The MAK Collection for Occupational Health and Safety

Dimethyl sulfoxide (DMSO)

MAK Value Documentation, addendum – Translation of the German version from 2016

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Keywords: dimethyl sulfoxide; MAK value; maximum workplace concentration; peak limitation; developmental toxicity; irritation; nose

Citation Note: Hartwig A, MAK Commission. Dimethyl sulfoxide (DMSO). MAK Value Documentation, addendum – Translation of the German version from 2016. MAK Collect Occup Health Saf [Original edition. Weinheim: Wiley-VCH; 2017 Jul;2(3):1138-1143]. Corrected republication without content-related editing. Düsseldorf: German Medical Science; 2026. https://doi.org/10.34865/mb6768e6117_w

Republished (online): 07 Aug 2026

Originally published by Wiley-VCH Verlag GmbH & Co. KGaA; https://doi.org/10.1002/3527600418.mb6768e6117

Addendum completed: 25 Feb 2015

Published (online): 26 Jul 2017

The commission established rules and measures to avoid conflicts of interest.

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Dimethyl sulfoxide / methylsulfinylmethane

MAK Value Documentation

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DOI: 10.1002/3527600418.mb6768e6117

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the maximum concentration at the work place (MAK value) of dimethyl sulfoxide [67-68-5] of 50 ml/m³, considering the endpoints local and systemic toxicity as well as developmental toxicity. In a 13-week inhalation study the olfactory and respiratory epithelia and the pharynx of rats are the target tissues, and a reduction of body weight gain, possibly secondary to the irritation, is seen. The NOAEC for these effects is 964 mg/m³ (297 ml/m³, vapour). Since 2014 the Commission uses an empirical approach to set MAK-values for substances with critical effects on the upper respiratory tract or the eyes. According to this approach, a MAK value of 50 ml/m³ can be calculated from this study, taking into account that a lower NOAEC has to be expected with chronic exposure. Therefore, the previous MAK value is confirmed. As local effects are critical, the assignment to Peak Limitation Category I and the excursion factor of 2 are confirmed. In a screening study with rats according to OECD test guideline 421, the borderline increase in incidences of pups with dilated renal pelvis seen in a developmental toxicity study, are not confirmed. However, in rabbits, dimethyl sulfoxide causes kidney malformations with a NOAEL of 300 mg/kg body weight. Therefore, damage to the embryo or foetus cannot be excluded even when the MAK value is observed and dimethyl sulfoxide is assigned to Pregnancy Risk Group B.

Keywords

dimethyl sulfoxide; methyl sulfoxide; methylsulfinylmethane; DMSO; sulfinylbismethane; (sub) acute toxicity; (sub)chronic toxicity; irritation; reproductive toxicity; fertility; developmental toxicity; peak limitation; prenatal toxicity; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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Dimethyl sulfoxide (DMSO)

[67-68-5]

Supplement 2016

MAK value (2008)	**50 ml/m³ (ppm) ≙ 160 mg/m³**
Peak limitation (2008)	**Category I, excursion factor 2**
Absorption through the skin (1990)	**H**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2015)	**Pregnancy Risk Group B**
Germ cell mutagenicity	**–**
BAT value	**–**

In 2014, the Commission adopted a method for the derivation of MAK values for substances that have effects on the upper respiratory tract and eyes that is based on physiological and empirical aspects and which also includes criteria for the classification of the substance as a sensory irritant (Brüning et al. 2014). The MAK value is reviewed here on the basis of this procedure.

Animal Experiments and in vitro Studies

Subacute, subchronic and chronic toxicity

Inhalation

In an inhalation study in rats with exposure for 4 or 13 weeks on 7 days per week, a concentration of 2783 mg/m³ (vapour/aerosol) led to pseudoglandular changes in the respiratory epithelium, hyperplasia and minimal inflammation of the squamous epithelium, eosinophilic inclusions in the olfactory epithelium of the nose, prominent goblet cells in the pharynx and decreased body weight gains. The NOAEC (no observed adverse effect concentration) for the effects on the nasal epithelium detected histopathologically was 1886 mg/m³ after 4 weeks and 964 mg/m³ (297 ml/m³) after 13 weeks (Elf Atochem SA 2000).

Local effects on skin and mucous membranes

Eyes

Mild irritation was observed after the application of 0.1 ml undiluted dimethyl sulfoxide to the rabbit eye for 24 hours. In another test carried out according to OECD Test Guideline 405, dimethyl sulfoxide induced very mild irritation of the conjunctiva, which was no longer detected after 3 days (Atofina SA 2003).

Reproductive and developmental toxicity

Fertility

In a study carried out according to OECD Test Guideline 421 in groups of 12 rats per sex and dose, gavage doses of DMSO of 0, 100, 300 or 1000 mg/kg body weight and day 15 days before mating, during mating and gestation, and up to the end of lactation in the female animals, and 15 days before mating and during mating for a maximum of 4 weeks in the male animals, did not lead to toxic effects on reproduction. The NOAEL (no observed adverse effect level) for parental toxicity and reproductive toxicity was 1000 mg/kg body weight and day, which was the highest dose tested (Arkema France 2011).

Developmental toxicity

In a valid study of developmental toxicity in rats described in the 2009 supplement (supplement "Dimethyl sulfoxide" 2009), an increased number of dilated ureters without histopathological changes and of delayed ossification of ribs were seen at the highest dose of 5000 mg/kg body weight and day. The body weight gains of the dams were decreased at this dose. An increase in the incidence of dilation of the renal pelvis was observed in all dose groups, but this was not associated with microscopic or other histopathological changes. Therefore, the lowest dose tested of 200 mg/kg body weight and day was the LOAEL (lowest observed adverse effect level) for developmental toxicity in rats; it was not possible to derive a NOAEL. As the increased incidences of dilation of the renal pelvis were close to the historical control values and were not clearly dose-dependent, the relevance of this finding is unclear. The NOAEL for maternal toxicity was 1000 mg/kg body weight and day (Elf Atochem SA 1997).

The screening study described above, which was carried out according to OECD Test Guideline 421, revealed on postnatal days 1 to 4 a statistically significant difference in the survival of the offspring of the group given 100 mg/kg body weight, compared with that in the control group. Dead offspring were found in 6 litters. There were no changes in the survival indices of the offspring of the higher dose groups compared with those in the control group. Therefore, the effect on the survival of the offspring is not regarded as substance-induced. In the high dose group,

the number of foetuses with dilation of the renal pelvis was increased on postnatal day 22, but the increase was not statistically significant and was still within the historical control values. The NOAEL for foetotoxicity or developmental toxicity as regards dilation of the renal pelvis and for maternal toxicity was 1000 mg/kg body weight and day, which was the highest dose tested. Teratogenicity was not examined (Arkema France 2011).

On the basis of the results of the screening study, in which foetuses were also examined for dilation of the renal pelvis, the Commission does not regard the dilation of the renal pelvis found in the first study as relevant to the present evaluation. Dilation of the renal pelvis in the later stage of gestation in rats seems to be a normal occurrence during renal development and seems to be reversible in the further course of development (Woo and Hoar 1972).

Based on these studies, the Commission has established a NOAEL of 1000 mg/kg body weight and day for developmental toxicity and maternal toxicity in rats.

A developmental toxicity study in New Zealand White rabbits revealed an increased incidence of rare malformations in the form of malpositioned and fused kidneys in 3 foetuses from 2 litters after oral administration of 1000 mg/kg body weight and day. The incidences were above the range of both the historical laboratory control values and those in the published literature (Allais and Reynaud 2013; Ema et al. 2012). Therefore, a substance-specific effect on the kidneys cannot be ruled out. The NOAEL for developmental toxicity in rabbits was 300 mg/kg body weight and day. The feed consumption of the dams was decreased at 300 mg/kg body weight and day and above. The NOAEL for maternal toxicity was 100 mg/kg body weight and day (Atofina SA 2002).

Manifesto (MAK value, classification)

The critical effects are irritation of the olfactory and respiratory epithelium and decreased body weight gains in rats.

MAK value. The NOAEC from the 13-week study for effects on the respiratory and olfactory epithelium of rats was about 300 ml/m^3. In this study, the animals were exposed daily instead of the usual 5 exposures per week.

Although dimethyl sulfoxide caused only mild irritation of the eyes, exposure to the vapour/aerosol induced effects on the nasal epithelium of rats at relatively high concentrations. A concentration of 70 ml/m^3 is obtained by applying the method described by Brüning et al. (2014), taking into account the intensification of the effects after chronic exposure, extrapolation of the effects on the respiratory epithelium to exposed persons and an additional correction because of the 7-day exposure per week instead of 5-day workplace exposure. The MAK value of 50 ml/m^3 has therefore been retained.

Peak limitation. Dimethyl sulfoxide is classified in Peak Limitation Category I because the local effects on the nose are critical. As dimethyl sulfoxide caused only

mild irritation of the eyes, the potential for sensory irritation is probably low. As the difference between the MAK value and the NOAEC of 300 ml/m³ for histopathological findings is sufficiently large, the excursion factor of 2 has been retained.

Prenatal toxicity. In a valid study of developmental toxicity in rats described in the supplement from 2009 (supplement "Dimethyl sulfoxide" 2009), increased incidences of dilation of the renal pelvis were observed in all dose groups up to 5000 mg/kg body weight and day. The relevance of this finding is unclear because these incidences were close to the historical control values and were not dose-dependent. The extended screening study in rats carried out according to OECD Test Guideline 421 that has become available did not reveal dilation of the renal pelvis or foetotoxicity and maternal toxicity up to the highest dose tested of 1000 mg/kg body weight and day up to postnatal day 21 (Arkema France 2011). On the basis of these two studies, the Commission has established a NOAEL of 1000 mg/kg body weight and day for developmental toxicity and maternal toxicity in rats. In the developmental toxicity study in rabbits, the NOAEL for developmental toxicity was 300 mg/kg body weight and day, and renal malformations were observed at the LOAEL of 1000 mg/kg body weight and day. The feed consumption was decreased in the dams at 300 mg/kg body weight and above. Therefore, the NOAEL for maternal toxicity was 100 mg/kg body weight and day.

For a toxicokinetic extrapolation of the NOAEL of 1000 mg/kg body weight for developmental toxicity in rats and 300 mg/kg body weight in rabbits to a concentration in workplace air the following data are used: the species-specific correction values for rats and rabbits (1 : 4 or 1 : 2.4) corresponding to the toxicokinetic differences to humans, the oral absorption (100%, rabbits; Kolb et al. 1967), the body weight (70 kg) and the respiratory volume (10 m³) of the person, and the assumed 100% absorption by inhalation. The concentrations calculated from this are 1750 mg/m³ or 875 mg/m³, which are 11 or 5 times higher than the MAK value of 50 ml/m³ (160 mg/m³). As the difference between the concentration in air calculated from the rabbit data and the MAK value of 50 ml/m³ is not sufficiently large and rare malformations were observed in rabbits outside the range of the historical control values, dimethyl sulfoxide has been classified in Pregnancy Risk Group B.

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completed 25.02.2015