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Bis[*O*,*O*-bis(2-ethylhexyl) dithiophosphorato-*S*,*S*′]dioxodi-μ-thioxodimolybdenum

MAK Value Documentation – Translation of the German version from 2022

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Keywords

bis[O,O-bis(2-ethylhexyl) dithiophosphorato-S,S′]dioxodi-μ-thioxodimolybdenum; thyroid-stimulating hormone; kidney; toxicity; genotoxicity; reproductive toxicity; sensitization

Abstract

The German Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) summarized and evaluated the data for bis[*O*,*O*-bis(2-ethylhexyl) dithiophosphorato-*S*,*S*′]dioxodi-μ-thioxodimolybdenum [68958-92-9; 72030-25-2] to derive an occupational exposure limit value (maximum concentration at the workplace, MAK value) considering all toxicological end points. The documentation is based primarily on the REACH registration dossier. A study described in the REACH registration dossier that was carried out according to OECD Test Guideline 422 found increased kidney weights in male rats and elevated levels of thyroid-stimulating hormone in female rats at 100 mg/kg body weight and day. As the percentage change in kidney weights was not specified and the study was not made available to the Commission, a maximum concentration at the workplace (MAK value) cannot be derived and bis[*O*,*O*-bis(2-ethylhexyl) dithiophosphorato-*S*,*S*′]dioxodi-μ-thioxodimolybdenum has been assigned to Section II b of the List of MAK and BAT Values. Bis[*O*,*O*-bis(2-ethylhexyl) dithiophosphorato-*S*,*S*′]dioxodi-μ-thioxodimolybdenum was not found to be genotoxic in vitro; neither in vivo genotoxicity data nor carcinogenicity studies are available. There is no clear evidence of a contact sensitizing potential and no data for sensitization of the respiratory tract. Bis[*O*,*O*-bis(2-ethylhexyl) dithiophosphorato-*S*,*S*′]dioxodi-μ-thioxodimolybdenum is not expected to be taken up via the skin in toxicologically relevant amounts.

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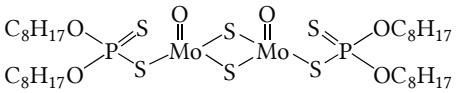
MAK value	**not yet established, see Section II b of the List of MAK and BAT Values**
Peak limitation	–
Absorption through the skin	–
Sensitization	–
Carcinogenicity	–
Prenatal toxicity	–
Germ cell mutagenicity	–
BAT value	–
Synonyms	molybdenum, bis[*O*,*O*-bis(2-ethylhexyl) phosphorodithioato-κ*S*,κ*S*´]dioxodi-μ-thioxodi-, (Mo-Mo)
Chemical name (IUPAC)	bis(2-ethylhexoxy)-sulfanylidene-sulfido-λ^5-phosphane;molybdenum
CAS number	68958-92-9 72030-25-2
Structural formula	
Molecular formula	$C_{32}H_{68}Mo_2O_6P_2S_6$
Molar mass	995.12 g/mol (ECHA 2020)
Melting point	no data; liquid at 20 °C (ECHA 2020)
Boiling point at 1013 hPa	no data (ECHA 2020)
Density at 20 °C	1.25 or 1.28 g/cm³ (ECHA 2020)
Vapour pressure	< 0.000015 hPa (20 °C); < 0.00004 hPa (25 °C) (ECHA 2020)
log K_{OW} at 20 °C	≥ 8.7 (ECHA 2020)
Solubility	≤ 250 ng/l water (ECHA 2020)
1 ml/m³ (ppm) ≙ 41.29 mg/m³	**1 mg/m³ ≙ 0.0242 ml/m³ (ppm)**
Hydrolytic stability	hydrolysis cannot be determined because of poor solubility in water (ECHA 2020)
Stability	decomposes at 200 °C (ECHA 2020)
Production	no data
Purity	no data
Impurities	no data
Uses	additive in metal-working fluids and lubricants (ECHA 2020)
Concentrations used	in metal-working fluids not miscible with water 1–2.5% (ECHA 2020; Houghton 2016)

The documentation is based primarily on the dataset publicly available through REACH (ECHA 2020). Statistics show that 10 to 100 tons of bis[*O,O*-bis(2-ethylhexyl) dithiophosphorato-*S,S*′]dioxodi-μ-thioxodimolybdenum (BDDT) are produced and used in the European Economic Area each year (ECHA 2020).

1 Toxic Effects and Mode of Action

Due to its physicochemical properties, BDDT is expected to be absorbed in only small amounts after inhalation, oral and dermal exposure.

In a combined study of subchronic toxicity and a screening test for reproductive and developmental toxicity carried out according to OECD Test Guideline 422, the kidney weights in male rats and the thyroid-stimulating hormone (TSH) in female rats were increased at dose levels of 100 mg/kg body weight and day and above.

In vitro studies did not find evidence that BDDT causes irritation of the human skin. Findings of eye irritation in the BCOP (bovine cornea opacity and permeability) test were not substantiated by the results of the EpiOcular Eye Irritation Test.

A local lymph node assay yielded questionable and, at most, borderline positive results for skin sensitizing effects. Clinical findings for contact sensitization or sensitization of the airways are not available.

Adverse effects on fertility or perinatal toxicity in rats were not determined up to the highest dose tested of 400 mg BDDT/kg body weight and day.

BDDT was not aneugenic, clastogenic or mutagenic in bacteria and mammalian cells in vitro. Studies of genotoxicity in vivo or carcinogenicity studies are not available.

2 Mechanism of Action

There are no data available.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

There are no studies available that investigated the absorption, distribution and elimination of BDDT.

Substance-related effects were induced after repeated oral exposure of rats (see Section 5.2.2), suggesting that the substance is absorbed in solution.

Inhalation exposure is limited by the low vapour pressure of BDDT ($\leq 4 \times 10^{-5}$ hPa), but can occur in the form of aerosols, which may arise when BDDT is used as a component of metal-working fluids. As a result of its poor solubility in water, BDDT is not assumed to be soluble in the mucous covering the airways. Furthermore, absorption via the respiratory epithelium is limited by the high molar mass of BDDT.

There are no data available for absorption through the skin. Models (Fiserova-Bergerova et al. 1990; Tibaldi et al. 2014) cannot be used to predict dermal absorption because BDDT has a log $K_{OW} > 6$ (ECHA 2020) and is thus outside their range of validity. However, BDDT is not expected to be absorbed through the skin in relevant amounts as a result of its poor solubility in water and high molar mass.

3.2 Metabolism

There are no data available.

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

In a test carried out according to OECD Test Guideline 423, female Crlg:Wistar rats (n = 3) were treated by gavage with a single dose of BDDT of 2000 mg/kg body weight and then observed for 14 days. Hunched posture, uncoordinated movements and piloerection were noticeable on days 1 and 2, but mortality did not occur. Likewise, no effects on body weights were observed. No unusual findings were determined by gross pathological examination after 14 days (ECHA 2020).

5.1.3 Dermal application

There are no data available.

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

There are no data available.

5.2.2 Oral administration

In a study carried out according to OECD Test Guideline 422 as a combined study of subchronic toxicity and reproductive and developmental toxicity, groups of 10 female and 10 male Crlg:Wistar rats per dose were treated with BDDT (purity not specified) in corn oil. The rats were given daily gavage doses of BDDT of 0, 25, 100 or 400 mg/kg body weight, the male rats for 29 days and the female rats with offspring for 51 to 62 days. In addition, unmated animals were treated with a BDDT dose of 400 mg/kg body weight and day (males for 29 days, females for 55 days) and then observed for 28 to 29 days.

As a copy of the original study report could not be obtained, the results listed in the registration dossier have been used for this documentation.

The faeces of all female and male animals of the high dose group (400 mg/kg body weight and day) were light in colour and soft in consistency from treatment day 4 onwards. This effect was observed in the males up to day 7 after the

last exposure. The females continued to have soft faeces up to about a week before the end of treatment and their faeces remained light in colour until the end of treatment. The faeces of females were normal during the observation period. All animals of the high dose group displayed hunched posture from treatment day 10 onwards; this effect was observed in the males up to day 3 following the end of treatment and in most of the females until about a week before the end of treatment (4/9 animals displayed hunched posture until the end of treatment). Piloerection was observed in all animals of the high dose group from treatment days 10 to 16 and in one female also on treatment day 17. The absolute and relative liver weights (no data for percentage changes) were increased in both sexes at 400 mg/kg body weight and day. In the males, the absolute and relative kidney weights were increased at 100 mg/kg body weight and day and above; in the females, only the absolute kidney weights were increased at 400 mg/kg body weight and day. In the high dose group, centrilobular hepatocellular hypertrophy occurred to a minimal extent in males and to a minimal to slight extent in females and correlated with increased liver weight. Follicular cell hypertrophy of the thyroid gland occurred in the females of the high-dose group with increased incidence and up to a minor degree of severity. All effects in the organs were reversible during the observation period. In the group treated with 400 mg/kg body weight and day, the alanine aminotransferase (ALT) and bile acid levels were increased with statistical significance and the alkaline phosphatase (ALP), bilirubin (in the males also at 100 mg/kg body weight and day) and potassium levels were decreased with statistical significance at the end of treatment; however, these effects did not persist to the end of the recovery phase. The cholesterol levels were decreased with statistical significance and the urea levels were increased significantly only in the females; this was not completely reversible. In comparison with the historical control data, the ALT and urea levels were slightly above the 95th percentile and the bilirubin levels were far below the values of the historical controls. The mean values for ALP, bile acids, cholesterol and potassium were in the range of the historical control data. In the females, the TSH levels in serum were increased 1.94-fold and 1.74-fold, respectively, at 100 and 400 mg/kg body weight and day, in some cases without statistical significance (no other details). However, the values were in the range of the historical controls. Thyroxine (T4) remained unchanged. Hearing, the pupillary reflex and the static righting reflex were in the normal range in all examined animals. The grip strength of the front and hind extremities was decreased by 13% to 20% in the high dose group in comparison with the values found in the control animals, but remained within the range of the historical controls. The authors established a NOAEL (no observed adverse effect level) of 100 mg/kg body weight and day (ECHA 2020). At this dose and above, the kidney weights in the males and the TSH levels in the females were found to be increased.

The Commission regards these effects on the kidneys and TSH as potentially critical. A conclusive evaluation of the effects cannot be made because it was not possible to obtain a copy of the original study report and the percentage changes in the kidney weights and statistical data for TSH levels were not reported in detail.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

In a test carried out according to OECD Test Guideline 431, reconstructed human epidermis (non-transformed human keratinocytes) was treated with 50 µl of undiluted BDDT for either 3 minutes or 1 hour (n = 2 in both cases). Cell viability was determined to be 93% of the control value after treatment for 3 minutes and 92% after 1 hour. Therefore, the substance was not found to have a potential for causing irritation in this test. The functioning of the test system was verified by the positive control (8 N potassium hydroxide solution) (ECHA 2020).

In a test carried out according to OECD Test Guideline 439, reconstructed human epidermis was treated for 15 ± 0.5 minutes with 25 µl of undiluted BDDT and then incubated without the substance for 42 hours. After treatment, cell viability was reduced to 89% of the level of viability determined in untreated tissue. The substance was thus not found to have an irritation potential in these tests. The functioning of the test system was verified by the positive control, a 5% solution of sodium lauryl sulfate (ECHA 2020).

Summary: In vitro, BDDT was not found to have the potential to cause skin irritation.

5.3.2 Eyes

In a BCOP test carried out according to OECD Test Guideline 437, the corneas of three cows were treated with 750 µl of undiluted BDDT for 10 ± 1 minutes followed by a post-treatment incubation period of 120 ± 10 minutes. The in vitro irritation score (IVIS) was calculated to be 5.3. According to the evaluation criteria, substances with an IVIS score ≤ 3 are not regarded as eye irritating or damaging and thus do not require classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). Substances with a score ≥ 55 are regarded as corrosive or severe irritants and classified as damaging to the eye (UN-GHS Category 1). The corneal opacity score was 2.2 and the permeability score 0.206. The functioning of the test system was verified by the positive control. According to these findings, BDDT induces effects on the cornea, but does not cause irreversible eye damage (ECHA 2020).

In a test with reconstructed human cornea-like epithelium (EpiOcular Eye Irritation Test) carried out according to OECD Test Guideline 492, BDDT was not found to cause irritation. The tissue (n = 2) was treated for 30 ± 2 minutes with 50 µl of undiluted BDDT followed by a post-treatment incubation period of 120 ± 15 minutes. After treatment, tissue viability was 110% of the control value. The functioning of the test system was verified by the positive control. The pre-treatment and post-treatment periods deviated from those of the OECD test guideline (no other details); however, the authors concluded that these deviations did not affect the reliability of the study (ECHA 2020).

Summary: The result of an in vitro test investigating eye irritation induced by BDDT in the bovine cornea was inconclusive. Another test in human cornea-like epithelium did not find evidence of an irritation potential. Therefore, BDDT was evaluated as not eye irritating (ECHA 2020).

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

The skin sensitizing effects of BDDT were investigated in a local lymph node assay carried out in female CBA/J mice according to OECD Test Guideline 429. Stimulation indices of 1.8, 2.2 and 3.0, respectively, were calculated for concentrations of 25%, 50% and 100% (w/v) in acetone/olive oil (4:1) (ECHA 2020). The results of the test are, however, questionable because of the broad variation in the reference values of the vehicle control group.

BDDT was additionally to be studied in vitro in a KeratinoSens test carried out according to OECD Test Guideline 442D. However, the authors reported that it was not possible to dissolve the test substance in a solvent compatible with the KeratinoSens test system (no other details) (ECHA 2020).

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 study of subchronic toxicity and a screening test for reproductive and developmental toxicity carried out according to OECD Test Guideline 422 (see Section 5.2.2 and 5.5.2), no effects on the oestrous cycle, sperm or fertility were observed in rats up to the highest dose tested of 400 mg/kg body weight and day (ECHA 2020). The NOAEL for effects on fertility was 400 mg/kg body weight and day.

5.5.2 Developmental toxicity

In a combined study of subchronic toxicity and a screening test for reproductive and developmental toxicity carried out according to OECD Test Guideline 422 (see Section 5.2.2 and 5.5.1), no effects on survival and the body weights of

the offspring were observed up to postnatal day 4 at exposure levels up to the highest dose tested. The findings and the NOAEL for subchronic toxicity for the parent animals are described in Section 5.2.2. The body weight gains of the treated dams did not differ from those of the control animals. The NOAEL for perinatal toxicity was the highest dose tested of 400 mg/kg body weight and day (ECHA 2020). Studies carried out according to OECD Test Guideline 422 do not include a complete evaluation of teratogenicity.

5.6 Genotoxicity

5.6.1 In vitro

In vitro genotoxicity data for BDDT are listed in Table 1.

BDDT yielded negative results in a mutagenicity test with the Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and E. coli WP2 uvrA in the concentration range of 5.4 to 1600 μg/plate both with and without the addition of a metabolic activation system. The threshold for cytotoxicity was not reached, but the substance was tested up to precipitation, which was observed at concentrations of 512 μg/plate and above (ECHA 2020).

A micronucleus test with human lymphocytes (sex and number of donors not specified) carried out according to OECD Test Guideline 487 yielded negative results at BDDT concentrations up to 125 μg/ml and 250 μg/ml, respectively, in test systems with and without metabolic activation. The lymphocytes were treated with BDDT for 3 hours both with and without a metabolic activation system and for 24 hours without metabolic activation (ECHA 2020).

In the $TK^{+/-}$ test in L5178Y mouse lymphoma cells, the incidence of mutations was not increased with statistical significance by the addition of BDDT up to precipitating and cytotoxic concentrations, both with and without metabolic activation (ECHA 2020). No differentiation was made between small and large colonies.

In summary, BDDT did not induce aneugenic, clastogenic or mutagenic effects in bacteria or in mammalian cells in vitro.

Tab. 1 In vitro studies of the genotoxicity of BDDT (ECHA 2020)

End point	Test system	Concentration	Effective concentration	Cytotoxicity	Results	
					−m. a.	+m. a.
gene mutation	Escherichia coli WP2 uvrA	0, 5.4, 17, 52, 164, 512, 1600 μg/plate	–	not cytotoxic; precipitation ≥ 512 μg/plate	–	–
	Salmonella typhimurium TA98, TA100, TA1535, TA1537	≤ 1600 μg/plate	–	not cytotoxic; precipitation ≥ 512 μg/plate	–	–
micronuclei	human lymphocytes	3-hour incubation: ±m. a.: 0, 31, 63, 125 μg/ml; 24-hour incubation: −m. a.: 0, 7.8, 16, 31, 63, 125, 250 μg/ml	–	not cytotoxic; precipitation ≥ 125 μg/ml	–	–
$TK^{+/-}$ test	cultured murine lymphoblasts (L5178Y)	3-hour incubation: −m. a.: 0, 0.3, 0.6, 1.3, 2.5, 5, 7.5, 10, 12.5, 15, 20, 25 μg/ml; +m. a.: 0, 0.3, 0.6, 1.3, 2.5, 7.5, 15, 30, 62.5 μg/ml; 24-hour incubation: −m. a.: 0, 0.16, 0.31, 0.63, 1.25, 2.5, 5, 10, 20 μg/ml	–	−m. a.: 3 hours: cytotoxic ≥ 15 μg/ml; 24 hours: precipitation ≥ 20 μg/ml; +m. a.: 3 hours: precipitation ≥ 62.5 μg/ml	–	–

m. a.: metabolic activation; TK: thymidine kinase

5.6.2 In vivo

There are no data available.

5.7 Carcinogenicity

There are no data available.

6 Manifesto (MAK value/classification)

After oral administration, kidney weights were increased in male rats and TSH levels were increased in female rats.

MAK value and peak limitation. There are no studies of inhalation exposure available. BDDT did not cause irritation of the skin or eyes in vitro. In a study carried out according to OECD Test Guideline 422, the most sensitive end points at a dose of 100 mg/kg body weight and day were increased kidney weights in the males and increased TSH levels in the females; however, it was not possible to obtain a copy of the original study report (ECHA 2020). Data for the percentage changes in kidney weights and detailed information for the increased TSH levels are not provided. As a copy of the original study report is not available, a MAK value cannot be derived from this study and the substance has been assigned to Section II b of the List of MAK and BAT Values. Peak limitation is not applicable.

Prenatal toxicity. A NOAEL for perinatal toxicity of 400 mg/kg body weight and day, the highest dose tested, was derived from the findings of a combined study carried out according to OECD Test Guideline 422. Studies that comply with OECD Test Guideline 422 do not include a complete evaluation of teratogenicity. As a MAK value was not derived, the substance has not been classified in a pregnancy risk group.

Carcinogenicity and germ cell mutagenicity. Negative results were obtained in genotoxicity tests using Salmonella typhimurium and mouse lymphoma cells. A micronucleus test with human lymphocytes did not provide evidence of a clastogenic or aneugenic potential for BDDT. In vivo data for genotoxic or carcinogenic effects are not available for the substance. Therefore, the substance has not been classified in the categories for germ cell mutagens or carcinogens.

Absorption through the skin. There are no data available. The models for predicting dermal absorption cannot be applied (Section 3.1) because the substance has a log K_{OW} of ≥ 8.7. However, absorption through the skin is not expected to occur in relevant amounts in view of the poor solubility of the substance in water and its high molar mass of about 1000 g/mol. For this reason, the substance has not been designated with an “H” (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are no findings in humans available for the sensitizing effects of BDDT on the skin and only one local lymph node assay that obtained questionable and, at most, borderline positive results. There are no findings available for sensitizing effects on the respiratory tract. For this reason, BDDT has 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.

References

ECHA (European Chemicals Agency) (2020) Bis[O,O-bis(2-ethylhexyl) dithiophosphorato-S,S']dioxodi-µ-thioxodimolybdenum (CAS Number 68958-92-9 or 72030-25-2). Registration dossier. Joint submission, first publication 18 Mar 2019, last modification 13 Mar 2020. https://echa.europa.eu/de/registration-dossier/-/registered-dossier/27857, accessed 13 Mar 2020

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