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Acetone – Addendum: (re-)evaluation of the BAT value and a BAR

Assessment Values in Biological Material – Translation of the German version from 2022

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Abstract

In 2018, the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated acetone [67-64-1] and has derived a biological tolerance value (BAT value) and a biological reference value (BAR).

In correlation to the maximum concentration at the workplace (MAK value) of 500 ml acetone/m^3, a BAT value of 50 mg acetone/l urine was derived. Sampling time is at the end of exposure or the end of the shift. According to currently available information damage to the embryo or foetus cannot be excluded after exposure to acetone concentrations at the level of the MAK and BAT value (Pregnancy Risk Group B). The MAK value documentation indicates that based on the NOAEC (no observed adverse effect concentration) for developmental toxicity of 2200 ml/m^3 no prenatal toxic effects of acetone are to be expected at about 200 ml/m^3. The corresponding internal exposure of 20 mg acetone/l urine would be the prerequisite for an assignment to Pregnancy Risk Group C, which means that damage to the embryo or foetus is unlikely at this concentration. Based on the 95th percentile of the urinary acetone excretion in occupationally unexposed persons, a BAR of 2.5 mg acetone/l urine was derived.

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BAT value (2021)	**50 mg acetone/l urine** Sampling time: end of exposure or end of shift
BAR (2021)	**2.5 mg acetone/l urine** Sampling time: end of exposure or end of shift
MAK value (1993)	**500 ml/m³ ≙ 1200 mg/m³**
Peak limitation (2000)	Category I, excursion factor 2
Absorption through the skin	–
Carcinogenicity	–
Germ cell mutagenicity	–
Prenatal toxicity (2012)	Pregnancy Risk Group B[a)]

[a)] Note regarding prerequisite for Pregnancy Risk Group C see Section "Prenatal Toxicity"

Re-evaluation

In 1996, the working group "Assessment Values in Biological Material" evaluated a biological tolerance value (BAT value) for acetone excretion in urine (translated in Schaller and Triebig 1999). Since the database available on the correlation between internal exposure and effects was considered to be small, the evaluation of the BAT value was based on the relationship between external and internal exposure. In correlation to the maximum workplace concentration (MAK value) of 500 ml/m³ (1200 mg/m³) set in 1993 (translated in Greim 1996), an acetone excretion of 80 mg/l urine was derived according to the ceiling value concept valid at that time. Since this concept is no longer valid, the available studies for deriving a BAT value were now re-evaluated according to the average value concept. In addition, the data on background exposure were evaluated and a biological reference value (BAR) was derived.

Exposure and Effects

Relationship between internal exposure and effects

Since the publication of the last evaluation of the BAT value, a study on the neurotoxicity of occupationally exposed acetone workers was published in 1997 (Mitran et al. 1997). In this study, 71 exposed and 86 non-exposed employees of a coin and metal factory were examined. The inhalation exposure of the workers was in the range of 988 to 2114 mg acetone/m³ air. The study focused on the effects of acetone on the central and peripheral nervous system. Overall, the authors reported differences between exposed and control persons regarding irritative symptoms, gastrointestinal and rheumatic complaints. Significant differences were reported for the nerve conduction velocity of motor nerves and visual perception. Although these results suggest a neurotoxic potential of acetone, some methodological points have been criticised about the study, for example that symptom recording was not blinded, that no dose-response relationship could be derived and that the company studied was a coin and metal factory where exposures to other substances could not be excluded. Given these limitations, this study cannot be included in the evaluation of a BAT value based on a dose-response relationship.

Ma et al. (2019) investigated acetone exposure of owners and employees in nail salons and reported exposure to acetone concentrations between 3 and 58 ml/m³. In addition, they asked the participants about health effects, such as irritant effects and problems in pregnancy (miscarriage). Here they found evidence of an increase in the miscarriage rate among workers exposed to acetone. However, since the study is more concerned with access to a group of employees that is difficult to reach for preventive measures, the focus of this study was not on dose-response relationships. This study can therefore also not be used to derive a BAT value.

In addition, a review by Arts et al. (2002) aimed to investigate the wide divergence of threshold concentrations for irritant effects reported in the literature for inhalation exposure to acetone. The authors report that the systematically searched studies show that the olfactory threshold of acetone is between 20 and 400 ml/m^3, while the threshold for sensory irritation seems to be more in the range between 10 000 and 40 000 ml/m^3. Also, habituation effects probably occur in occupationally exposed collectives, which could explain the large heterogeneity between the reports. Overall, this analysis does not contribute to deriving a BAT value based on an exposure-effect relationship.

Relationships between external and internal exposure

Thus, the re-evaluation of a BAT value continues to be based on the measured relationship between inhalation exposure to acetone at the workplace and acetone excretion in urine. Since the last evaluation of a BAT value, no new experimental or occupational studies relevant for assessment providing new findings have been identified. However, some information about the Rhône-Poulenc Rhodia AG that was taken into account for the derivation of the BAT value at that time has not been available for the current assessment, so that it is no longer listed in the following compilation.

Table 1 lists the studies that were included in the considerations for deriving the BAT value. In general, almost all of these studies have the values at 500 ml/m^3 (MAK value) derived from linear regression equations. Only a few studies measured personal acetone exposures in the breathing air of workers at the workplace at the level mentioned.

Tab. 1 Studies on the evaluation of a BAT value (experimental and field studies)

Exposure	Persons	Acetone in air [ml/m^3]	Acetone in urine [mg/l]		References
				at 500 ml/m^3 [a]	
Experimental studies					
Experimental exposure	12	550	8.5		Wigaeus et al. 1981
Experimental exposure	15	23–210 (56–500 mg/m^3)	1.7–5.5 20–160 µmol/l		Pezzagno et al. 1986
Experimental exposure	6	100–400		29	Satoh et al. 1990
Experimental exposure	16	950 (AM)		43	Blaszkewicz et al. 1991
Field studies					
Work in plastic boat, chemical, plastic button, paint and shoe factories.	104	10–300	< 35	39	Ghittori et al. 1987; Pezzagno et al. 1986
Acetate fibre production	30 30	549–653 948–1048	62 93	53 47	Grampella et al. 1987 cited after ACCAP 2003
Factory for fibre-reinforced plastics	28	0.1–45.4		200	Kawai et al. 1990
Acetate fibre production	110	364 (MW)[b] 19.6–1018	37.8 (MW)[b] 0.75–170	52[c]	Fujino et al. 1992; Satoh et al. 1995, 1996
Production of bathtubs with fibre-reinforced plastics	45	1–70	0.1–17.5	133	Kawai et al. 1992
Working with fibre-reinforced plastics	41	1–165	1–55	104	Mizunuma et al. 1993
Production of plastics	22	336	22	33	Wang et al. 1994

AM: arithmetic mean; MV: mean value
[a] Calculated from regression equation
[b] Values at the end of the workshift (Satoh et al. 1996)
[c] Calculated from regression equation y [mg/l] = 0.10x [ml/m^3] + 1.61 (Fujino et al. 1992)

Re-evaluation of the BAT value

Various studies (i. a. Kumagai and Matsunaga 1995; Wigaeus et al. 1981) suggest that when considering correlations between inhalation exposure to acetone at the workplace and acetone concentrations in urine, several factors must be taken into account. These include, among others, the physical work-load, the duration of exposure, the sampling time, exposure to other substances (e. g. styrene) and the general level of inhalation exposure to acetone. These factors could be the reason for the suspected non-linear relationship between external and internal concentration, although in almost all studies the relationship was based on a linear regression equation.

The available studies showed acetone levels in urine, which (derived) at the currently valid MAK value for acetone of 500 ml/m^3 were in the range between 40 and 200 mg acetone/l urine. The study collective whose workplace exposures included the MAK value of 500 ml/m^3 (Fujino et al. 1992; Satoh et al. 1995, 1996) revealed an average level of about 50 mg acetone/l urine. Also, in comparison with the experimental studies, longer exposure times (approx. 8 hours) were normally taken as a basis in the study methods and it can be assumed that a possible habituation effect of the employees (due to their occupational exposure duration of usually several years) as well as a probably average physical activity at the workplace were also represented in the measurements. Therefore, from the averaged value,

a BAT value of 50 mg acetone/l urine

is derived. Sampling should take place at the end of exposure or end of shift.

Prenatal Toxicity

For acetone, damage to the embryo or foetus cannot be ruled out in the case of exposure at the level of the MAK value of 500 ml/m^3 (1200 mg/m^3). Based on the correlation now established, a pregnancy risk cannot be ruled out even if the BAT value of 50 mg acetone/l urine is observed (Pregnancy Risk Group B). In the MAK documentation (translated in Hartwig and MAK Commission 2016), however, it is stated with regard to the prerequisite for Pregnancy Risk Group C that, starting from the NOAEC for developmental toxicity of 2200 ml acetone/m^3, an exposure to about 200 ml acetone/m^3 (480 mg/m^3) or less is not to be assumed to have a damaging effect on the embryo or foetus (Hartwig and MAK Commission 2016). This air concentration corresponds to an acetone excretion of 20 mg/l in the post-shift urine sample. At this urinary concentration, therefore, prenatal toxicity is not to be expected.

Background Exposure

The excretion of acetone in urine depends on various physiological factors that have nothing to do with exposure to inhaled acetone (e. g. diseases such as diabetes or also dietary habits (fasting) play a role). In extreme cases, acetone levels in urine may be close to the suggested BAT value.

In addition, (non-occupational) acetone exposure through the use of household products (e. g. nail polish remover, paints, etc.) is conceivable, which can lead to a misinterpretation of measured values.

In any case, the evaluation of a biomonitoring result of acetone in urine requires the prior (clinical) exclusion of competing or distorting confounders. Concurrent exposure to 2-propanol, which can also influence the measurement results, must also be taken into account.

Even without external exposure, the physiological metabolite acetone can be detected in the urine of "normal people". In order to be able to assess the expected level of these measurements, available study results on acetone concentrations in urine in these non-exposed collectives are listed in Table 2.

Tab. 2 Acetone concentrations in the urine of occupationally not exposed persons

Persons	Acetone in urine [mg/l]		References
	MV ± SD (range)	95th percentile	
8	1.4 ± 1.1 mg/kg		Wigaeus et al. 1981
15	0.76 ± 0.63		Pezzagno et al. 1986
343	0.29 ± 0.65	1.51	Kawai et al. 1992
49	0.84 ± 1.5 (0.127–9.350)	2.206	Brugnone et al. 1994; Wang et al. 1994
66	1.3 ± 2.4 (< DL–14.1)		Satoh et al. 1995
207	1.12 ± 0.47 (95%-CI 0.20–1.95)	2.2	de Oliveira and Pereira Bastos de Siqueira 2004

95%-CI: 95%-confidence interval; DL: detection limit; MV: mean value; SD: standard deviation

Evaluation of a BAR

In the studies with data on a 95th percentile for the concentrations of acetone in urine in occupationally unexposed persons, this is in the range of 1.5 to 2.2 mg acetone/l urine. It can be assumed that in healthy, non-fasting persons who are not occupationally or privately exposed to acetone, not more than 2.5 mg acetone/l urine are detectable. Therefore, a

BAR of 2.5 mg acetone/l urine

is derived.

When interpreting the results, personal confounders such as the health situation and dietary behaviour of the people being studied are of great importance.

Interpretation

The BAT value and the BAR refer to normally concentrated urine, in which the creatinine content should be in the range between 0.3 and 3.0 g/l urine. As a rule, for urine samples outside the above limits, it is recommended to repeat the measurement in the normally hydrated test person (translated in Bader et al. 2016).

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.

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