The MAK Collection for Occupational Health and Safety

1,3-Dioxolane

MAK Value Documentation, addendum – Translation of the German version from 2018

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1,3-Dioxolane

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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 workplace (MAK value) and the Pregnancy Risk Group of 1,3-dioxolane [646-06-0].

1,3-Dioxolane causes a reduction in white blood cell count and in relative spleen weight at 1000 ml/m³ and above in female rats after 13 weeks whole body inhalation. The NOAEC is 298 ml/m³. As the percentage of white blood cell count reduction is the same after four and 13 weeks, no decrease of the NOAEC after chronic exposure is expected. The former MAK value of 100 ml/m³ was derived from the NOAEC. The MAK value is now lowered to 50 ml/m³ which takes into account the increased respiratory volume at the workplace because the blood:air partition coefficient of 1,3-dioxolane is > 5 (see List of MAK and BAT Values, Sections I b and I c). Since a systemic effect is critical, Peak Limitation Category II is retained. The default excursion factor of 2 is retained as well, as no half-life in blood is known.

In a prenatal toxicity study in rats with gavage application, 1,3-dioxolane results in reduced fetal body weights and gross external, soft tissue and skeletal malformations or variations at 1000 mg/kg body weight and day. The NOAEL for developmental toxicity is 500 mg/kg body weight and day. After toxicokinetic scaling this dose corresponds to a concentration of 875 mg/m³ (285 ml/m³) at the workplace. The difference to the MAK value of 50 ml/m³ is not sufficient. Therefore, the assignment to Pregnancy Risk Group B, for substances, for which damage to the embryo or foetus must be expected even when the MAK value is observed, is confirmed.

Keywords

1,3-dioxolane; (sub)acute toxicity; (sub)chronic toxicity; reproductive toxicity; peak limitation; prenatal toxicity; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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1,3-Dioxolane

[646-06-0]

Supplement 2018

MAK value (2017)	**50 ml/m³ (ppm) ≙ 150 mg/m³**
Peak limitation (2006)	**Category II, excursion factor 2**
Absorption through the skin (2006)	**H**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2011)	**Pregnancy Risk Group B**
Germ cell mutagenicity	**–**
BAT value	**–**
Vapour pressure at 20 °C	105 hPa (SRC 2013)
log K_{OW}[1)]	–0.37 (SRC 2013)
1 ml/m³ (ppm) ≙ 3.074 mg/m³	**1 mg/m³ ≙ 0.325 ml/m³ (ppm)**

Documentation for 1,3-dioxolane was published in 2007 (documentation "1,3-Dioxolan" 2007, available in German only) followed by a supplement reviewing prenatal toxicity in 2012 (supplement "1,3-Dioxolan" 2012, available in German only).

In 2016, the Commission began using a revised approach for assessing substances with a MAK value based on systemic effects and derived from inhalation studies in animals or studies with volunteers at rest; this new approach takes into account that the respiratory volume at the workplace is higher than under experimental conditions. However, this does not apply to gases or vapour with a blood:air partition coefficient < 5 (see List of MAK and BAT Values). The experimentally derived blood:air partition coefficient of 1,3-dioxolane is 500 (Dahl et al. 1991). This supplement evaluates whether the MAK value for 1,3-dioxolane needs to be re-assessed as a result of the higher respiratory volume at the workplace.

1) octanol/water partition coefficient.

Animal Experiments and in vitro Studies

Subacute, subchronic and chronic toxicity

Inhalation

In a 13-week inhalation study in F344 rats carried out according to OECD Test Guideline 413 with exposure to 1,3-dioxolane vapour at concentrations of 0, 300, 1000 or 3000 ml/m³ (analysed values: 298, 1000 and 3010 ml/m³) for 6 hours per day, on 5 days per week, in whole animal exposure chambers (whole-body exposure), a decreased number of leukocytes and reduced spleen weights were observed in female animals at 1000 ml/m³ and above. In male animals, these effects were first observed at the next-higher concentration of 3010 ml/m³. The NOAEC (no observed adverse effect concentration) was 298 ml/m³. At the interim examination after 4 weeks, the NOAEC for a decrease in the number of leukocytes was likewise 298 ml/m³. Although the decrease was not statistically significant in female animals at 1000 ml/m³, this 16% decrease in the number of leukocytes was similar to that calculated after 13 weeks (documentation "1,3-Dioxolan" 2007, available in German only; Dow Chemical Company 1990). Therefore, the NOAEC is not expected to decrease further with an increase in the exposure period.

After 14-day inhalation exposure of male and female F344 rats to 1,3-dioxolane concentrations of 0, 516, 2319 or 5132 ml/m³, a decrease in the number of leukocytes in comparison with the number in the control group was observed at 2319 ml/m³ and above. The NOAEC was 516 ml/m³, which was the lowest concentration tested (DMC 2001).

In another 14-day inhalation study with exposure of male and female Sprague Dawley rats to 1,3-dioxolane concentrations of 0, 984 or 3280 ml/m³, a decrease in the number of leukocytes was found in male animals at 3280 ml/m³. The NOAEC was 984 ml/m³ (Celanese Corporation 1981).

Reproductive and developmental toxicity

Developmental toxicity

In a study of the toxic effects on prenatal development carried out according to a procedure similar to OECD Test Guideline 414, 1,3-dioxolane concentrations of 0, 125, 250, 500 or 1000 mg/kg body weight and day were given to Crl:CDBR rats by gavage from gestation days 6 to 15. Increased incidences of tail and heart malformations (ventricular septal defects) and a large number of different vertebral variations were observed in the foetuses at 1000 mg/kg body weight and day. At concentrations of 500 mg/kg body weight and day and above, maternal toxicity, reduced body weight gains and reduced feed consumption were recorded at the beginning of the treatment. However, the body weight gains in the dams were reduced only slightly (14%) during gestation at 1000 mg/kg body weight and day. The NOAELs (no observed adverse effect levels) for developmental and maternal toxicity were 500 and 250 mg/kg body weight and day, respectively (documentation "1,3-Dioxolan" 2007, available in German only; Hoechst Celanese Corporation 1991).

In another study of the toxic effects on prenatal development, 1,3-dioxolane concentrations of 0, 145, 580 or 1160 mg/kg body weight and day were given to rats by gavage every second day from gestation days 8 to 20. The rats were examined on day 21 of gestation. The incidence of malformations was not increased. Delayed ossification of the cranial bones was observed in the foetuses at 580 mg/kg body weight and day; the NOAEL for developmental toxicity was therefore 145 mg/kg body weight and day. The body weight of the dams was reduced at 1160 mg/kg body weight and day and the NOAEL for maternal toxicity was 580 mg/kg body weight and day (Sitarek et al. 1992). The results of this study, which does not comply with current test guidelines, do not contradict those of the valid study of the toxic effects on prenatal development described above.

Manifesto (MAK value/classification)

The critical effects are a decrease in the number of leukocytes and reduced spleen weights in rats exposed by inhalation for 13 weeks in whole animal exposure chambers.

MAK value.
In a 13-week inhalation study in F344 rats carried out according to OECD Test Guideline 413 with whole-body exposure to 1,3-dioxolane vapour, a decrease in the number of leukocytes and reduced spleen weights were observed in female animals at 1000 ml/m^3 and above. The NOAEC was 298 ml/m^3. Based on a comparison of the percentage decrease in the number of leukocytes at the interim examinations after 4 weeks and after 13 weeks (documentation "1,3-Dioxolan" 2007, available in German only; Dow Chemical Company 1990), no intensification of the effect is to be expected after long-term exposure.

Based on the NOAEC of 298 ml/m^3 derived from the 13-week inhalation study and extrapolation of the findings from animal studies to humans (1:2), and after taking into consideration the increased respiratory volume of the person at the workplace compared with that of the test animal at rest (1:2) and applying the preferred value approach, the MAK value has been lowered to 50 ml/m^3.

Peak limitation.
As the MAK value for 1,3-dioxolane was based on systemic effects, this substance remains classified in Peak Limitation Category II. No specific data for the half-life are available. For this reason, the default excursion factor of 2 has been retained.

Prenatal toxicity.
1,3-Dioxolane was classified in Pregnancy Risk Group B in 2011. Decisive for this classification was the mere 3-fold margin between the concentration in the air calculated for 1,3-dioxolane from the NOAEL for developmental toxicity of 875 mg/m^3 and day and the MAK value at that time of 100 ml/m^3, which is equivalent to 300 mg/m^3 (supplement "1,3-Dioxolan" 2012, available in German only).

The following toxicokinetic data are taken into consideration for the extrapolation of the NOAEL for the toxic effects on prenatal development in rats of 500 mg/kg body weight and day to a concentration in workplace air: the corresponding spe-

cies-specific correction value for the rat (1:4), the assumed oral absorption of 100%, the body weight (70 kg) and the respiratory volume (10 m^3) of the person as well as the assumed 100% absorption by inhalation. The concentration calculated from this is 875 mg/m^3, or 285 ml/m^3. The 6-fold margin between this and the MAK value of 50 ml/m^3, or 150 mg/m^3, is not sufficiently large, particularly because a significantly increased incidence of similar malformations was observed at only slight maternal toxicity at the LOAEL (lowest observed adverse effect level) of 1000 mg/kg body weight and day (1750 mg/m^3; 570 ml/m^3, 12-fold difference to the MAK value). For this reason, 1,3-dioxolane remains classified in Pregnancy Risk Group B.

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