# SIDS INITIAL ASSESSMENT PROFILE

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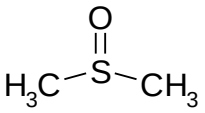
| **CAS Nos.** | 67-68-5 |
| **Chemical Names** | Dimethyl sulfoxide |
| **Structural Formula** |  |

## SUMMARY CONCLUSIONS OF THE SIAR

### Human Health

No data is available on the absorption of DMSO by inhalation exposure. However, its physico-chemical properties (low molecular size, high polarity and water solubility) suggest that DMSO is significantly absorbed by the inhalation route. DMSO appears to be readily absorbed through the skin. An *in vitro* permeability rate of 176 $g/m^2$.hour has been reported for human skin. Maximal serum concentration of DMSO occurred at 4 to 8 hours following skin contact in humans, and at 2 hours in rats. DMSO is also well absorbed after oral exposure. Peak plasma concentration of DMSO was attained at 4 hours after oral dosing in humans and at 0.5 hours in rats. DMSO is widely distributed to all body tissues. Higher concentrations of DMSO were found in the kidney, spleen, lung, heart and testes of rats given an oral dose, while higher levels were noted in the spleen, liver and lungs following a dermal dose. In humans, the plasma DMSO clearance half-life was about 11 to 14 hours, and 20 hours after dermal and oral dosing, respectively. A shorter clearance half-life of 6 hours was observed in rats after both routes of exposure. Metabolism of DMSO takes place primarily in the liver and kidneys. The principal metabolite is dimethyl sulfone ($DMSO_2$). Peak plasma levels of $DMSO_2$ in humans were observed at 72 to 96 hours after dosing, and then declined with a half-life of about 60 to 72 hours. DMSO is excreted unchanged or as the metabolite $DMSO_2$ in the urine. In the human, about 13 and 18% of a dermal dose, and 51% and 10% of an oral dose were accounted for by urinary excretion of DMSO and $DMSO_2$, respectively.

DMSO is of low acute toxicity. In non-guideline studies, $LD_{50}$ in rats are generally higher than 20,000 mg/kg bw and 40,000 mg/kg bw by the oral and dermal routes, respectively. In an acute inhalation study performed following the OECD TG 403, the $LC_{50}$ in rats was higher than 5000 $mg/m^3$ for a 4-hour exposure.

A skin irritation assay performed in rabbit according to the OECD TG 404 revealed no more than a very slight or well-defined erythema, which disappeared in 3 days. In humans, repeated application of DMSO solution for up to several months could induce transient erythema, burning, stinging and itching, which returned to normal after discontinuation of treatment. In one study in humans, occlusive exposure to DMSO caused cell death of the outer epidermis, followed by rapid regeneration.

DMSO is slightly irritating for the eye. In studies performed following the OECD TG 405 or the EEC method B.5, a slight to moderate conjunctival irritation, which cleared in 3 days, was observed in the eyes of rabbits. A repeated instillation (100% DMSO, 3 times/day for 6 months) in the eyes of rabbits induced only a temporary lacrimation but did not show any changes in the iris, cornea, lens, retina, conjunctiva and lids. In humans, the instillation of solutions containing 50 to 100% DMSO has caused transient sensation of burning which was reversible within 24 hours.

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DMSO is not a skin sensitizer. Sensitization tests performed in guinea pigs and mice following methods comparable to the OECD TG 406 were uniformly negative. A skin sensitization assay performed in humans was also negative.

DMSO is of low toxicity by repeated administration. According to the results of a 13-week inhalation toxicity study compliant with the OECD TG 413, the No Adverse Effects Concentration (NOAEC) for DMSO could be established at *ca.* 1000 mg/m$^3$ for respiratory tract irritation and *ca.* 2800 mg/m$^3$ (the highest concentration tested) for systemic toxicity. Other non-guideline repeated dose toxicity studies performed by different routes of administration and with several mammalian species have also shown that DMSO produced only slight systemic toxicity. With the exception of a decrease of the body weight gain and some hematological effects (which could be secondary to an increased diuresis) at very high dose levels, the most common finding observed in these studies is changes of the refractive power of the lens. These ocular changes were observed following repeated oral application of DMSO at doses of around 3000 mg/kg bw/d in rats for 18 months and 1000 mg/kg bw/d in dogs for 2 years. Following repeated dermal application, the same effects were observed at doses of around 1000 mg/kg bw/d in rabbits for 30 days, in dogs for 118 days and in pigs for 18 weeks. Similar ocular changes were not observed in monkeys following dermal application at doses of up to 9000 mg/kg bw/d for 18 months (dose levels that caused marked ocular toxicity in sensitive species). Clinical signs of systemic toxicity and the alterations of the lens were also never observed or reported in clinical and epidemiological studies performed in humans, even after exposure to a high dose level (1000 mg/kg/d for 3 months) or for a long period of time (up to 19 months). Overall, primates appear to be much less sensitive to DMSO ocular toxicity, and the ocular changes observed in rats, rabbits, dogs or pigs are not considered relevant for human health. Then, it is possible to estimate that the No Observed Adverse Effect Levels (NOAELs) by oral or dermal routes would be close to 1000 mg/kg bw/d.

In studies performed with methods compliant or comparable to OECD guidelines, no genotoxic activity was observed for DMSO in gene mutation assays in *Salmonella typhimurium,* an *in vitro* cytogenetics assay in CHO cells and an *in vivo* micronucleus assay in rats. With few exceptions, a large battery of additional *in vitro* and *in vivo* non-guideline studies confirmed the lack of genotoxic potential.

There is no valid carcinogenicity study conducted with DMSO.

DMSO is not a reproductive toxicant. In a Reproduction/Developmental Toxicity Screening Test performed following the OECD TG 421, the NOAEL for parental toxicity, reproductive performance (mating and fertility) and toxic effects on the progeny was considered to be 1000 mg/kg/day. In addition, no effect was observed on the estrus cycle, the sperm parameters (count, motility and morphology) and the reproductive organs of male and female rats after a 90-day inhalation exposure to DMSO concentrations up to 2800 mg/m$^3$. In developmental toxicity studies performed according to the OECD TG 414, oral administration of DMSO to pregnant female rats or rabbits during the period of organogenesis was not teratogenic. The NOAELs for maternal toxicity were 1000 and 300 mg/kg bw/d in rats and rabbits, respectively, and the NOAELs for embryo/foetotoxicity were 1000 mg/kg bw/d in both species.

**Environment**

DMSO is a liquid (density 1.1) with no color but in some cases a light characteristic sulfur odor due to traces of the raw material dimethyl sulfide. DMSO has a melting point of 18.5°C and a boiling point of 189°C (at 1,013 hPa). Its log $K_{ow}$ is of –1.35 (measured). DMSO has a vapor pressure of 0.81 hPa at 25°C and a Henry law's constant of $1.17*10^5$ mol.kg$^{-1}$.atm$^{-1}$. DMSO is miscible in all proportion with water and with most of the common organic solvents such as alcohols, esters, ketones, ethers, chlorinated solvents and aromatics. DMSO is stable in water and is not expected to volatilize. DMSO Log $K_{oc}$ is estimated to be equal to 0.64. This value suggests that DMSO is mobile in soil. DMSO is not expected to adsorb to suspended solids, sediments and soils. In atmosphere, DMSO is not susceptible to direct photolysis by sunlight. Calculations indicate DMSO half-life values, for reaction with OH radicals, from *ca* 2 to 6 h.

Distribution modeling using Mackay Fugacity model Level III, for equal release in the environment (*i.e.*

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1000 kg/h), indicates that the main target compartment will be soil (60.4%) and water (39.5%) with the remainder partitioning between air (0.0334%) and sediment (0.0723%). DMSO is not expected to bioaccumulate in the aquatic environment based on a measured bioconcentration factor lower than 4.

One readily biodegradation test performed following the norm AFNOR NF T 90-312 concluded that DMSO is readily biodegradable. Nevertheless, based on literature data and weight-of-evidence approach, better expectation is to consider DMSO as inherently biodegradable. For instance, 500 mg/L DMSO were entirely biodegraded within *ca*. 37h with aerobic settling sludge obtained from the activated sludge process at an opto-electronic plant, under optimized pH/temperature conditions. In a test report following OECD TG 303A, it has been validated that more than 90% DMSO was biodegraded at a concentration of 65 mg/L after 32 days of exposure.

Acute toxicity studies, carried out for some of them according to guidelines similar to OECD guidelines, reveal 48-hour $EC_{50}$'s ranging from 24,600 to 58,200 mg/L for daphnid (*Daphnia magna*) and 96-hour $LC_{50}$'s ranging from 32,300 to 43,000 mg/L for fish according to the species considered (*eg. Ictalurus punctatus, Lepomis cyanellus)*. Modeling calculation for algae indicates 96-hour $EC_{50}$ value of about 400 mg/L. On this basis DMSO can be considered non-toxic for aquatic compartment.

**Exposure**

The worldwide consumption of DMSO is estimated for the year 2004 between 30,000 T and 40,000 T. The production sites are located, one in Europe, one in Japan, one in the United States and several sites (3-4) of smaller size in China. With its high polarity combined with a high electric constant, DMSO is known to be an excellent solvent for polar or polarizable organic compounds, and also many acids, alkalis and mineral salts. DMSO is used industrially, and not exclusively, as a reaction, polymerization, clean-up and pharmaceutical solvents, paint and varnish removers, analytical reagent, in the manufacture of synthetic fibers, industrial cleaners and pesticides and in the electronic industry. DMSO is also used as a preservative for organ transplantation and for the treatment for the symptoms of interstitial cystitis. There is a well-known phenomenon of use of DMSO by patients for other than the treatment of interstitial cystitis purposes, primarily to treat sprains, bruises, minor burns and arthritis. It should be noted, that only a medical purity grade DMSO is safe, and the technical grade DMSO should not be used for the curative dermal applications. In addition, DMSO enhances the permeability of skin to other substances. Fifty percent of the DMSO applications are in the pharmaceutical and agrochemical industries, 25% in the electronics, 10% in fine chemistry and 15% in other applications.

DMSO naturally occurs in natural water. DMSO is produced and released into seawater by phytoplankton, as is dimethylsulfide (DMS). DMS, which is estimated to comprise 90% of the reduced sulfur flux from the ocean to the atmosphere, is subsequently oxidized to DMSO and then sulfur dioxide and sulfate as part of the global atmospheric sulfur cycle. A representative surface sample of seawater from the North Pacific contained 0.49 ppb of DMSO. However, its occurrence in seawater is restricted to the zone where light penetrates (the euphotic zone < 100 m depth). DMSO also occurs in rain (*ca*. 5 nmol/L) from marine air masses, suggesting that DMSO participates in the transfer of sulphur between ocean and atmosphere

DMSO production and use may result in its release to the environment through various waste streams. As already mentioned, DMSO is used in many industries. Therefore, the anthropogenic environmental sources are numerous.

Comprehensive surveys of wastewater identified DMSO in discharges of industrial sites with highest effluent concentration of 1266 ppb in the laundry industry. In fact, DMSO concentrations are variable in the environment ranging from no quantified concentrations to *ca*. a thousand of ppb, depending on the sampling site (*eg*. below the LOQ in leachate plumes under sanitary landfills; 10-80 ppb in kraft mills effluent.).

Occupational exposure to DMSO is most likely via the inhalation and/or dermal routes of exposure. However, manufacturing and distribution processes utilize closed system engineering practices to eliminate/reduce potential exposure to DMSO. In addition, adequate ventilation and chemical-specific personal protective equipment (PPE) is utilized for additional protection. The American Industrial

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Hygiene Association (AIHA) has established a Workplace Environmental Exposure Level (WEEL) 8-hr time-weighted average (TWA) of 250 ppm.

Environmental monitoring data indicate that the general population may be exposed to DMSO *via* inhalation of ambient air and ingestion of food and drinking water contaminated with DMSO. Exposure through dermal contact with a small number of consumer products containing DMSO is also a possibility. The SPIN database for Substances in Preparations in Nordic Countries lists a few uses of DMSO in consumer preparations for products registered in Sweden, but no record was found for DMSO in the U.S. National Institutes of Health Household Products database.

**RECOMMENDATIONS AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED**

**Human health:** DMSO is currently of low priority for further work for the Human health due to its low hazard profile.

**Environment:** DMSO is currently of low priority for further work for the environment due to its low hazard profile.

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