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Methylene bis(dibutyldithiocarbamate)

MAK Value Documentation – Translation of the German version from 2020

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Keywords

methylene bis(dibutyldithiocarbamate); chemical compound in the work area; maximum workplace concentration; MAK value; toxicity; hazardous substance; peak limitation

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated methylene bis(dibutyldithiocarbamate) [10254-57-6] considering all toxicological end points. Available publications and unpublished study reports are described in detail. In a study carried out according to OECD Test Guideline 422, increased liver weights and reduced body weight gains were observed in female rats at 375 mg/kg body weight and day with a NOAEL of 75 mg/kg body weight and day. Inhalation studies are not available for methylene bis(dibutyldithiocarbamate); however, irritation of the eyes or airways is not expected as the substance is not irritating to the skin or eyes of rabbits. The bioavailability of the substance is assumed to be almost negligible after oral and inhalation exposure because of its physico-chemical properties. Based on the NOAEL and these considerations, the maximum concentration at the workplace (MAK value) is set at 20 mg/m^3 for the inhalable fraction (I). Inhalation of the inhalable fraction results in gastrointestinal exposure via mucociliary clearance, decreasing any concentration peaks. Therefore, Peak Limitation Category II with an excursion factor of 8 is established. The toxicity of the respirable fraction (R) of methylene bis(dibutyldithiocarbamate) in the lung is expected to be similar to that of severely refined mineral oil, for which a MAK value of 5 mg/m^3 R has been derived on the basis of inhalation studies. Therefore, the MAK value for methylene bis(dibutyldithiocarbamate) is also set at 5 mg/m^3 R. The substance is likewise assigned to Peak Limitation Category II with an excursion factor of 4 by analogy with severely refined mineral oil. Methylene bis(dibutyldithiocarbamate) does not cause foetotoxicity in rats up to an oral dose of 1500 mg/kg body weight and day; this dose is toxic to the dams. However, a teratogenicity study has not been performed on methylene bis(dibutyldithiocarbamate). As the available data are not sufficient for an evaluation, methylene bis(dibutyldithiocarbamate) is assigned to Pregnancy Risk Group D. Methylene bis(dibutyldithiocarbamate) is not genotoxic in vitro; in vivo data are not available. A carcinogenicity study has not been performed on methylene bis(dibutyldithiocarbamate). Skin contact is not expected to contribute significantly to systemic toxicity. Limited data show no sensitization.

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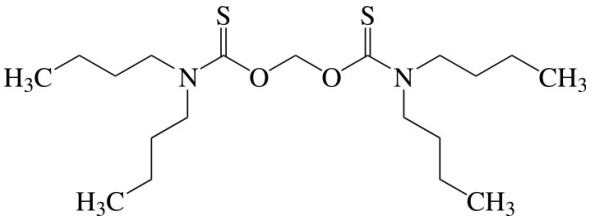
MAK value (2019)	**5 mg/m³ R (respirable fraction)** **20 mg/m³ I (inhalable fraction)**
Peak limitation (2019)	**R fraction: Category II, excursion factor 4** **I fraction: Category II, excursion factor 8**
Absorption through the skin	–
Sensitization	–
Carcinogenicity	–
Prenatal toxicity (2019)	**Pregnancy Risk Group D**
Germ cell mutagenicity	–
BAT value	–
Synonyms	*N,N*-dibutylcarbamodithioic acid methylene ester bis(di-*n*-butylthiocarbamoylthio)methane 4,4′-methylene bis(dibutyldithiocarbamate)
Chemical name	dibutylcarbamothioylsulfanylmethyl N,N-dibutylcarbamodithioate
CAS number	10254-57-6
Structural formula	
Molecular formula	$C_{19}H_{38}N_2S_4$
Molar mass	422.77 g/mol
Melting point	−40 °C (ECHA 2017 a)
Boiling point at 1013 hPa	decomposes at > 250 °C (ECHA 2017 a)
Density at 20 °C	1.06 g/cm³ (ECHA 2017 a)
Vapour pressure	$< 1.3 \times 10^{-10}$ hPa at 20 °C (ECHA 2017 a) $< 1.7 \times 10^{-10}$ hPa at 25 °C (ECHA 2017 a)
log K_{OW} at 35 °C	8.42 (ECHA 2017 a)
Solubility	0.243 mg/l water (ECHA 2017 a)
Stability	no data (ECHA 2017 a)
Production	alkylation of the dithiocarbamate with dichloromethane (Céspedes and Vega 1994)
Purity	< 1%; no other data (ECHA 2017 a)
Impurities	no data (ECHA 2017 a)
Use	in lubricants, greases, metal-working fluids (ECHA 2017 a) as an antioxidant in all types of mineral oil-based lubricants (Vanderbilt Company 2009)

The documentation is based mainly on the publicly available registration data under REACH (ECHA 2017 a) and the compilation of toxicological data under the US EPA's HPV programme (Vanderbilt Company 2009).

In lubricants, the concentration of methylene bis(dibutyldithiocarbamate) in general use is 0.5% (Hartwig and MAK Commission 2018, available in German only). Undiluted methylene bis(dibutyldithiocarbamate) is not irritating to the skin.

1 Toxic Effects and Mode of Action

Methylene bis(dibutyldithiocarbamate) is of low acute toxicity. The poor solubility in water and high log K_{OW} of methylene bis(dibutyldithiocarbamate) suggest low absorption.

In a combined repeated oral dose and reproductive/developmental toxicity study carried out according to OECD Test Guideline 422 in Sprague Dawley rats, the parent animals exhibited increased relative and absolute liver weights and reduced body weight gains at 5000 mg/kg diet (375 mg/kg body weight and day) and above. Up to the highest dose tested of 20 000 mg/kg diet (1500 mg/kg body weight and day), there were no substance-related effects on fertility, reproductive ability, offspring viability, growth and development up to day 5 of lactation.

Methylene bis(dibutyldithiocarbamate) is not a skin or eye irritant in rabbits.

Human data for skin sensitization to methylene bis(dibutyldithiocarbamate) are not available. The substance was not sensitizing in the local lymph node assay in mice. There are no data for a sensitizing effect of methylene bis(dibutyldithiocarbamate) on the airways.

In in vitro genotoxicity studies, methylene bis(dibutyldithiocarbamate) was neither mutagenic nor clastogenic. Studies of the genotoxicity of methylene bis(dibutyldithiocarbamate) in vivo or of its carcinogenicity are not available.

2 Mechanism of Action

There are no data available.

3 Toxicokinetics and Metabolism

Toxicokinetic studies have not been conducted.

The poor water solubility and high log K_{OW} of methylene bis(dibutyldithiocarbamate) suggest low absorption. There is no information available on its metabolism and degradation products (ECHA 2017 a).

4 Effects in Humans

There are no data available.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

There are no data available.

5.1.2 Oral administration

The acute oral LD_{50} of methylene bis(dibutyldithiocarbamate) in male Sherman Wistar rats is greater than 16 000 mg/kg body weight. In a study from the 1980s, groups of 5 animals were given gavage doses of 1000, 2000, 4000, 8000 or 16 000 mg/kg body weight; this was followed by a 14-day recovery period. No deaths occurred. There were no substance-related clinical signs up to 8000 mg/kg body weight. At 16 000 mg/kg body weight, the animals were slightly dirty and their fur was ruffled after 18 to 24 hours. They appeared normal and clean after 48 hours. The body weight gains of the animals were not affected and gross pathological examination did not reveal substance-related findings (ECHA 2017 a).

5.1.3 Dermal application

The acute dermal LD_{50} of methylene bis(dibutyldithiocarbamate) in albino rabbits (no other details) is greater than 2000 mg/kg body weight. In a limit test from 1980, groups of 3 male and 3 female rabbits received 2000 mg/kg body weight, applied occlusively to their backs for 24 hours and were subsequently observed for 14 days. No deaths and no substance-related clinical signs occurred. The body weight gains of the animals were not affected and the gross pathological examination did not yield substance-related findings (ECHA 2017 a).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

There are no data available.

5.2.2 Oral administration

In a combined repeated oral dose and reproductive/developmental toxicity study according to OECD Test Guideline 422 from 2006, groups of 10 male and 10 female Sprague Dawley rats were given methylene bis(dibutyldithiocarbamate) in concentrations of 0, 1000, 5000 or 20 000 mg/kg diet for 14 days prior to mating, during mating and pregnancy, and until day 5 of lactation. The concentrations were reduced to 900, 4500 and 18 000 mg/kg diet on day 29 to adjust the substance intake to the increased feed requirement of the females during pregnancy. From the authors' data for food intake, to the daily doses were estimated to be 0, about 75, 375 or 1500 mg/kg body weight. On day 5 of lactation, all female and male animals and the offspring were subject to gross-pathological examination. Up to the highest doses tested of 20 000/18 000 mg/kg diet (about 1500 mg/kg body weight and day), neither deaths nor clinical signs were observed. The body weights of the females were decreased in a statistically significant manner during the final week of gestation and the early lactation period, and feed intake was reduced in a statistically significant manner during the last week of gestation. In the females, the absolute and relative liver weights were increased in a statistically significantly fashion compared with the values for the controls. In the males, the increases in the activated partial thromboplastin time and clotting time were statistically significant. At 5000/4500 mg/kg diet (about 375 mg/kg body weight and day), the decrease in body weight gains during gestation was statistically significant compared with the weight gains in the control animals, and a statistically significant increase in the liver weights (no other details) of the females was found. There were no statistically significant effects on the food intake of the females. At and above 1000/900 mg/kg diet (about 75 mg/kg body weight and day), the grade of severity ("slight" to "minimal") of extramedullary haematopoiesis in the

spleen of the male animals was lower than that in the control animals (see Table 1). In the female animals of the high concentration group, the grade of severity ("minimal") of extramedullary haematopoiesis in the spleen was lower than that of the control animals ("minimal" to "slight"). As there was no dose-dependence, the effect was regarded by the authors as not adverse and the NOAEL (no observed adverse effect level) was given as 1000 mg/kg diet (about 75 mg/kg body weight and day) for the parent animals. The LOAEL (lowest observed adverse effect level) was 5000 mg/kg diet (about 375 mg/kg body weight and day) based on the increased liver weights and reduced body weight gains (ECHA 2017 a; Vanderbilt Company 2006, 2009).

Tab. 1 Incidence and severity of extramedullary haematopoiesis in the spleen of rats after administration of methylene bis(dibutyldithiocarbamate) (Vanderbilt Company 2006)

	Dose (mg/kg body weight and day)			
	0	**75**	**375**	**1500**
	n = 10	n = 5	n = 5	n = 10
♂:				
minimal	0/10 (0%)	5/5 (100%)	4/5 (80%)	3/10 (30%)
slight	5/10 (50%)	0/5 (0%)	1/5 (25%)	2/10 (20%)
♀:				
minimal	2/10 (20%)	1/5 (20%)	0/5 (0%)	5/10 (50%)
slight	3/10 (30%)	4/5 (80%)	5/5 (100%)	0/10 (0%)

5.2.3 Dermal application

There are no data available.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

In a skin irritation study from 1980, 0.5 ml of methylene bis(dibutyldithiocarbamate) was applied occlusively to the intact or abraded skin of 6 rabbits (no other details) for 4 or 24 hours. No erythema or oedema occurred after 4 hours, nor after 24 to 72 hours. Methylene bis(dibutyldithiocarbamate) was therefore regarded as not irritating to the skin (ECHA 2017 a).

5.3.2 Eyes

In an eye irritation study from 1980, 0.1 ml of methylene bis(dibutyldithiocarbamate) was instilled into one eye of 6 rabbits (no other details), not rinsed out and observed for 7 days. There were no effects on the cornea, iris or conjunctiva at 24, 48 or 72 hours or after 7 days. Methylene bis(dibutyldithiocarbamate) was therefore regarded as not irritating to the eyes (ECHA 2017 a).

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

A local lymph node assay carried out according to OECD Test Guideline 429 with concentrations of 25%, 50% and 100% methylene bis(dibutyldithiocarbamate) (purity 99%) in acetone/olive oil (4:1) in female CBA/J mice (5 animals per group) led to stimulation indices of 1.4, 1.3 and 1.5, respectively, and thus to an unequivocal negative result (ECHA 2017 a).

5.4.2 Sensitizing effects on the airways

There are no data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

In a combined repeated oral dose and reproductive/developmental toxicity study according to OECD Test Guideline 422 (see also Section 5.2.2 and 5.5.2), no substance-related effects on fertility or reproductive performance occurred up to the highest dose tested of 20 000 mg/kg diet (about 1500 mg/kg body weight and day) (ECHA 2017 a; Vanderbilt Company 2006, 2009). The NOAEL for effects on fertility is thus 1500 mg/kg body weight and day, the highest dose tested.

5.5.2 Developmental toxicity

In the study carried out according to OECD Test Guideline 422 mentioned in the previous section (see also Section 5.2.2), no substance-related effects on the viability of the offspring and their growth and development occurred up to day 5 of lactation. The LOAEL for the parent animals was 5000 mg/kg diet (about 375 mg/kg body weight and day) based on increased liver weights and reduced body weight gains. The NOAEL was 1000 mg/kg diet (about 75 mg/kg body weight and day) for the parent animals and 20 000 mg/kg diet (about 1500 mg/kg body weight and day) for the offspring (ECHA 2017 a; Vanderbilt Company 2006, 2009).

5.6 Genotoxicity

5.6.1 In vitro

A gene mutation test (plate incorporation) carried out according to OECD Test Guideline 471 with the Salmonella typhimurium strains TA98, TA100, TA102, TA1535 and TA1537 yielded negative results at methylene bis(dibutyldithiocarbamate) concentrations of 0, 50, 150, 500, 1500 or 5000 µg/plate with and without the addition of a metabolic activation system. Cytotoxicity did not occur. At 1500 µg/plate and above, oily precipitates were observed (ECHA 2017 a; Vanderbilt Company 2009).

Likewise, the results of a second gene mutation test carried out according to the guidelines in the Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 and the Escherichia coli strain WP2 uvrA were negative with and without the addition of a metabolic activation system and methylene bis(dibutyldithiocarbamate) concentrations of 0, 50, 150, 500, 1500 or 5000 µg/plate. The preincubation time was 10 hours and the exposure time 48 hours. Cytotoxicity was not observed up to the highest concentration tested; precipitates occurred at 5000 µg/plate (ECHA 2017 a).

A chromosomal aberration test carried out according to OECD Test Guideline 473 in human lymphocytes was performed with methylene bis(dibutyldithiocarbamate) concentrations of 0, 7.5, 15, 30, 60 or 120 µg/ml with preincubation for 48 hours. The cells were treated for 4 hours in the first experiment followed by culture in a control medium for 20 hours; in the second experiment, the cells were exposed for 24 hours. Both with and without the addition of a metabolic activation system, no increased incidences of aberrations were observed in either experiment up to 120 µg/ml. The highest concentration tested led to the formation of precipitates. In a pre-test, concentrations of up to 4220 µg/ml were not cytotoxic (ECHA 2017 a; Vanderbilt Company 2009).

In a $TK^{+/-}$ mutation assay using L5178Y mouse lymphoma cells carried out according to OECD Test Guideline 476, methylene bis(dibutyldithiocarbamate) concentrations of 0, 0.03, 0.1, 0.3, 1, 3, 10, 33 or 100 µg/ml with and without the addition of a metabolic activation system were not cytotoxic or mutagenic. The cells were exposed for 3 hours in the first experiment and for 24 hours in the second, and evaluated after another two days (ECHA 2017 a).

5.6.2 In vivo

There are no data available.

5.7 Carcinogenicity

There are no data available.

6 Manifesto (MAK value/classification)

Critical effects are increased relative and absolute liver weights and reduced body weight gains in rats after oral administration.

MAK value. There are no studies available for toxic effects after inhalation of methylene bis(dibutyldithiocarbamate).

Metal dithiocarbamates such as Ziram (**zinc** bis(di**methyl**dithiocarbamate)) are highly toxic to the lungs (MAK value 0.01 mg/m^3; Hartwig 2016). There are no studies investigating whether methylene bis(dibutyldithiocarbamate) is metabolized to an analogous locally toxic metal complex. Ziram is corrosive to the eyes, whereas methylene bis(dibutyldithiocarbamate) is not irritating. **Zinc** bis(dibutyldithiocarbamate), which has the same structure as methylene bis(dibutyldithiocarbamate) except for the central metal cation, is, unlike Ziram, at most mildly irritating to the eyes (ECHA 2017 b), so that toxic effects of methylene bis(dibutyldithiocarbamate) on the respiratory tract are unlikely. After ingestion, no local effects in the stomach or intestine like those seen with Ziram were observed, nor was lung toxicity described. Methylene bis(dibutyldithiocarbamate) is barely toxic even after prolonged administration: in a combined repeated oral dose and reproductive/developmental toxicity study carried out according to OECD Test Guideline 422 in Sprague Dawley rats, effects were observed only at and above 5000 mg/kg diet (375 mg/kg body weight and day). At this dose, the relative and absolute liver weights of the female parents were increased and the body weight gains reduced. The NOAEL was 1000 mg/kg diet (75 mg/kg body weight and day). Since methylene bis(dibutyldithiocarbamate) is not irritating to the skin or eyes of rabbits, a MAK value can be derived from the oral study.

Inhalable fraction: Methylene bis(dibutyldithiocarbamate) is probably hardly absorbed orally due to its physicochemical properties. The inhalable fraction is not absorbed after inhalation and deposition in the respiratory tract, but is swallowed after mucociliary transport and then enters the gastrointestinal tract. Therefore, the low oral absorption plays a role also for absorption by inhalation. Oral absorption and absorption after inhalation can therefore be assumed to be largely similar and need not be considered in the following calculation. Irritant effects in the upper respiratory tract are not to be expected when the aerosol is inhaled, as the substance is not irritating to the skin or eyes.

The following toxicokinetic data are taken into consideration for the extrapolation of the NOAEL of 75 mg/kg body weight and day to a concentration in workplace air: the daily exposure of the animals in comparison with the 5 days per week exposure at the workplace (7:5), the corresponding species-specific correction value for the rat (1:4), the body weight (70 kg) and respiratory volume (10 m^3) of the person. The concentration calculated from this is 184 mg/m^3. As this value comes from a NOAEL from experimental studies with animals (1:2), and since an increase in effects with chronic exposure cannot be ruled out (1:4, because the duration of the experiment is between subacute and subchronic), the concentration obtained using the preferred value approach is 20 mg/m^3 for the inhalable fraction. A MAK value of 20 mg/m^3 I has therefore been set for methylene bis(dibutyldithiocarbamate).

Respirable fraction: The low water solubility and the high log K_{OW} of methylene bis(dibutyldithiocarbamate) suggest low absorption also for the alveolar fraction. A corresponding inhalation study is not available. Methylene bis(dibutyldithiocarbamate) is a viscous liquid. The risk of accumulation is low because this substance is deposited as an aerosol with a high log K_{OW} on a surfactant film consisting of 90% lipids; mixing probably occurs. The surfactant has a half-life of less than 24 hours (catabolism to about 70% by type II cells and to about 30% by macrophages) and it

can be assumed that the xenobiotic is degraded by the cells. At high levels of deposition, the physical function of the surfactant could be disturbed and, as a result, the physical dynamics of the alveoli.

The properties in the lungs are therefore similar to those of mineral oil, which has an even lower water solubility (< 0.1 mg/l depending on the carbon number (Hartwig and MAK Commission 2019)). For mineral oil, a MAK value of 5 mg/m^3 R was derived from inhalation studies for the effects on the lungs. This value would protect against both the systemic toxicity of methylene bis(dibutyldithiocarbamate) (see above) and possible toxic effects on the lungs. In analogy to that for mineral oil, a MAK value of 5 mg/m^3 R has therefore been set for methylene bis(dibutyldithiocarbamate).

Peak limitation. Due to the systemic effect, the substance has been assigned to Peak Limitation Category II.

Inhalable fraction: In the case of exposure to the inhalable fraction, systemic exposure occurs via the swallowing of the substance deposited in the respiratory tract after mucociliary clearance. Due to the distribution of the substance in the respiratory tract and as this clearance occurs with a certain half-life, concentration peaks are levelled out. Therefore, an excursion factor of 8 has been set.

Respirable fraction: For the respirable fraction, an excursion factor of 4 has been set in analogy to that for mineral oil.

Prenatal toxicity. In a combined repeated oral dose and reproductive/developmental toxicity study carried out according to OECD Test Guideline 422 in Sprague Dawley rats, increased liver weights and reduced body weight gains at 5000 mg/kg diet (375 mg/kg body weight and day) and above were observed in the parent animals. Up to the highest dose tested of 20 000 mg/kg diet (1500 mg/kg body weight and day), there were no substance-related effects on fertility, reproductive performance, offspring viability, growth and development up to day 5 of lactation. The NOAEL for foetotoxicity was 1500 mg/kg body weight and day, the highest dose tested. There are no teratogenicity studies for the substance. As the available data are not sufficient for a conclusive assessment, methylene bis(dibutyldithiocarbamate) has been assigned to Pregnancy Risk Group D.

Carcinogenicity and germ cell mutagenicity. In in vitro genotoxicity studies, methylene bis(dibutyldithiocarbamate) was neither mutagenic nor clastogenic. Studies of the genotoxicity of methylene bis(dibutyldithiocarbamate) in vivo or its carcinogenicity are not available. No such effects are to be suspected due to its structure.

The available studies do not justify classification in one of the categories for carcinogens or germ cell mutagens.

Absorption through the skin. No data are available for dermal absorption. The solubility of the substance in water is low; in view of this and together with the high log K_{OW}, absorption through the skin is assumed to be low. The log K_{OW} is greater than 6 and thus outside the scope of application of the mathematical models, so that dermal absorption cannot be calculated. In addition, the high molar mass indicates poor absorption through the skin. The substance has therefore not been designated with an “H” (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are no data available for skin sensitizing effects of methylene bis(dibutyldithiocarbamate) in humans. A local lymph node assay in mice yielded unequivocally negative results. There are also no data available for respiratory sensitization. Methylene bis(dibutyldithiocarbamate) has therefore not been designated with “Sh” or “Sa” (for substances which cause sensitization of the skin or airways).

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

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