The MAK Collection for Occupational Health and Safety

Acetonitrile

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

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Acetonitrile

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 maximum concentration at the workplace (MAK value) and the Pregnancy Risk Group of acetonitrile [75-05-8].

Acetonitrile causes an increased incidence of liver adenomas and carcinomas in rats at 400 ml/m³ with a statistically significant trend. The number of basophilic foci in the liver is positively correlated with the exposure concentration. At 100 ml/m³ the elevation is not statistically significant, however, these foci are regarded as preneoplastic lesions. From this concentration the former MAK value of 20 ml/m³ was derived. It is now lowered to 10 ml/m³ taking into account the increased respiratory volume at the workplace because the blood:air partition coefficient of acetonitrile 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. As the effects are probably due to the metabolites, the default excursion factor of 2 is confirmed despite the long half-life of acetonitrile.

For rabbits, the NOAEL for developmental toxicity after gavage is 15 mg/kg body weight and day. After toxicokinetic scaling this dose corresponds to a concentration of 34 ml/m³ at the workplace. Rabbits are more sensitive to acetonitrile than rats and humans and the developmental toxicity of acetonitrile is higher after gavage than after inhalation exposure as shown with rats. Therefore, the rabbit gavage data are not used to assign a Pregnancy Risk Group. The NOAEC for developmental toxicity in rats is 1600 ml/m³ and after considering the increased respiratory volume at the workplace the difference to the MAK value is sufficient. Therefore, damage to the embryo or foetus is unlikely when the MAK value is observed and acetonitrile remains assigned to Pregnancy Risk Group C.

Keywords

acetonitrile; cyanomethane; ethanenitrile; methyl cyanide; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; reproductive toxicity; fertility; developmental toxicity; genotoxicity; carcinogenicity; peak limitation; prenatal toxicity; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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Acetonitrile

[75-05-8]

Supplement 2018

MAK value (2017)	**10 ml/m³ (ppm) ≙ 17 mg/m³**
Peak limitation (2001)	**Category II, excursion factor 2**
Absorption through the skin (2001)	**H**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2001)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
Vapour pressure at 20 °C	96.6 hPa (documentation "Acetonitrile" 2003)
log K_{OW} [1)]	–0.34 (documentation "Acetonitrile" 2003)
1 ml/m³ (ppm) ≙ 1.70 mg/m³	**1 mg/m³ ≙ 0.59 ml/m³ (ppm)**

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 applies only to gases or vapours with a blood:air partition coefficient > 5 (see List of MAK and BAT Values, Sections I b and I c). According to the formula of Buist et al. (2012), the blood:air partition coefficient of acetonitrile is 622. This supplement evaluates whether the MAK value for acetonitrile needs to be re-assessed as a result of the higher respiratory volume at the workplace. In addition, the Pregnancy Risk Group is re-examined, as the toxicokinetic procedure for extrapolating oral doses to a concentration in air was not yet applied to this end point in the documentation published in 2001 (documentation "Acetonitrile" 2003).

1) octanol/water partition coefficient.

Toxicokinetics and metabolism

The metabolic products of acetonitrile are cyanide, formaldehyde, thiocyanate and carbon dioxide. Of the acetonitrile inhaled with cigarette smoke, 90% is absorbed via the lungs. When cigarette smoke was held in the mouth for 2 seconds, 74% of the acetonitrile was retained (documentation "Acetonitrile" 2003). The exposure period in this study was too short to achieve a steady state (apparently only 35 ml of cigarette smoke was inhaled from a smoke-dosage apparatus) (Dalhamn et al. 1968). Therefore, the 90% retention that was reported is an overestimation. This is confirmed by the fact that the retention values recorded for acetaldehyde and isoprene (99%) and for acetone (86%) are significantly higher than the retention values after longer exposure periods: acetaldehyde (humans, 45 to 75 seconds) 60% (supplement "Acetaldehyde" 2013b), isoprene (rats, 6 hours) 4.5% to 19% (documentation "Isoprene" 2009), acetone (humans, 2–4 hours) 54% (Pezzagno et al. 1986). For this reason, it is assumed that 75% of the acetonitrile is retained after inhalation exposure, whereby exposure for 2 seconds is considered the worst-case scenario. The actual retention is probably lower.

After oral doses of 1.8 mg of radioactively labelled acetonitrile were given to male and female Sprague Dawley rats, 24% of the dose was exhaled by the males as carbon dioxide and 47.8% in the form of other volatile compounds, 6.25% was excreted with the urine, 0.59% with the faeces and 1.95% was determined in the liver, kidneys and fat. The values were similar for females. In all, only about 80% of the radioactivity was recovered. It is to be assumed that the substance is almost completely absorbed orally because less than 1% was excreted with the faeces, which suggests that this fraction may not have been absorbed. Urine and faeces were collected for up to 72 hours after administration. In a similar study, total recovery was again only about 80%. The reason given for this was that some of the exhaled compounds could not be collected completely (ECHA 2016).

Subacute, subchronic and chronic toxicity

Inhalation

There are no new inhalation studies available.

In 13-week studies carried out by the NTP, B6C3F1 mice and F344 rats were whole-body exposed to acetonitrile in concentrations of 0, 100, 200, 400, 800 or 1600 ml/m^3. Hyperplasia of the forestomach, which was observed in mice at concentrations of 200 ml/m^3 and above, was attributed to local irritation, which may have been caused by cyanide. Hyperplasia of the forestomach was not detected in rats even at a concentration of 1600 ml/m^3. These findings are of little relevance for humans. The NOAEC (no observed adverse effect concentration) for systemic effects in mice was 200 ml/m^3; mortality and cytoplasmic vacuolation in the hepatocytes were observed at 400 ml/m^3. The NOAEC was 400 ml/m^3 in rats; effects on the central nervous system (CNS), anaemia and reduced thymus weights were observed at 800 ml/m^3 (NTP 1996).

The MAK value was derived from the 2-year study in F344 rats:

In the documentation from 2001 (documentation "Acetonitrile" 2003), a concentration of 100 ml/m³ was determined to be the LOEC (lowest observed effect concentration). In the 2-year carcinogenicity study carried out by the NTP (1996), exposure of male F344 rats to this concentration for 6 hours per day, on 5 days per week, led to a numerical, but not statistically significant, increase in the incidence of basophilic foci in the liver. The increase in incidence was statistically significant at 200 and 400 ml/m³ (Table 1 in the Section "Carcinogenicity").

Reproductive and developmental toxicity

Fertility

A NOAEC of 600 ml/m³ was determined in a screening study carried out in Japan according to OECD Test Guideline 422, in which groups of 10 male and 10 female Sprague Dawley rats were whole-body exposed to concentrations of 0, 150, 300, 600 or 1200 ml/m³. Slightly reduced fertility, changes in the oestrus cycle and mortality were observed at 1200 ml/m³ (ECHA 2016).

Developmental toxicity

There are no new data available.

The following studies were discussed in the 2001 documentation (documentation "Acetonitrile" 2003):

Two valid inhalation studies in rats reported NOAECs for developmental toxicity of 1200 ml/m³ (highest concentration tested) and 1592 ml/m³. The number of resorptions was increased at 1827 ml/m³ (NTP 1994; Saillenfait et al. 1993).

The NOAEL (no observed adverse effect level) for the developmental toxicity of acetonitrile given by gavage to rats was 190 mg/kg body weight and day. An increased incidence of early resorptions, a reduction in the average number of foetuses and delayed ossification of the sternum were observed at 275 mg/kg body weight and day (Johannsen et al. 1986).

A study with gavage administration in rabbits reported a NOAEL of 15 mg/kg body weight and day for prenatal toxicity and a LOAEL (lowest observed adverse effect level) of 30 mg/kg body weight and day. The number of viable foetuses was reduced at this dose. Body weight gains in the dams were reduced at doses of 15 mg/kg body weight and day and above and 5 dams died at 30 mg/kg body weight and day (Spanish Ministry of Health 2000).

Genotoxicity

Mutagenicity tests with Salmonella typhimurium strains in the presence and absence of rat liver S9 fraction yielded negative results, as did the hypoxanthine guanine phosphoribosyl transferase (HPRT) test and the mouse lymphoma test. In Saccharomyces cerevisiae, acetonitrile induced gene conversion and mitotic chromosome loss and duplication at very high concentrations. An aneugenic effect was

demonstrated in Drosophila. At very high intraperitoneal doses (60% of the oral LD_{50}; no other details), acetonitrile induced micronuclei in the bone marrow of NMRI mice. In a valid 13-week inhalation study, there was no concentration-dependent increase in the incidence of micronuclei in the peripheral blood cells of mice (documentation "Acetonitrile" 2003).

In another micronucleus test carried out according to OECD Test Guideline 474, 5 male and 5 female NMRI mice per test time point were given a single intraperitoneal dose of acetonitrile in corn oil corresponding to the maximum tolerated dose of 100 or 125 mg/kg body weight for males and females, respectively. Control animals were treated with the vehicle alone. After exposure to acetonitrile, clinical signs of toxicity were observed in the animals and 1 male and 2 females had to be sacrificed prematurely. After 18, 24 and 36 hours, the incidences of polychromatic erythrocytes with micronuclei in the bone marrow of male animals were not increased. Only 36 hours after application, a slight, but statistically significant, increase in comparison with the respective control value was observed in the females. However, this increase was so slight in comparison with the control value after 24 hours (125 mg/kg body weight: 0.7/1000; controls: 0.6/1000) that it is not considered to be of biological significance. The ratio of polychromatic to normochromatic erythrocytes in the bone marrow of the males was increased after 18 hours. The incidences of polychromatic erythrocytes with micronuclei in the peripheral blood were not increased after 24, 48, 72 and 96 hours in additional groups of 5 male and 5 female mice that were treated with the same doses. The ratio of polychromatic to normochromatic erythrocytes was slightly increased at different test time points. Both tests used cyclophosphamide as the positive control, which yielded the expected results (Jones et al. 2001). Therefore, in this study the positive findings of the earlier micronucleus test with intraperitoneal administration (see above) could not be confirmed.

Carcinogenicity

In a 2-year study with whole-body exposure, female and male F344 rats inhaled acetonitrile in concentrations of 0, 100, 200 or 400 ml/m^3 and female and male B6C3F1 mice were exposed to concentrations of 0, 50, 100 or 200 ml/m^3. The incidence of liver adenomas and carcinomas was slightly increased in male rats of the 400 ml/m^3 group. A significant positive trend for the sum of hepatocellular adenomas and carcinomas was found both in the logistic regression test ($p = 0.045$) and the Cochran-Armitage trend test ($p = 0.026$). However, the results of the trend tests were strongly influenced by the incidence in the high concentration group. There were no significant differences in tumour incidences if the control group and the exposed groups were compared pairwise (Table 1; documentation "Acetonitrile" 2003; NTP 1996).

In the 400 ml/m^3 group, the incidences of liver tumours were therefore only slightly higher than the upper limit of the historical control incidence. The carcinogenic effect in male F344 rats was assessed as "equivocal" (NTP 1996).

In the logistic regression test, male rats of the 200 and 400 ml/m^3 groups were found to have a significantly higher number of basophilic liver foci than the control group. In the documentation from 2001 (documentation "Acetonitrile" 2003), the

Table 1 Findings in male F344 rats from the carcinogenicity study (NTP 1996)

Effect	Incidence of the effects after exposure to acetonitrile (ml/m³)			
	0	100	200	400
survival after 2 years[a)]	11/48	13/48	9/48	17/48
basophilic liver foci (not atypical in the microscopic examination)	15/48	22/47	25/48[b)]*	31/48[b)]**
eosinophilic foci	3/48	7/47	5/48	10/48[c)]
clear cell foci	3/48	1/47	2/48	5/48
mixed cell foci	1/48	1/47	1/48	5/48
hepatocellular adenomas	0/48 (0%)	1/47 (2%)	1/48 (2%)	3/48 (6%)
hepatocellular carcinomas	1/48 (2%)	0/47 (0%)	0/48 (0%)	3/48 (6%)
hepatocellular adenomas and carcinomas[d)]	1/48 (2%)	1/47 (2%)	1/48 (2%)	5/48 (10%)
hepatocellular adenomas and carcinomas[e)]	3.3%	3.4%	4.8%	25.2%

[a)] no difference between control group and exposed groups
[b)] significant in the logistic regression test, * $p \leq 0.05$, ** $p \leq 0.01$
[c)] $p = 0.038$, Fisher's exact test, one-sided; $p = 0.04$, Cochran-Armitage trend test, one-sided; both tests calculated retrospectively
[d)] significant positive trend in the logistic regression test and Cochran-Armitage trend test; no significant differences if the control group and the exposed groups were compared in pairs
[e)] adjusted according to Kaplan-Meier, not significant in the life table test
historical control incidences (data from 1993, time period not specified):
liver carcinomas: 4/398 (1.0% ± 1.5%), range 0%–4%
sum of liver adenomas and carcinomas: 15/398 (3.8% ± 2.7%), range 2%–8%

basophilic liver foci were considered preneoplastic lesions, even though they were not atypical. Atypical foci are also called diffuse basophilic foci (Goodman et al. 1994). Diffuse basophilic foci are preneoplastic lesions (Bannasch and Zerban 1992). In this study, the incidence of basophilic foci in female F344 rats was 71% in the control animals and up to 76% in the exposed animals. A hepatocellular adenoma was found in the 100 ml/m³ group only (NTP 1996).

Likewise, the 2-year study in male and female B6C3F1 mice yielded no conclusive evidence of carcinogenicity. The incidence of alveolar/bronchiolar adenomas in the males of the 200 ml/m³ group was significantly increased, as was the incidence of hepatocellular adenomas in the 100 ml/m³ group. It was not possible to establish a relationship between tumour incidence and exposure concentration. Therefore, the tumours are considered chance findings. The incidence of forestomach papillomas was not significantly increased (documentation "Acetonitrile" 2003; NTP 1996).

For this reason, the Commission considers it unlikely that acetonitrile has carcinogenic effects (documentation "Acetonitrile" 2003).

Manifesto (MAK value/classification)

The critical effect is the induction of basophilic liver foci in rats.

MAK value. In a long-term NTP study in F344 rats, the incidences of basophilic liver foci were significantly increased at concentrations of 200 ml/m³ and above. At 100 ml/m³, the incidence was slightly, but not statistically significantly, increased. However, in the documentation from 2001 (documentation "Acetonitrile" 2003), this concentration was considered to be the LOEC because of the numerical increase in incidence. A provisional MAK value of 20 ml/m³ was derived from this. As the blood:air partition coefficient of acetonitrile is > 5, the increased respiratory volume needs to be taken into consideration. For this reason, the MAK value has been lowered to 10 ml/m³.

Peak limitation. Acetonitrile remains classified in Peak Limitation Category II because of its systemic effect. The current default excursion factor of 2 has been retained even though acetonitrile has a long half-life of 32 hours (documentation "Acetonitrile" 2003) because the half-lives of the metabolites are not known, and the effects are more probably caused by the metabolites than by acetonitrile itself.

Prenatal toxicity. Two valid studies in rats determined NOAECs for developmental toxicity of 1200 ml/m³ and about 1600 ml/m³. A study with gavage administration in rabbits yielded a NOAEL of 15 mg/kg body weight and day for prenatal toxicity with a LOAEL of 30 mg/kg body weight and day. The number of viable foetuses was reduced at this dose. The body weight gains of dams were reduced at 15 mg/kg body weight and day and 5 dams died at 30 mg/kg body weight and day. The following toxicokinetic data are taken into consideration for the extrapolation of the NOAEL of 15 mg/kg body weight and day to a concentration in workplace air: the corresponding species-specific correction values for the rabbit (1:2.4), the almost complete oral absorption (ECHA 2016), the body weight (70 kg) and the respiratory volume (10 m³) of the person and the assumed 75% absorption by inhalation (Section "Toxicokinetics and metabolism"). The concentration calculated from this is 58 mg/m³ (34 ml/m³), which means that there is a 3.4-fold margin between this concentration and the MAK value of 10 ml/m³.

The NOAEL for developmental toxicity after gavage administration in rats was 190 mg/kg body weight and day. Taking into consideration the species-specific correction value for rats (1:4) and using the same procedure as described above, this results in a concentration of 443 mg/m³ (261 ml/m³). There is a 26-fold margin between this concentration and the MAK value of 10 ml/m³. This concentration is a third of the NOAEC for developmental toxicity of 800 ml/m³ determined after inhalation exposure of rats and after taking into consideration the increased respiratory volume (1600 ml/m³/ 2). There is an 80-fold margin between this concentration and the MAK value. Oral bolus administration is thus the worst-case scenario for acetonitrile. The reason for this may be that the amount of cyanide formed in response to the peak in concentration that occurs through bolus administration may exceed the detoxification capacity. The rabbit is much more sensitive than the rat, which can also be seen by comparing the 4-hour LC_{50} values (rat 16 000 ml/m³,

rabbit 2800 ml/m³; documentation "Acetonitrile" 2003). It is to be assumed that the rabbit is also more sensitive than the human: a dose of 30 mg/kg body weight and day leads to mortality in the dams and is equivalent to 69 ml/m³ after extrapolation using the procedure described above. Assuming that oral administration is 3 times more effective than inhalation exposure also in the rabbit, the LAEC (lowest adverse effect concentration) for the rabbit would be 210 ml/m³. In comparison, no cyanide was detected in the blood of humans after exposure to an acetonitrile concentration of 160 ml/m³ (documentation "Acetonitrile" 2003). As, in a comparison between bolus administration and inhalation exposure, bolus administration represents the worst-case scenario in both the rat and the rabbit, the rabbit is more sensitive than the human, the margins after inhalation exposure and bolus administration are sufficiently large in rats and no malformations are induced, acetonitrile remains classified in Pregnancy Risk Group C even though the margin to the MAK value after bolus administration in rabbits is not sufficiently large.

Carcinogenicity. In a 2-year inhalation study in F344 rats and mice, the incidences of hepatocellular adenomas and carcinomas were slightly increased in male rats of the high concentration group (400 ml/m³) only. As both the authors and the Commission consider it unlikely that acetonitrile has a carcinogenic effect, no tumours were induced at other localizations in either rats or mice, and it is assumed that acetonitrile does not have genotoxic potential, acetonitrile has again not been classified in any of the categories for carcinogens.

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