabbits indicated a small number of malformations at high doses. Mice and rats were dosed each day on Days 6–12 of gestation. Exposures included both oral gavage

and intraperitoneal (IP) injection. Mice were divided into four oral dose groups and four IP dose groups with doses ranging from 5 to 12 g/kg each day. There were a total of 102 exposed mice and 29 controls. Rats were dosed orally at either 5 or 10 g/kg per day, or IP at 5, 8, or 10 g/kg per day. There were 91 treated rats and 59 controls. There were no malformations observed in orally treated mice. Only one malformation was seen in each of the three lower IP-dose groups of mice and four malformed fetuses were observed in the highest IP-dose mouse group (out of 100 total fetuses). A total of 12 malformed fetuses (out of 729 total fetuses) were observed among exposed rats, but these did not occur in a dose-related manner. Two of the malformed rat fetuses had neural tube defects, which were similar in nature to those found in the hamster study cited below. Rabbits were dosed each day on Day 6 through 14 of gestation, either orally at 5 g/kg per day or by subcutaneous injection at 4 g/kg per day (five exposed dams and three controls for each route of exposure). Only one malformation was observed among the 83 rabbit fetuses from the exposed groups, and they were otherwise not significantly different from the controls. The author does not discuss maternal toxicity.[16]

In a study primarily directed at testing pesticides, DMSO was included as a control, since it was used in formulations to make pesticides soluble in water. DMSO was administered via gavage to pregnant hamsters in single doses of 5.5 g/kg on Day 7 (7 dams) or of 11 g/kg on either Day 7 (14 dams) or Day 8 (14 dams) of gestation. When DMSO was administered at the higher dose on Day 7, fetal mortality was 24%, with 24% of the fetuses having malformations. When administered at the higher dose on Day 8, fetal mortality was 9.7% and there were malformations in 18.1% of the fetuses. At 5.5 g/kg, there was 9.3% fetal mortality and 2% malformations. The rates for the untreated controls were 4.5% (mortality) and 0.5% (malformations). The author does not discuss the statistical significance of these differences. Also, other than stating that one of the high dose dams died as a result of treatment, the author does not discuss maternal toxicity. It should be noted that these doses are in the 1/3 to 2/3 range of the expected LD_{50}.[34]

In a mouse study, the animals were orally dosed with DMSO at 0, 2.5, 5.0 or 10.0 g/kg per day (7 dams per dose level), before and during pregnancy (males were also exposed prior to mating). There was no observed decrease in litter size, and no observed effect on size, birth weight, gross development or weight gain. There was a marked decrease, not dose-dependent, in the percentage of females impregnated, which the authors speculate may be related to interference with olfactory signals involved in mating with mice.[10]

Pregnant hamsters were administered DMSO on Day 8 of gestation at various doses (5 or 6 dams per dose level). Those given 50, 250, 500, 1000, or 2500 mg/kg were dosed intravenously, and those given 5500 or 8250 mg/kg were dosed intraperitoneally (IP). At the two IP doses there was a high rate of fetal malformation, including specific deformation in the central nervous system tissues (exencephaly — failure of closure of the anterior neural tube). Only a few embryos at the 2500 mg/kg dose had any malformations, and no effects were observed at the lower doses. The only discussion of maternal toxicity is mention that dams in the highest three dose groups experienced generalized muscular tremors for approximately one minute after dosing and that the highest two dose groups also experienced abdominal muscle rigidity for about the same time period.[35]

Pregnant rats were given subcutaneous injections of DMSO at 12.25 g/kg per day on Day 8, Days 8 and 9, or Days 8, 9, and 10 of gestation. There were 10 control animals and 10 per dose group. This exposure scenario did not result in a decrease in maternal weight gain or birth weight of live offspring. There was a significant decrease in the number of fetuses per litter among those dams given three injections. No gross or skeletal malformations were observed, in the 338 live fetuses, except for two umbilical hernias in the middle (2 injection) dose group.[36]

Pregnant mice (2 or 3 dams per group) were given doses of 0.0, 2.8, 5.5 or 11 g/kg, intraperitoneally, on Day 13 of gestation. The authors conclude that DMSO, at all these doses, had no statistically significant impact on sister-chromatid exchange in either maternal or fetal cells. DMSO was actually included in this study as a control, since it was being used as a solvent for other materials, which were the primary focus of the study.[37]

E. Subacute (6–28 days):

Rats (10 per group) were dosed by gavage, 5 times per week for two consecutive weeks at 0, 1.1, 3.9, 5.5, and 11 g/kg per day. The authors attribute two deaths each in the two highest dose groups to injuries sustained in dosing. They further concluded that there were “no changes in the formed elements of the blood” at 10 days post exposure.[8]

Eight rats were each given 8.2 g/kg per day of DMSO via intraperitoneal injection on four consecutive days Two of the eight died, but the

remaining six were described as healthy at 10 days post exposure.[8]

Mice (10 animals) injected intraperitoneally with DMSO at 4.4 g/kg per day for 7 consecutive days were observed to have significant decreases in serum IgG and IgA but not IgM. Treated animals later immunized with sheep red blood cells demonstrated moderate but significant decreases in "both spontaneous and facilitated plaque-forming cells, hemagglutination titers and serum concentrations of IgG_1.[38]

In a similar study, mice were injected (IP) with DMSO at 2.5 g/kg per day for one week, then 1.25 g/kg every other day for the second week, followed by resumption of the 2.5 g/kg per day dose for three additional weeks. There were 10 test animals and 10 controls. The reduced dose in the second week was adopted because the test animals "appeared weak." The mice were challenged, as above, with sheep red blood cells to assess immune response. The authors concluded that the treatment had not resulted in any adverse effect to the humoral immune response. In addition, no adverse effects were observed in leukocyte counts, body weight, or the size of the heart, lungs, spleen, thymus or kidneys. Livers of exposed animals were enlarged. The hematocrits of the exposed animals were significantly lower than controls, but were within normal laboratory values.[39]

Rats were given intraperitoneal injections of DMSO daily for 28 consecutive days at either 2 g/kg per day or 4 g/kg per day (ten rats per dose level) to examine the potential for kidney injury. One of 20 died at the low dose level, and 3 of 20 at the high dose level died. Both doses impaired growth, but neither caused kidney injury.[40]

Six rhesus monkeys (plus one control) were exposed to DMSO via intravenous injection for 9 consecutive days. Four were given 3 g/kg per day, and two were given 2 g/kg per day. One of the high dose group was sacrificed and examined on Day 4 of the experiment. The others were observed and tested for 4 months before being sacrificed and examined. Among hematological factors the only finding was a decrease in the white blood cell count. Urinalysis, cardiac and respiratory exams, ocular exams, and neurological exams were all within normal limits. No adverse findings were noted during pathological exams at sacrifice.[41]

Daily application of undiluted DMSO (amount and number of test animals not specified) to the clipped backs of guinea pigs for 28 consecutive days produced neither macroscopic nor microscopic signs of injury.[8]

Rats (12 males) and guinea pigs (12 females) were repeatedly exposed via dermal contact to examine the mechanism by which DMSO causes swelling. Upon a single application (1.0 ml, occluded, for 1 hour), some swelling was measured, which increased with each additional daily application at the same site until beginning to subside on the fourth application. The fifth and subsequent applications had no effect. The authors conclude that, rather than being due to injury from the exothermic reaction of DMSO upon contact with the skin, the swelling arises from DMSO affecting the permeability of cells by causing release of histamine at the site of contact. After the fourth day, the histamine is suspected to be exhausted, and thus there is no longer an effect.[42]

In summary, much of the subacute data is based on routes of exposure of little help in deriving an occupational exposure limit (many tests were intravenous or intraperitoneal route). Overall the data indicate that DMSO is toxic at very high doses, but shows few, if any, effects below about 2 g/kg per day, even with the more extreme exposure regimens.

F. Subchronic (29 days to 6 months):

Undiluted DMSO (amount not specified) was applied to the skin of hairless mice twice per week for 30 weeks resulted in no discernable effect on the skin.[8]

Mice were fed DMSO in their drinking water at concentrations of 1%, 2.5%, and 5% for six weeks (35 test animals per dose level, plus 35 controls). Water consumption calculations indicated a daily dose in the highest group of about 27 g/kg per day in the first week, increasing to about 52 mg/kg per day by the third week (note that water consumption increased over these first 3 weeks). Those in the higher group consumed considerably more water. Those in the highest dose group experienced weight loss, and a decrease in the relative spleen weight. There was also an initial loss in serum volume in the high-dose group, which later came back into line with controls. There were no histopathological changes noted.[38]

In an inhalation exposure study, 32 rats were exposed to approximately 200 mg/M^3 (about 60 ppm) of DMSO for 7 hours per day, 5 days per week for 30 exposures (6 weeks). There were no outward toxic signs noted in any of the exposed animals throughout the exposure period. There were no adverse effects on growth and no differences from controls for "biochemical or hematologic" factors or for "gross or histopathologic" factors. Nearly all animals, including controls, exhibited non-specific inflammatory changes in the lungs and livers.[11]

Mice were exposed to DMSO by intraperitoneal injection, subcutaneous injection or gavage, 6 times per week for 3 to 12 weeks; 20 mice per exposure group. From one to three mice per week were sacrificed and subjected to histopathological examination. Those exposed by IP injection were given 2.5 g/kg per day for up to 33 doses. These mice were noted to have tubulonephritis and diffuse necrosis at the point of injections. Those subjected to subcutaneous injection were given 2 g/kg per day for up to 34 doses. These were noted to have "less evidence of tissue damage." Those orally exposed were given 5 g/kg per day for up to 20 doses or 3.3 g/kg per day for up to 33 doses. Those at the higher dose initially suffered a weight loss but later gained weight at the same rate as the control animals. Those at the lower oral dose were not observed to suffer any adverse effects.[16]

In a parallel study, rats were exposed to DMSO by either intraperitoneal injection or gavage, 6 times per week for 3 to 12 weeks; 20 animals per exposure group. Those given the IP injections were given 1 g/kg per day for up to 45 doses and were observed to have normal weight gains and normal histopathological findings. Rats given 5 g/kg IP per day, also for up to 45 doses, were observed to have retarded growth, but normal histopathology. Rats dosed by gavage at 5 g/kg per day for up to 45 doses were observed to also have retarded growth rates and found to have liver necrosis upon histopathological examination. Rats dosed orally at 2 g/kg per day for up to 45 doses had normal weight gain and histopathology.[16]

DMSO was orally administered to six pairs of beagles at doses of 0, 2.5, 5, 10, 20 or 40 g/kg per day, five days per week. None of the four highest dose animals, and only one of those at 10 g/kg per day were able to tolerate the dose. Exposure of the seven surviving animals was continued for 23 weeks (107 doses), and the animals continued to be observed an additional 31 weeks. Ocular examination was performed at least monthly and histopathology examination was performed at the end of the observation period. All animals administered DMSO demonstrated refractoriness to mydriasis by tropicamide by the 4th week of testing. This effect continued throughout exposure, but disappeared upon termination of dosing. Changes in lenses of the eyes appeared in which the refractive power of the lens changed. The changes were in distinct zones, typically at the center and in a ring surrounding the central area, in a kind of "target" pattern. These appeared in the three surviving high dose animals by Week 9 and were seen in all five exposed animals by Week 18. The severity of the effect was dose dependent. Termination of exposure did not result in any significant improvement. The histopathological examination did not result in any other abnormal findings.[43]

In a parallel study, four groups of ten Corgi dogs each were orally administered DMSO. For the first 45 days, the dogs were given 0, 0.6, 1.7, or 5 g/kg per day. The doses were doubled from Day 46 through Day 132, and were continuing at the time of the report. No eye effects were noted at the first eye examination on Day 28. At the second examination on day 68, all dogs in the highest two groups were affected and 3 of 10 in the low dose group were affected. Effects in the mid-dose animals were reported as less severe than the high-dose animals, and those in the low-dose group were "slight." Some improvement was observed in some animals upon withdrawal from exposure.[43]

Ocular effects, similar to the two dog studies cited here, were seen in rabbits exposed dermally to DMSO. Seven groups of four rabbits each were exposed for 90 days. Four groups were exposed to 100% DMSO applied at doses of 2.2, 4.4, or 8.8 g/kg per day; four were exposed to 50% DMSO in water at doses of 4.4, 8.8 or 18.2 g/kg per day; and one was used as a control, with only water. At the end of 90 days, none of the animals receiving 2.2 g/kg per day of 100% DMSO, or 4.4 g/kg per day as 50% DMSO were affected. Three of four in both higher dose groups with 50% DMSO solution and 4 of 4 in each of the higher dose groups receiving 100% DMSO developed changes to the lens resembling that observed in dogs. The authors also report that similar effects were obtained in dermal exposure of pigs.[43]

Another study examined ocular effects in dogs and primates via dermal exposure. Beagles (2 per dose level) and rhesus monkeys (8 per dose level) were dermally administered DMSO (as a solution of 90% DMSO with water) at 1.1, 3.3, or 11 g/kg per day. The dogs were exposed for 118 days and the monkeys for 185 to 200 days. Both species developed malodorous breath and desquamation at the site of application. The dogs experienced lens changes as described in the studies above, which did not improve upon cessation of exposure (observation was for 71 to 92 additional days). No ocular effects were observed in the monkeys. Skin lesions and the halitosis resolved upon cessation of exposure for both species.[44]

Overall the subchronic data indicate an absence of effects below about 2 g/kg per day, except for a unique ocular effect. The ocular effect is not seen in primates, however, even at doses as high as 11 g/kg per day.

G. Chronic Toxicity and Carcinogenicity:

In a series of tests, chronic effects of DMSO exposure were evaluated in four different species of test animal. Rats and dogs were exposed orally at doses of 0, 1.1, 3.3, or 9.9 g/kg per day, five days per week. Rabbits and pigs were exposed dermally at doses of 0, 1.7, 3, 5, or 9 g/kg per day, five days per week. Dogs (ten animals per dose group) were exposed for 2 years; pigs (8 animals per dose group) for one year; rats (100 animals per dose group) for 18 months and rabbits (number animals per dose group not clearly reported, appears to be 20+) for 6 months. Lens changes, as described in subchronic studies above, were seen in all four species. Dogs and rabbits at all exposure levels experienced lens changes, with dogs much more severely affected. Eye changes were not seen in the lowest dose group of pigs, and were present only in the highest exposure group in rats. Otherwise, the only effects observed were minor changes in body weight and hematology values and some diuretic effect.[45]

Rhesus monkeys were exposed orally and dermally at doses of 0, 1.1, 3.3, or 9.9 g/kg per day (3 or 4 animals per group), 7 days per week, divided into 2 equal portions each day. Exposure continued for 74 to 87 weeks. Animals were observed for water consumption, electrocardiogram, neurological (reflexes), heart rate, body weight, blood pressure, body temperature, respiratory rate, and ophthalmologic changes. Complete blood counts, SGPT, serum alkaline phosphatase, blood urea nitrogen, blood glucose, 45-minute sulfabromophthalein (BSP) retention, and endogenous creatinine clearance were also routinely measured. Animals that died or were sacrificed were submitted to detailed necropsy and histopathology examination. The highest oral dose killed approximately half that group of animals. Those treated dermally developed scaly, flaky skin at the point of administration during the initial phase of the study. Animals at the highest oral dose experienced dose-related emesis and anorexia. The exposed animals had somewhat lower body weight gains than controls but this was not judged to be biologically significant by the authors, except for the highest oral dose group. No differences were noted in any other parameters. Testing for refractoriness to tropicamide also indicated no differences between exposed animals and controls.[46]

DMSO was administered subcutaneously to thirty mice in a lifetime carcinogenicity study. DMSO was tested only because it was being used as a solvent for other chemicals that were the primary materials of interest. Weekly injections of 0.05 ml (about 2.5 g/kg) were administered. No increase in tumors was observed in the DMSO-treated mice.[47]

A co-carcinogenicity test was performed to evaluate whether administering DMSO together with a chemical known to cause breast tumors; DMBA, (7, 12- dimethylbenz(α)anthracene); would alter the carcinogenicity of DMBA alone. Female rats were administered DMBA by gavage. One group received DMBA alone, the second group the same dose of DMBA, plus 50 ppm of DMSO in their drinking water, while a control group received neither. There were 50 animals per group. After 18 months, there was no difference in the tumor incidence between those exposed to DMBA plus DMSO and those exposed to DMBA alone.[48]

In another co-carcinogenicity study, DMSO was evaluated for its effects in conjunction with five substances known to be strongly carcinogenic by skin application in mice. The number of animals per group is not clearly reported but appears to be about 10. For some scenarios, tumor incidence increased. For others it decreased. In some cases it remained unaffected. In one test, it was observed that tumors increased if DMSO was applied to a different part of the animal's body than the primary carcinogen, but decreased when DMSO was used as a solvent for the same carcinogen at the point of application.[49]

V. HUMAN USE AND EXPERIENCE

DMSO is widely used in the general population, often as a local analgesic for the treatment of arthritis. The number of uses for which it is actually approved are extremely limited, but it is readily available outside pharmaceutical channels. There are many anecdotal reports of potential benefits, but little corroboration in serious medical studies.

DMSO was included in a battery of materials tested for dermal sensitization using a maximization protocol in human subjects. The test involved applying 1 mL of 5% aqueous lauryl sulfate under an occluded patch for 24 hours to produce a moderate inflammatory reaction, then applying the test substance under an occluded patch at the same point for 48 hours, then repeating the procedure five times. The subject was then given a final challenge with a modified version of this same procedure. The subject's test reaction was scored at each stage of the testing and substances rated according to the severity of the reactions. No sensitization was noted when 23 subjects were tested according to this protocol using 75% DMSO in the "induction" phase and 25% DMSO in the "challenge" test.[50]

The toxicity of DMSO was evaluated in humans in a two-stage test. In the first, 78 men were exposed by

dermal application of an 80% gel of DMSO at a dose of 1 g/kg per day for 14 consecutive days. Of these, 13 dropped out of the study due to irritant effects associated with the skin application or because of the persistent halitosis, which resulted from the exposure. All 65 remaining subjects were extensively monitored for both objective and subjective responses and compared to a similar control group from the same penitentiary. Examinations, performed before, during and after exposure, included complete ophthalmologic exams, bone marrow exams, pulmonary function studies, hematology, blood chemistry testing, urinalysis, blood pressure, heart rate, temperature, and respiratory rate. Complete physical exams were also performed. Only healthy individuals were included in the study. Local irritation at the site of administration was common and all subjects experienced the characteristic, persistent halitosis. The only observed difference between the subjects and controls was eosinophilia in 10 of the 65 test subjects. Even then, only one subject was observed to have a markedly elevated response, and this was not considered a serious effect by the authors. The eosinophilia was judged by the authors to be a secondary response to histamine release at the site of application. Subjective responses were recorded in regular interviews with exposed subjects, but unfortunately, the controls were not similarly interviewed to elicit subjective complaints for comparison of frequencies. The primary subjective complaints were sedation (52% of subjects), headache (42%), nausea (32%), and dizziness (18%). In no instance was the complaint described as serious. Most notably, there were no ocular effects.[29,51]

In the second part of the same study DMSO was administered to a smaller group of subjects by the same route and dose (1 g/kg per day) for 90 days (one reference cites 38 participants and the other cites 40). The participants were monitored with the same range of tests as in the 2-week study above, plus neurological exams. Transient eosinophilia was noted in half the test subjects during the first two weeks of exposure. No other significant observed differences were noted between test subjects and controls. Of particular note was the absence of any ocular effect. In this study, the control group was also interviewed to elicit subjective complaints so that a comparison could be made with the test subjects. The only significant differences between test subjects and controls were increased sedation and occasional insomnia and nausea. It was subjectively observed that the characteristic halitosis became less marked as the study progressed, but it remained throughout.[51-52]

Testing was performed to evaluate kidney function in 14 humans receiving DMSO at 1 g/kg per day, for three successive days, via intravenous injection, as an experimental treatment for spinal cord injuries. Hemoglobinuria was observed, but there were no indications of kidney injury.[53]

DMSO was also evaluated as a potential treatment for retinitis pigmentosa by instillation of a 50% solution of DMSO at a dose of 125 mg per eye per day. There were 65 test subjects and 58 matched controls in the study. This study explicitly states that neither patients nor the examining physicians were aware of which persons were the test subjects and which were the controls. The study involved exposures as long as 7 years. While the treatment was not shown to be beneficial, no adverse effects were observed in the detailed ophthalmologic exams performed throughout this study. While not specifically cited by the authors, it would appear that this dose does not result in the characteristic halitosis, since neither patient nor examining physician knew which were the test subjects and which were the controls.[54]

VI. RATIONALE

DMSO has been shown to have low acute toxicity. The weight of evidence indicates it is not genotoxic or carcinogenic. Although it has been shown to be teratogenic, this appears to be only at very high doses, which are also high enough to present a concern for adults. In animal testing in the laboratory, the primary long-term effect of concern has been specific adverse effects upon the eye, as described above. However, extensive testing indicates that such an effect is not seen in primates, including man.

Skin contact with DMSO can cause irritation, apparently due to local release of histamine. Human studies via dermal contact indicate great variability in this response. DMSO does not appear to be a sensitizer.

The data clearly show that DMSO is readily absorbed through intact skin, so absorption via skin may be a factor in the total dose absorbed in the workplace.

Dermal doses as high as 1 g/kg per day have been shown to have no significant adverse clinical effects in well-controlled human studies. These studies also indicated no serious subjective complaints at such doses. These studies thus form a strong scientific basis for the recommended OEL guide. The OEL value should provide an adequate margin to prevent the mild sedation reported in human studies.

One side effect of DMSO exposure is a characteristic halitosis, which is experienced at doses well below those shown to have any adverse effect. No published information was found to indicate at what dose the halitosis may become problematic. Thus, the OEL guide does not provide assurance that this concern would be averted.

It should also be noted that DMSO can increase dermal absorption of many substances. However, these effects vary so widely across substances, relative concentrations and exposure scenarios that discussion of such

effects is beyond the scope of this document. Specific case-by-case consideration is recommended where effects on dermal absorption might be a concern.

VII. RECOMMENDED OEL

8-Hour time weighted average (TWA): 250 ppm

VIII. REFERENCES

1. **Lide, D.R. (ed.):** *CRC Handbook of Chemistry and Physics, 71st Ed.* Boca Raton, FL: CRC Press, 1990.
2. **Dean, J.A. (ed.):** Lange's Handbook of Chemistry, 13th Ed. New York: McGraw-Hill Book Company, 1985.
3. **Lewis, R.J., Sr. (ed.):** *Hawley's Condensed Chemical Dictionary, 12th Ed.* New York: Van Nostrand Reinold Company, 1993.
4. **Matheson Tri-Gas, Inc.:** Material Safety Data Sheet: Dimethyl Sulfoxide. Matheson Tri-Gas, Inc., 959 Route 46 East, Parsipany, NJ 07054. March 2001.
5. **Mallinkrodt-Baker, Inc.:** Material Safety Data Sheet: Dimethyl Sulfoxide. Mallinkrodt-Baker, Inc., 222 Red School Lane, Phillipsburg, NJ 08865. November 1999.
6. **National Academy of Sciences:** Laboratory Chemical Safety Sheet: Dimethyl Sulfoxide. Published at: http://www.holidaylectures.org/science/labsafe/lcsstxt/ lcsstx33.htm. 1995.
7. **National Toxicology Program:** NTP Chemical Repository: Dimethyl Sulfoxide. Published at: http://ntpserver.niehs.nih.gov/htdocs/CHEM_H&S/ NTP_Chem6/Radian67-68-5.hmtl. October, 2000.
8. **Brown, V.K., J. Robinson, and D.E. Stevenson:** A Note on the Toxicity and Solvent Properties of Dimethyl Sulfoxide. *Journal of Pharmacy and Pharmacology 15*:688–692 (1963).
9. **Bartsch, W., et. al.:** Acute Toxicity of Various Solvents in the Mouse and Rat. *Arzneimittel-Forshung (Drug Research 26(8)*:1581–1583 (1976).
10. **Todd, G.P. and H.J. Burford:** Dimethyl Sulfoxide: Acute Toxicity and Study of Subacute Effects on Fertility and Growth in Mice. *North Carolina Medical Journal 28(7)*:268–272 (1967).
11. **Fishman, E. G., et. al.:** Effects of Acute and Repeated Inhalation of Dimethyl Sulfoxide in Rats. *Toxicology and Applied Pharmacology 15*:74–82 (1968).
12. **Elf Atochem S.A.:** Department of Industrial Toxicology. Toxicity Review: Dimethyl Sulfoxide. [Unpublished Report] Prepared by Elf Atochem S. A., Department of Industrial Toxicology, La Defense 10, Dedex 42, 92091 Paris-la-Defense, France. December 1997.
13. **Smith, E.R., Z. Hadidian, and M.M. Mason:** The Toxicity of Single and Repeated Dermal Applications of Dimethyl Sulfoxide. *Journal of Clinical Pharmacology 8(5)*:315–321 (1968).
14. **Tenjarla, S.N., et. al.:** Evaluating The Irritation Potential of Skin Penetration Enhancers in the Hairless Guinea Pig. *Journal of Toxicology — Cutaneous & Ocular Toxicology 14(4)*:299–307 (1995).
15. **Gad, S.C., et. al.:** Development and Validation of an Alternative Dermal Sensitization Test: The Mouse Ear Swelling Test (MEST). *Toxicology and Applied Pharmacology 84*:94–114 (1986).
16. **Caujolle, F.M.E., et. al.:** Limits of Toxic and Teratogenic Tolerance of Dimethyl Sulfoxide. *Annals of the New York Academy of Sciences 141*:110–126 (1967).
17. **Willson, J.E., D.E. Brown, and E.K. Timmons:** A Toxicologic Study of Dimethyl Sulfoxide. *Toxicology and Applied Pharmacology 7*:104–112 (1965).
18. **Loveday, K.S., et. al.:** Chromosome Aberration And Sister Chromatid Exchange Tests in Chinese Hamster Ovary Cells *In Vitro*. V: Results With 46 Chemicals. *Environmental and Molecular Mutagenesis 16*:272–303 (1990).
19. **Amacher, D.E. and I. Zelljadt:** Mutagenic Activity of Some Clastogenic Chemicals at the Hypoxanthine Guanine Phosphoribosyl Transferase Locus of Chinese Hamster Ovary Cells. *Mutation Research 136*:137–145 (1984).
20. **Traut, H.:** The Solvent Dimethylsulfoxide (DMSO) Does Not Induce Aneuploidy in Oocytes of Drosophila Melanogaster." *Environmental Mutagenesis 5*:273–277 (1983).
21. **Simon, V.F., et. al.:** Mutagenic Activity of Chemicals in Drinking Water. *Developments In Toxicology and Environmental Science 2*:249–258 (1977).
22. **DeFlora, S.:** Study of 106 Organic and Inorganic Compounds in the Salmonella/Microsome Test. *Mutagenesis 2(4)*:283–298 (1981).
23. **Brams, A., et. al.:** A Comparative Study, With 40 Chemicals, of the Efficiency of the Salmonella Assay and the SOS Chromotest (Kit Procedure). *Toxicity Letters 38*:123–133 (1987).
24. **Williams, G.M., H. Mori, and C.A. McQueen:** Structure-Activity Relationships in the Rat Hepatocyte DNA-Repair Test for 300 Chemicals. *Mutation Research 221*:263–286 (1989).
25. **Hayes, S., et. al.:** RK Bacterial Test for Independently Measuring Chemical Toxicity and Mutagenicity: Short-Term Forward Selection Assay. *Mutation Research 130*:97–106 (1984).
26. **Amacher, D.E., et. al.:** Point Mutations at the Thymidine Kinase Locus in L5178Y Mouse Lymphoma Cells. II: Test Validation and Interpretation. *Mutation Research 72*:447–474, 1980.

27. **DeMarini, D.M., et. al.:** Compatibility of Organic Solvents with Microscreen Prophage-Induction Assay: Solvent – Mutagen Interactions. *Mutation Research 263*:107–113 (1991).
28. **Hakura, A., H. Mochida, and K. Yamatsu:** Dimethyl Sulfoxide (DMSO) is Mutagenic for Bacterial Mutagenicity Tester Strains. *Mutation Research 303*:127–133 (1993).
29. **Swanson, B.N.:** Medical Use of Dimethyl Sulfoxide (DMSO). *Reviews in Clinical and Basic Pharmacology 5*:1–33 (1985).
30. **Hucker, H.B., et. al.:** Studies on the Absorption, Excretion, and Metabolism of Dimethylsulfoxide (DMSO) in Man. *Journal of Pharmacology and Experimental Therapeutics 155(2)*:309–317 (1967).
31. **Hucker, H.B., P.M. Ahmad, and E.A. Miller:** Absorption, Distribution, and Metabolism of Dimethyl Sulfoxide in the Rat, Rabbit and Guinea Pig. *Journal of Pharmacology and Experimental Therapeutics 154(1)*:176–184 (1966).
32. **Kolb, K.H., et. al.:** Absorption, Distribution, and Elimination of Labeled Dimethyl Sulfoxide in Man and Animals. *Annals of the New York Academy of Sciences 141*:85–95 (1967).
33. **Brayton, C.F.:** Dimethyl Sulfoxide: A Review. *Cornell Veterinarian 76*:61–90 (1986).
34. **Robens, J.F.:** Teratologic Studies of Carbaryl, Diazinon, Norea, Disulfiram, and Thiram in Small Laboratory Animals. *Toxicology and Applied Pharmacology 15*:152–163 (1969).
35. **Ferm, V.H.:** Congenital Malformations Induced by Dimethyl Sulfoxide in the Golden Hamster. *Journal of Embryology and Experimental Morphology 16(1)*:49–54 (1966).
36. **Juma, M.B. and R.E. Staples:** Effect of Maternal Administration of Dimethyl Sulfoxide on the Development of Rat Fetuses. *Proceedings of the Society for Experimental Biology and Medicine 125*:567–569 (1967).
37. **Sharma, R.K., et. al.:** Sister-Chromatid Exchange and Cell Replication Kinetics in Fetal and Maternal Cells after Treatment with Chemical Teratogens. *Mutation Research 158*:217–231 (1985).
38. **Nash, D.R., V.A. Steingrube, and R.J. Warrington:** Primary Immune Responsiveness and Other Observations in Mice Given Oral Dimethyl Sulfoxide. *Immunopharmacology 6*:191–201 (1983).
39. **Caren, L.D., H.M. Oven, and A.D. Mandel:** Dimethyl Sulfoxide: Lack of Suppression of the Humoral Immune Response in Mice. *Toxicology Letters 26*:193–197 (1985).
40. **Small, A. and R.S. Ide:** Failure to Detect Nephrotoxicity of Chronically Administered Dimethyl Sulfoxide (DMSO) In Rats. *Cryobiology 12*:328–333 (1976).
41. **de la Torre, J.C., et. al.:** Subacute Toxicity of Intravenous Dimethyl Sulfoxide in Rhesus Monkeys. *Journal of Toxicology And Environmental Health 7*:49–57 (1981).
42. **Förster, O. and Stoklaska:** The Effect of Repeated Application of Dimethylsulfoxide (DMSO) to Paws of Rats and Guinea Pigs. *Pharmacology 2*:9–13 (1969).
43. **Rubin, L.F. and K.C. Barnett:** Ocular Effects of Oral and Dermal Application of Dimethyl Sulfoxide in Animals. *Annals of The New York Academy of Sciences 141*:333–345 (1967).
44. **Smith, E.R., M.M. Mason, and E. Epstein:** The Ocular Effects of Repeated Dermal Applications of Dimethyl Sulfoxide to Dogs and Monkeys. The *Journal of Pharmacology and Experimental Therapeutics 170(2)*:364–370 (1969).
45. **Noel, P.R.B., et. al.:** The Toxicity of Dimethyl Sulfoxide (DMSO) for the Dog Pig, Rat and Rabbit. *Toxicology 3*:143–169 (1975).
46. **Vogin, E.E., et. al.:** Chronic Toxicity of DMSO in Primates. *Toxicology and Applied Pharmacology 16*:606–612 (1970).
47. **Van Duuren, B.L., et. al.:** Carcinogenicity of Isoesters of Epoxides and Lactones: Aziridine Ethanol, Propane Sulfone, and Related Compounds. *Journal of the National Cancer Institute 46(1)*:143–149 (1971).
48. **Fletcher, W.S. and D.L. Dennis:** The Effect of Dimethyl Sulfoxide on the Induction of Breast Cancer in the Rat. *Annals of the New York Academy of Sciences 141*:214–220 (1967).
49. **Jacoby, W.T. and H.S. Weiss:** Inhibition and Enhancement of Skin Tumors in Mice by Dimethyl Sulfoxide Depending on Method of Application. *Journal of the National Cancer Institute 77(4)*:983–987 (1986).
50. **Kligman, A.M.:** The Identification of Contact Allergens by Human Assay. J*ournal of Investigative Dermatology 47(5)*:393–409 (1966).
51. **Brobyn, R.D.:** The Human Toxicology of Dimethyl Sulfoxide. *Annals of the New York Academy of Sciences 243*:497–506 (1975).
52. **Hull, F.W., D.C. Wood, and R.D. Brobyn:** Eye Effects of DMSO: Report of Negative Results. *Northwest Medicine 68(1)*:39–41 (1969).
53. **Muther, R.S.:** Effects of Dimethyl Sulfoxide on Renal Function in Man. J*ournal of the American Medical Association 244*:2081–2083 (1995).
54. **Garcia, C.A.:** Ocular Toxicity of Dimethyl Sulfoxide and Effects on Retinitis Pigmentosa. *Annals of the New York Academy of Sciences 411*:48–51 (1983).