Methyl bromide / Bromomethane

MAK Value Documentation

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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 developmental toxicity of methyl bromide [74-83-9]. Available unpublished study reports and publications are described in detail. The maximum concentration at the workplace (MAK value) of methyl bromide is 1 ml/m³, based on the irritant effect on the upper respiratory tract.

NOAECs for prenatal developmental toxicity in rats and rabbits were 70 ml/m³ and 40 ml/m³, respectively. NOAELs of 30 and 10 mg/kg body weight and day in rats and rabbits, respectively, were obtained in gavage studies, corresponding to 14 and 8 ml/m³ after scaling to a concentration at the workplace. Thus, there is an adequate margin between NOAEC/L for developmental toxicity and the MAK value.

However, methyl bromide is a neurotoxin and no data on developmental neurotoxicity exist. In adult mice and rats, neurotoxic symptoms like convulsions and paralysis of the hind limbs are observed. In a two-generation study the adult F0 and F1 generations do not show such neurotoxic effects at 90 ml/m³, which would have been expected particularly in the F1-animals, who have a longer exposure time which included complete gestation. It can be inferred that offspring are not more sensitive to the neurotoxicity of methyl bromide than adults. Thus, damage to the embryo or foetus is unlikely when the MAK value is observed and methyl bromide is re-assigned to Pregnancy Risk Group C.

Keywords

methyl bromide; bromomethane; toxicokinetics; reproductive toxicity; fertility; developmental toxicity; prenatal toxicity; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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Methyl bromide

[74-83-9]

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MAK value (2010)	**1 ml/m³ (ppm) ≙ 3.9 mg/m³**
Peak limitation (2010)	**Category I, excursion factor 2**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity (1992)	**Category 3B**
Prenatal toxicity (2015)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BLW (2002)	**12 mg bromide/l plasma or serum**
log K_{OW}[1)]	1.19 (SRC 2013)

Developmental toxicity

For methyl bromide, documentation from 1974 and supplements from 1983 and 1992 are available (combined in one English translation documentation "Methyl bromide" 1996). In 2011, the MAK value for methyl bromide was revised, and methyl bromide was classified in Pregnancy Risk Group D as there were no data available for developmental neurotoxicity (supplement "Methyl bromide" 2011). In a 2-generation study in rats (Methyl Bromide Panel 1986) already described in the 1992 supplement, the animals of the F0 and F1 generations were subjected to additional histopathological and neuropathological examinations of the brain (Chemical Manufacturers Association 1993 a, b). These results are discussed in this supplement and are used in the evaluation of the prenatal toxicity of the substance.

Methyl bromide is an alkylating agent used as a pesticide and methylating agent. The colourless gas is irritating to the skin and mucous membranes, it is nephrotoxic and affects the CNS especially after long-term exposure. Here, methyl bromide has

1) octanol/water partition coefficient

a very specific effect on the cortex, cerebellum, pallidum and nucleus ruber (documentation "Methyl bromide" 1996).

Toxicokinetics

Dermal application

Assuming whole-body exposure for 8 hours (17 000 cm^2) to an external concentration of 1 ml/m^3 (3.9 mg/m^3), and a body weight of 70 kg, the dermal absorption of 0.001 mg methyl bromide/kg body weight was estimated from a flux of $5.2 \cdot 10^{-7}$ mg/cm^2 and hour calculated according to the model of Fiserova-Bergerova et al.(1990). Under these conditions, absorption by inhalation is about 4/3.9 mg/$m^3 \cdot 10$ m^3/70 kg body weight, corresponding to 0.56 mg/kg body weight. Therefore, when the MAK value is observed, absorption through the skin is very low compared with that after inhalation (documentation "Methyl bromide" 1996).

Reproductive and developmental toxicity

Fertility

A 2-generation inhalation study with groups of 25 Sprague Dawley rats exposed in whole-animal chambers to methyl bromide concentrations of 0, 3, 30 or 90 ml/m^3 on 5 days a week was already described in the 1992 documentation (American Biogenics Corporation (1985) in documentation "Methyl bromide" 1996). Up to the highest concentration, the F0 and F1 parents and their respective offspring did not develop any abnormal neurotoxic symptoms such as tremor, nervousness, convulsions and paralysis of the hind legs (see also the section on subchronic toxicity in supplement "Methyl bromide" 2011). In the offspring, from birth up to the end of lactation (examined once a week on the days the body weight was determined), no external malformations were observed. The highest concentration tested of 90 ml/m^3 resulted in a marginal delay in body weight gains as from birth; at concentrations of 30 ml/m^3, body weight gains were delayed from postnatal day 14 onwards in the F1 offspring and from postnatal day 4 onwards in the F2 offspring. At concentrations of 90 ml/m^3 the absolute brain weights of the F1 offspring and of the female F2 offspring were reduced on postnatal day 28, as were those of the adult male F0 animals and of the adult F1 animals of both sexes. In addition, in the female F2 offspring, the absolute weights of the kidneys, heart and liver were decreased. No changes were observed at 3 or 30 ml/m^3. The no observed adverse effect concentration (NOAEC) for systemic toxicity and foetotoxicity can therefore be assumed to be 30 ml/m^3, the NOAEC for fertility 90 ml/m^3 (Methyl Bromide Panel 1986).

Subsequently, additional histopathological and neuropathological examinations of the brain were carried out in the animals of the F0 and F1 generations of this study. The brain weights after fixation were determined, and slides stained with hematoxylin and eosin from three areas of the brain were examined in the adult

F1 animals of all treated groups. Necropsy did not reveal any gross pathological changes. Neither microscopic changes nor inflammatory or degenerative lesions were observed in the three areas of the brain of the adult F1 animals compared with the findings in the controls. Histopathological examination revealed a slight dilation of the lateral cerebral ventricle in only one male F1 animal of the 30 ml/m³ group. This was considered to be a chance finding (Chemical Manufacturers Association 1993 a). To further clarify the reduced brain weights, in the controls and the 90 ml/m³ group of adult F0 and F1 animals, five planes of section of the brain were examined for signs of toxicity, proliferation and cell death and the severity was assessed on a scale from 1 to 5. In addition, morphometric examinations were carried out according to the Rodier technique in the F0 and F1 animals. The following areas of the brain were included in the sections: olfactory bulb, cerebral cortex, hippocampus, basal ganglia, thalamus, hypothalamus, midbrain, brain stem and cerebellum. In the case of the F0 animals, also the brain weights after fixation were determined. Morphometric analysis could not be carried out with some preparations, as they were either damaged or no longer suitable for this method. No statistically significant differences in the mean values of the different parameters investigated were found for the adult F0 and F1 animals. The histological and morphometric examinations of the brain in the different regions in the high concentration group did not reveal any changes compared with the findings in the controls (Chemical Manufacturers Association 1993 b).

Developmental toxicity

Inhalation

Rat

In the supplement of 1992, a study is described in which groups of 40 Wistar rats were exposed to methyl bromide concentrations of 0, 20 or 70 ml/m³ from 3 weeks prior to mating up to gestation day 19, for 7 hours a day, on 5 days a week. Neither maternal nor embryotoxic effects were found (see Sikov et al. (1981) in documentation "Methyl bromide" 1996).

Rabbit

In the supplement from 1992, a developmental toxicity study in New Zealand White rabbits is described. After inhalation exposure to methyl bromide for 7 hours a day from gestation days 1 to 15, the high concentration of 70 ml/m³ produced convulsions and paralysis of the hind legs, resulting in the death of the animals. The concentration of 20 ml/m³ produced neither maternal nor developmental toxicity (see Sikov et al. (1981) in documentation "Methyl bromide" 1996).

Groups of 26 New Zealand White rabbits were exposed from gestation days 7 to 19 to methyl bromide concentrations of 0, 20, 40 or 80 ml/m³ for 6 hours a day. At the high concentration, food consumption and body weights were reduced, and

lethargy, a tilted head, slight ataxia and lateral position were observed in the dams. No effects were found in either of the low concentration groups. Neither were there any effects with regard to the incidence of pregnancy, the number of resorptions, litter size, foetal weights, the sex ratio and uterus weights. After exposure to methyl bromide concentrations of 80 ml/m^3, the incidences of an absent gallbladder and a missing pulmonary lobe ("minor malformations") were increased in the foetuses. As both malformations occurred also in the control group with an unusually high incidence (number of foetuses with an absent gallbladder/total number of foetuses per group: 8.2% 13/159 at 80 ml/m^3; 1% 2/190 in concurrent controls; 0.0% 0/3597 in historical laboratory controls; number of foetuses with a missing pulmonary lobe/total number of foetuses per group: 3% 5/159 at 80 ml/m^3; 1% 2/190 in concurrent controls; 0.05% 2/3597 in historical laboratory controls), the authors initially assumed that these effects were not substance-related, but could have been caused by a genetic defect in one of the males. A second investigation was carried out in rabbits at the high concentration of 80 ml/m^3. Once more, the incidence of absent gallbladders in the offspring was increased (4.2%). The incidence for the absence of a pulmonary lobe was similar to that in the concurrent controls, but was increased compared with that in laboratory controls. At the same time, maternal toxicity was less pronounced in the second investigation than in the first. The authors therefore excluded a genetic defect as the cause of the results and regarded the effect on the gallbladder at 80 ml/m^3 as substance-related. Therefore, a NOAEC of 40 ml methyl bromide/m^3 was derived for developmental and maternal toxicity (see supplement "Methyl bromide" 2011; Methyl Bromide Industry Panel 1990).

Oral administration

Rat

Groups of 23 to 24 CD(SD) rats were given gavage doses of methyl bromide of 0, 3, 10 or 30 mg/kg body weight and day in corn oil from gestation days 6 to 15. On gestation day 20 the animals were killed and the foetuses were examined for external, visceral and skeletal malformations. In the high dose group, the body weight gains were delayed and food consumption was reduced in the dams. In the stomach, pathological changes such as erosion and thickened walls were found. No clinical effects occurred. The number of corpora lutea, implantations and live foetuses, the sex ratio, the number of resorptions, the number of dead foetuses, and the foetal and placental weights were unaffected compared with in the control animals. In the high dose group, in which maternal toxicity was clearly visible, there was a slight increase in the total number of foetuses and litters with variations; this was, however, not significant. The increase is attributable to a significantly increased incidence of foetuses with presacral (free) vertebrae and, as the results were not significant on a litter-related basis, is not considered to be substance-related. No other toxic effects on development occurred. In the rat, the no observed adverse effect level (NOAEL) for developmental toxicity is 30 mg/kg body weight and that for maternal toxicity 10 mg/kg body weight (see supplement "Methyl bromide" 2011; Kaneda et al. 1998).

Rabbit

Groups of 18 Kbl:JW rabbits were given gavage doses of methyl bromide of 0, 1, 3 or 10 mg/kg body weight and day in corn oil from gestation days 6 to 18. On gestation day 27, the animals were killed and the foetuses were examined for external, visceral and skeletal malformations. In the dams of the high dose group, body weight gains were delayed and food consumption was reduced. No developmental toxicity was observed. Therefore, in this strain of rabbit, the NOAEL for developmental toxicity in this study was 10 mg/kg body weight and the NOAEL for maternal toxicity 3 mg/kg body weight (see supplement "Methyl bromide" 2011; Kaneda et al. (1998)).

Manifesto (prenatal toxicity)

The most sensitive end points of methyl bromide are neurotoxic effects and local irritation.

Prenatal toxicity. In a 2-generation study in rats, the body weight gains were delayed from birth and the absolute brain weights were reduced in the offspring at the high concentration of 90 ml/m^3; in the female F2 offspring, also the absolute weights of the kidneys, heart and liver were decreased. In the 2-generation study, the NOAEC for foetotoxicity was 30 ml/m^3. In studies of the toxic effects on prenatal development with inhalation exposure, the NOAEC for developmental toxicity was 70 ml/m^3 in rats and 40 ml/m^3 in rabbits. In studies of the toxic effects on prenatal development with gavage administration, no developmental toxicity occurred up to the highest doses tested of 30 mg/kg body weight and day in the rat and 10 mg/kg body weight in the rabbit; at these doses maternal toxicity was observed. The following toxicokinetic data are taken into consideration for the extrapolation of the NOAELs to a concentration in workplace air: the corresponding species-specific correction values (1:4; 1:2.4) for the rat and the rabbit, the assumed oral absorption of 100%, the body weight (70 kg) and respiratory volume (10 m^3) of the person, and the assumed 100% absorption by inhalation. The concentrations calculated from this are 53 and 29 mg/m^3 (14 and 8 ml/m^3) and differ by factors of 14 and 8, respectively, from the MAK value. As the NOAEL given in both studies with gavage administration was the highest dose tested in each case and the actual (no adverse effect level) NAEL is presumably higher, and the calculated NOAECs for toxic effects on prenatal development after inhalation were 70 and 40 times higher than the MAK value, and the difference is thus sufficiently large, no developmental toxicity is to be expected when the MAK value of 1 ml/m^3 (3.9 mg/m^3) is observed.

However, methyl bromide is neurotoxic, and studies of its developmental neurotoxicity are not available. Neurotoxic symptoms such as convulsions and paralysis of the hind legs have been observed in adult mice at 40 ml/m^3 and above and in adult rats at 50 ml/m^3 and above (see the section on subchronic toxicity in supplement "Methyl bromide" 2011). In the F0 and F1 parents in the 2-generation study with rats given concentrations of 90 ml/m^3, no neurological abnormalities typical

for methyl bromide, such as convulsions and paralysis in the hind legs, which would be expected particularly in the F1 animals exposed from fertilization onwards, were observed. At this concentration, merely reduced brain weights without histological and morphometric correlates were determined in the parents and the F1 offspring (on postnatal day 28). This allows the conclusion that the offspring are not more sensitive as regards effects on the brain than the adult animals. For this reason, and in view of the sufficiently largemargin between the NOAEC for developmental toxicity and the MAK value, methyl bromide is classified in Pregnancy Risk Group C.

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