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Tetramethyllead

MAK Value Documentation, supplement – Translation of the German version from 2009

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MAK value (1995)	**0.05 mg/m³ (as Pb)**
Peak limitation (2001)	**Category II, excursion factor 2**
Absorption through the skin (1966)	**H**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2008)	**Pregnancy Risk Group B**
Germ cell mutagenicity	**–**
BAT value (1995)	**50 µg total lead/l urine**
CAS number	75-74-1

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Developmental toxicity

Studies of the developmental toxicity of tetramethyllead were described in the documentation of 1995 (Greim 2001). The studies relevant for the assessment are summarized in Table 1.

Tab. 1 Studies relevant for the assessment of the developmental toxicity of tetramethyllead

Species, strain, number of animals per group	Exposure	Findings	References
rat, SD, 4–8 ♀	**GD 9–11** or **GD 12–14**, 0, 40, 80, 112, 160 mg/kg body weight and day, oral, examination on GD 22	**40 mg/kg body weight and above**: dams: toxic; foetuses: foetal weights ↓ **80 mg/kg body weight and above**: foetuses: delayed ossification **112 mg/kg body weight**: dams: lethal (GD 12–14); foetuses: resorptions ↑ (GD 9–11) **160 mg/kg body weight**: dams: lethal (GD 9–11, GD 12–14)	McClain and Becker 1972
rat, Long Evans, 4 ♀	**GD 7, 14, 21, and PND 6 and 13**, 0, 22 mg/kg body weight and day, subcutaneous, examination on PND 13, 16	**22 mg/kg body weight**: offspring: no effects on myelination, dendrite growth and receptors of the retina (PND 13, 16)	Cragg and Rees 1984; Ferris and Cragg 1984

GD: gestation day; PND: postnatal day; SD: Sprague Dawley

Prenatal toxicity

Tetramethyllead caused reduced foetal weights at maternally toxic doses of 40 mg/kg body weight and day and above, delayed ossification at 80 mg/kg body weight and day and above and resorptions at 112 mg/kg body weight and day. The incidence of malformations was not increased (McClain and Becker 1972). A NOAEL (no observed adverse effect level) for prenatal developmental toxicity cannot be derived from this study.

For tetra**ethyl**lead, which has a stronger toxic effect than tetramethyllead, a prenatal developmental toxicity study in rats (exposure from days 6 to 16 of gestation) and mice (exposure from days 5 to 15 of gestation) yielded NOAELs for maternal and developmental toxicity of 0.1 mg/kg body weight and day in each case, corresponding to 0.064 mg Pb/kg body weight and day (Kennedy et al. 1975; see the documentation for tetraethyllead from 2009 (Hartwig and MAK Commission 2021)).

The NOAEL for tetra**ethyl**lead of 0.1 mg/kg body weight and day or 0.064 mg Pb/kg body weight and day corresponds to 0.4 mg Pb/m³ for a person (70 kg body weight; inhaled air volume of 10 m³ in 8 hours). The margin between this NAEC and the MAK value for tetramethyllead of 0.05 mg/m³ (calculated as Pb) would thus be sufficiently large to justify Pregnancy Risk Group C for the prenatal toxic effects investigated. Due to the neurotoxic effect of tetramethyllead (see Greim 2001), however, particular consideration must be given to the effects of prenatal exposure on postnatal development.

Postnatal effects after prenatal exposure

There are no studies available for the effects of prenatal exposure to tetramethyllead on the development of the central nervous system (CNS).

In the case of lead and its inorganic compounds, it has been shown that, in humans, damage to the developing nervous system is the most sensitive end point after prenatal exposure. Lead and its inorganic compounds were therefore classified in Pregnancy Risk Group B before withdrawal of the MAK value of 0.1 mg/m³ in 2004. However, a direct quantitative comparison with inorganic lead with regard to developmental neurotoxicity is not possible,

as organic lead compounds have stronger neurotoxic effects than inorganic lead. Furthermore, the metabolism of organic lead compounds is different from that of inorganic lead compounds. Thus, after exposure to tetramethyllead, not only demethylation and the excretion of trimethyllead and especially dimethyllead in urine occurs, but also further metabolism to inorganic lead. Total lead in urine is used as a parameter for biomonitoring. After exposure to inorganic lead, 95% of the lead is bound to erythrocyte membranes. Therefore, the parameter for the biomonitoring of inorganic lead compounds is lead in whole blood.

In a study in rats given tetramethyllead doses of 22 mg/kg body weight and day on 3 prenatal and 2 postnatal days no morphological changes in nerves or myelination were observed (Cragg and Rees 1984; Ferris and Cragg 1984). However, functional neurological examinations were not performed. Other studies of the effects of prenatal exposure to tetramethyllead on the postnatal development of the CNS are not available.

However, a study in neonatal rats with tri**ethyl**lead, the neurotoxic metabolite of tetraethyllead, suggests that even with organic lead compounds, neonatal exposure leads to CNS damage with hyperreactivity and damage to the hippocampus in adult animals (Booze and Mactutus 1990). A NOAEL was not obtained.

Manifesto (MAK value/classification)

At the MAK value for tetramethyllead of 0.05 mg Pb/m^3, about 200 µg Pb is absorbed in 8 hours (10 m^3; 40% retained). In the studies on which the previous MAK value for inorganic lead of 0.1 mg/m^3 was based, about 300 µg Pb was absorbed in 8 hours (10 m^3; 30% retained). Inorganic lead compounds were assigned to Pregnancy Risk Group B, since adverse effects in exposed children were still detectable at an internal exposure corresponding to 0.1 mg/m^3. As organic lead compounds have stronger neurotoxic effects than inorganic lead compounds and are metabolized also to inorganic lead, it is to be expected that even if the MAK value for tetramethyllead is observed, developmental neurotoxicity will occur as in the case of inorganic lead. Tetramethyllead is therefore assigned to Pregnancy Risk Group B.

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (https://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/conflicts_interest/index.html) ensure that the content and conclusions of the publication are strictly science-based.

References

Booze RM, Mactutus CF (1990) Developmental exposure to organic lead causes permanent hippocampal damage in Fischer-344 rats. Experientia 46: 292–297. DOI: 10.1007/BF01951770

Cragg B, Rees S (1984) Increased body:brain weight ratio in developing rats after low exposure to organic lead. Exp Neurol 86: 113–121. DOI: 10.1016/0014-4886(84)90072-4

Ferris NJ, Cragg BG (1984) Organic lead and histological parameters of brain development. Acta Neuropathol 63: 306–312. DOI: 10.1007/BF00687338

Greim H (ed) (2001) Tetramethyllead. MAK Value Documentation, 1995. In: Occupational Toxicants, vol 15. Wiley-VCH, Weinheim, 237–248. Also available from DOI: 10.1002/3527600418.mb7574e0015

Hartwig A, MAK Commission (2021) Tetraethyllead. MAK Value Documentation, supplement – Translation of the German version from 2009. MAK Collect Occup Health Saf: Doc903. DOI: 10.34865/mb7800beoj21_1ad

Kennedy GL, Arnold DW, Calandra JC (1975) Teratogenic evaluation of lead compounds in mice and rats. Food Cosmet Toxicol 13: 629–632. DOI: 10.1016/0015-6264(75)90152-2

McClain RM, Becker BA (1972) Effects of organolead compounds on rat embryonic and fetal development. Toxicol Appl Pharmacol 21: 265–274. DOI: 10.1016/0041-008X(72)90070-1