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Cresol (all isomers) – Addendum: re-evaluation of BLW and BAT value

Assessment Values in Biological Material – Translation of the German version from 2021

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Keywords

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated cresol (all isomers) [1319-77-3] and evaluated a maximum workplace concentration (MAK value) of 1 ml cresol/m^3. Only one study has been published in which the relationship between external exposure to cresol and cresol excretion in urine was investigated. However, the time-weighted average of external exposure in this study was far below the current MAK value. Data on the relationship between internal exposure and effects are not available. As appropriate data for deriving the critical internal dose for cresol are lacking, a biological tolerance value (BAT value) for this compound cannot be established and the biological guidance value (BLW) was withdrawn.

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BAT value (2020)	**not established**
BLW (2020)	**not established**
MAK value 2019	**1 ml/m³ ≙ 4.5 mg/m³**
Carcinogenicity	–
Absorption through the skin (1958)	H
Sensitization	–
Prenatal toxicity (2019)	Pregnancy Risk Group C

Chemical name	Synonyms	CAS number
Isomer mixture		
Methylphenol	Hydroxytoluene Methylhydroxybenzene Methyloxybenzene Oxytoluene	1319-77-3
Individual isomers		
o-Cresol	o-Cresylic acid 1-Hydroxy-2-methylbenzene 2-Hydroxytoluene 2-Methylphenol	95-48-7
m-Cresol	m-Cresylic acid 1-Hydroxy-3-methylbenzene 3-Hydroxytoluene 3-Methylphenol	108-39-4
p-Cresol	p-Cresylic acid 1-Hydroxy-4-methylbenzene 4-Hydroxytoluene 4-Methylphenol	106-44-5

Cresol (all isomers) was withdrawn from Carcinogen Category 3 B in 2019. Furthermore, a maximum workplace concentration (MAK value) of 1 ml/m³ (4.5 mg/m³) was set. The critical effect of cresols is local irritation, which manifests itself as a strong irritant to corrosive effect on the skin, eyes and mucous membranes of the upper respiratory tract. Valid inhalation studies with cresol to determine the irritation threshold of exposed persons, or animal studies are not available. Therefore, a 14-day inhalation study in rats with the structurally and physicochemically similar phenol was used to derive the MAK value. From the NOAEC (no observed adverse effect concentration) for local effects of 25 ml phenol/m³ determined in this study, a MAK value of 1 ml/m³ for cresol isomers is obtained after extrapolation from animal experiments to humans and application of the *preferred value approach* (Hartwig and MAK Commission 2020).

The previous biological guidance value (BLW) of 200 mg/l urine was derived from observations according to which the serum creatinine level does not rise above 10 mg/l if the proportion of free cresol determined in urine does not exceed 150 µg/l (Lewalter and Neumann 1998). Due to the lack of corresponding data, it was assumed, in analogy to the ratios between free and conjugated forms of phenol, that an excretion of 150 µg free cresols/l urine is not exceeded when up to 200 mg total cresol (free and conjugated) is excreted per litre urine. In the derivation, it was pointed out that approx. 6% of Central Europeans would not been sufficiently protected if only the excretion of total cresol would

be determined, due to a polymorphism of the isoenzymes of uridine diphosphate glucuronyltransferase (UDPG) that causes a delay of glucuronidation (Lewalter et al. 2005).

Since the derivation of the BLW for cresols in 2003, no studies have been published on the relationships between external and internal exposure or between internal exposure and effects. The only published data on occupationally exposed persons is the study by Bieniek (1997) with data on external exposure to cresol and cresol excretion in urine (18.7 mg total cresol/l urine) collected from 75 coke-plant workers. However, the external exposures determined in this study, with shift averages of 0.22 mg/m^3 (0.05 ml/m^3), are far below the current MAK value of 1 ml/m^3 (4.5 mg/m^3). Since there are no data for an extrapolation of these measured values to an concentration corresponding to the MAK value, a biological tolerance value (BAT value) cannot be derived.

Regarding the relationship between external exposure to cresol and effects, data are available from only one study. According to this study, eight out of ten persons exposed to o-cresol (vapour/aerosol mixture) at a concentration of 6 mg/m^3 (1.34 ml/m^3) for a short duration reported mucous membrane irritation, dryness, nasal constriction and irritation in the throat (Uzhdavini et al. 1972). Since information on the type and duration of exposure and on the analytical method is lacking, this study was not taken into account neither in the earlier evaluation of the BLW for cresols (Lewalter and Neumann 1998) nor in the current derivation of the MAK value (Hartwig and MAK Commission 2020).

When assessing the internal exposure, the physiological excretion of p-cresol in urine, which is due to the bacterial degradation of amino acids in the intestine and is dependent on the diet (Geypens et al. 1997; Patel et al. 2012), must be taken into account. Data on the excretion of cresols in persons not occupationally exposed to cresol or toluene are given in Table 1.

In 2019, p-cresol levels in the range from < 0.5 to 164 mg/l urine with a mean of 20.9 mg/l (SD: 23.4 mg p-cresol/l urine) and a median of 12.8 mg/l urine were determined in 1297 examinations of workers not occupationally exposed to p-cresol according to a communication (Leng 2020).

Tab. 1 Excretion of cresols in urine (free plus conjugated) in persons not occupationally exposed to cresols or to toluene.

Persons	Age	o-Cresol	m-Cresol	p-Cresol	References
[n]	[years]	[mg/l urine]			
16	n. d.	< LOD	< LOD	29.0 ± 21.6 [c)] 23 (med)	Woiwode et al. 1979
8 (NS)	n. d.	0.06 (med) [mmol/mol crea]	n. d.	n. d.	Nise 1992
13 (S)	n. d.	0.18 (med) [mmol/mol crea]	n. d.	n. d.	
246 (♂)	n. d.	0.042 ± 0.007 [e)] 0.065 (med)	n. d.	n. d.	Inoue et al. 1994
271 (♀)	n. d.	0.023 ± 0.006 [e)] 0.028 (med)	n. d.	n. d.	
n. d.	n. d.	n. d.	n. d.	5.3 ± 3.6 (0.6 ± 0.9) [b), c)]	Ogata et al. 1995
175 (♂, NS)	38.6 (mean) (19–71) [d)]	0.023 ± 0.003 [e)]	n. d.	n. d.	Kawamoto et al. 1996
176 (♂, S)		0.063 ± 0.002 [e)]	n. d.	n. d.	
28 (♂, S) 6 (♀, S)	30.3 ± 8.6 [c)]	0.041 ± 0.003 [a)]		14.4 ± 2.88 [c)]	Bieniek 1997
45 (♂)	n. d.	0.015 (med)	0.036 (med)	29 (med)	Dills et al. 1997
29 (♂, NS) 25 (♂, S)	27.6 ± 10.4 [c)] (14–62) [d)]	0.012 ± 0.01 [c)] [mg/g crea]	n. d.	n. d.	Çok et al. 2003
30 (♂)	45.6 ± 6.7 [c)] (32–61) [d)]	0.048 ± 0.043 [c)] 0.032 ± 0.003 [e)] (0.003–0.210) [d)]	n. d.	n. d.	Inoue et al. 2004

Tab. 1 *(continued)*

Persons	Age	o-Cresol	m-Cresol	p-Cresol	References
[n]	[years]	[mg/l urine]			
10	n. d.	0.042 ± 0.057 [c] 0.017 (med) (0.006–0.194) [d]	0.156 ± 0.151 [c] 0.089 (med) (0.024–0.423) [d]	n. d.	Fustinoni et al. 2005
18 (♂) 7 (♀)	32.8 ± 8.5 [c]	< LOD	29.3 (22.4–41.4) [f]		González-Yebra et al. 2006
57 (NS)	n. d.	0.029 ± 0.016 [c] 0.028 (med) (0.006–0.090) [d]	n. d.		Fustinoni et al. 2007
30 (S)	n. d.	0.085 ± 0.075 [c] 0.063 (med) (0.024–0.401) [d]	n. d.		
17 (NS)	n. d.	0.023 (med) (< 0.01–0.033) [d]	0.043 (med) (0.016–0.148) [d]	n. d.	Schettgen et al. 2015
13 (S)	n. d.	0.033 (med) (0.012–0.053) [d]	0.129 (med) (0.027–0.495) [d]	n. d.	

[a] n = 27
[b] conjugated and free form (in brackets)
[c] mean ± standard deviation
[d] range
[e] geometric mean ± standard deviation
[f] median (25^{th}–75^{th} percentile)
crea: creatinine; LOD: limit of detection; med: median; n. d.: no data; NS: non-smokers; S: smokers

Evaluation

Based on unpublished occupational health experience of Lewalter, the current MAK value of 1 ml/m³ would result in a BAT value of 75 mg cresol (sum of all isomers after hydrolysis)/l urine with a sampling time at the end of exposure or end of shift.

Since measurement results of Lewalter are no longer available, there are no published data that allow the derivation of a BAT value or a BLW for cresols.

Therefore, a BAT value could not be established; the BLW has been withdrawn.

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.

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