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# Carbon disulfide – Addendum: re-evaluation of the BAT value

## Assessment Values in Biological Material – Translation of the German version from 2009

T. Göen[1] H. Drexler[1]

[1] *Friedrich-Alexander-Universität Erlangen-Nürnberg, Institute and Outpatient Clinic of Occupational, Social, and Environmental Medicine, Henkestraße 9–11, 91054 Erlangen, Germany*

*Correspondence to: MAK Commission (arbeitsstoffkommission@dfg.de)*

**Keywords**

carbon disulfide; biological tolerance value; BAT value

| | |
|---|---|
| **BAT (2008)** | **2 mg 2-Thiothiazolidine-4-carboxylic acid (TTCA)/g creatinine**<br>Sampling time: End of exposure or end of shift |
| **MAK value (1997)** | **5 ml/m³ ≙ 16 mg/m³** |
| Absorption through the skin (1980) | H |
| Carcinogenicity | – |

# Re-evaluation

For the 1997 re-evaluation of the BAT value for carbon disulfide [75-15-0], the establishment of the assessment value was carried out using the 95% confidence interval of the correlation between 2-thiothiazolidine-4-carboxylic acid (TTCA) excretion and the individual carbon disulfide exposure in air of 351 workers occupationally exposed to carbon disulfide (Drexler et al. 1994). Due to the new definition of the BAT value in 2007 as the correlate for the average of several measurements in one worker, a re-evaluation of the BAT value is necessary.

## Exposure and effects

### Relationship between external and internal exposure

Since the last re-evaluation, a number of occupational-medical studies have been published which analysed both individual inhalation exposure to carbon disulfide and TTCA excretion in persons occupationally exposed to carbon disulfide during their work in rayon-processing plants (Table 1).

In a German study in 325 workers, the median concentration of 2.33 ml carbon disulfide/m³ corresponded to a median urinary TTCA excretion of 0.96 mg/g creatinine (Korinth et al. 2003). A study from the United States was assessed as not suitable for this evaluation, as only a range is given for TTCA excretion and the 10 workers studied wore respiratory protection (Cox et al. 1998).

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**Tab. 1** Studies of workers occupationally exposed to carbon disulfide in rayon-processing plants; external and internal exposure

| Country, collective | Air | Urine | References |
|---|---|---|---|
| | **Carbon disulfide [ml/m³]** | **TTCA [mg/g creatinine]** | |
| Germany<br>2 rayon factories,<br>325 workers | 2.33 (median)<br>6.04 (mean)<br>< 0.03–91.1 (range) | 0.96 (median)<br>1.14 (mean)<br>< 0.02–11.5 (range) | Korinth et al. 2003 |
| USA<br>rayon factory,<br>10 workers with protective respiratory masks | 5.82 ± 3.32 (GM ± SD)<br>8.54 (mean)<br>0.3–17.7 (range) | (n=6)<br><0.02–2.9 (range) | Cox et al. 1998 |
| Japan<br>11 rayon factories,<br>432 workers (majority of exposed persons with respiratory protection) | (n=216)<br>4.87 ± 1.81 (GM ± SD) | (n=216)<br>1.60 ± 1.91 (GM ± SD) | Nishiwaki et al. 2004[a)] |
| | (n=236)<br>5.02 ± 1.84 (GM ± SD) | (n=235)<br>1.61 ± 1.91 (GM ± SD) | Takebayashi et al. 2003, 2004[a)] |
| | (n=411)<br>4.48 (AM)<br>3.36 (GM)<br>4.1 (median)<br>LOD–39.7 (range) | (n=427)<br>1.99 (AM)<br>1.36 (GM)<br>1.48 (median)<br>LOD–14.75 (range) | Omae et al. 1998 |
| China<br>rayon factory | | | Tan et al. 2000, 2001 |
| coiling area,<br>277 workers, 8 h exposure | (n=69)<br>4.28 ± 0.34 (GM ± SD) | (n=74)<br>1.18 ± 0.43 (GM ± SD) | |
| filament area,<br>237 workers, max. 5 h exposure | (n=78)<br>6.27 ± 0.35 (GM ± SD) | (n=61)<br>1.07 ± 0.38 (GM ± SD) | |
| Taiwan<br>6 rayon factories,<br>75% of workers with respiratory protection | | | Chou et al. 2004 |
| spinning room,<br>18 workers | 10.5 (GM)<br>0.7–576.0 (range) | log [TTCA in mg/g creatinine] = $I_0 + S_0 \times \log [CS_2$ in ml/m³] | |
| rayon processing,<br>38 workers | 1.7 (GM)<br>0.3–16.9 (range) | $I_0$=0.24; $S_0$=0.19 | |
| 1 rayon factory,<br>workers without respiratory protection or only with a cotton mask | | | Shih et al. 2003 |
| 6 workers, 8-h shift | 6.30 ± 0.64 (AM ± SD) | 3.24 ± 1.21 (AM ± SD) | |
| 7 workers, 12-h shift | 11.31 ± 1.47 (AM ± SD) | 5.88 ± 2.04 (AM ± SD) | |

AM: arithmetic mean; GM: geometric mean; $I_0$: intercept; LOD: limit of detection; $S_0$: slope; SD: standard deviation
[a)] same study

Further studies in Asia have been published. A study in 432 workers in 11 Japanese rayon factories, found urinary TTCA excretions of about 1.6 mg/g creatinine at a carbon disulfide concentration of about 5 ml/m³ (Nishiwaki et al. 2004; Takebayashi et al. 2003, 2004), whereby the workers reportedly wore respiratory protection. In a study in 74 Chinese workers, who were exposed for 8 hours a day, a carbon disulfide concentration of 13.72 mg/m³ (4.28 ml/m³) yielded a urinary TTCA excretion of 1.18 mg/g creatinine (Tan et al. 2000, 2001). For Taiwanese workers, at an 8-hour mean value of 6.3 ml carbon disulfide/m³, the mean urinary TTCA excretion was found to be 3.24 mg/g creatinine (Shih et al. 2003). Another study of Taiwanese workers cannot be used for this evaluation as no urinary TTCA concentrations were reported and 75% of workers wore respiratory protection (Chou et al. 2004).

Consequently, findings from studies in Asian workers showed no substantial difference to results from studies in Caucasian workers.

In addition to these occupational health studies, a study from China also published data on TTCA excretion kinetics. In this investigation, the excretion of TTCA was measured in 10 persons exposed to carbon disulfide 24–38 hours after the end of exposure (Chang et al. 2002). Based on a TTCA excretion after the end of exposure in the range of 0.7 to 7.4 mg/g creatinine (mean: 3.0 mg/g), the excretion kinetics of TTCA were consistent with the first-order kinetic model. Assuming a biphasic kinetic, a half-life of 6.2 hours was determined for the first phase (up to 12.5 hours after exposure) and a half-life of 16.6 hours was determined for the second phase. Thus, the half-life of the first phase is consistent with early experiences on the excretion behaviour of TTCA (Drexler 2010). In this investigation, the correlations showed a lower probability-of-error level on the basis of the TTCA values normalised for urinary creatinine levels, confirming normalised creatinine as a suitable reference for this parameter.

### Relationship between internal exposure and effects

Available studies which provide information on the relationship between internal exposure and effects are presented in the MAK documentation from 2003 (translated in Greim 2005) as well as in the summary of the SCOEL documentation (SCOEL 2008).

In a study by Korinth et al. (2003), the hypothesis that carbon disulfide has a negative inotropic effect on the heart muscle could not be confirmed in workers with a median excretion of 0.96 mg TTCA/g creatinine. Cross-sectional studies in workers in Japanese rayon plants, which showed a urinary mean TTCA excretion of 1.36 mg/g creatinine and maximum values up to 20 mg/g creatinine, only reported subclinical effects on the nervous system (reduced nerve-conduction velocity) (Takebayashi et al. 1998) and retinal microaneurysms (Omae et al. 1998). In subsequent cohort studies, urinary TTCA concentrations were at about 1.6 mg/g creatinine. Endocrine changes were not observed (Takebayashi et al. 2003). Relevant cardiovascular effects were also not reported. Indications for changes potentially caused by carbon disulfide exposure were only observed in the most-exposed workers with 3.5 mg TTCA/g creatinine; such changes included ischemic ECG findings and retinal microaneurysms using the "Minnesota Code" (Takebayashi et al. 2004). The "Minnesota Code" is, however, controversial. Using generally accepted criteria, no significant differences could be observed between exposed workers and controls (SCOEL 2008).

Indications of increased "hyperintense spots" in T2-weighted MRT brain scans of exposed workers did not show a dose–response relationship (Nishiwaki et al. 2004). Due to methodological problems (differences between old and new MRT images) and a lack of criteria for related adverse effects (SCOEL 2008), the observed findings cannot be utilised for the purposes of this evaluation.

## Re-evaluation of the BAT value

Even though carbon disulfide is also partially absorbed into the organism via intact skin, inhalation represents the primary route of occupational exposure. For the evaluation of the BAT value, only studies which simultaneously investigated individual external and internal exposure may be used for reference. Therefore, most studies published since the last re-evaluation cannot be used due to the very large number of persons who wore respiratory protection at the time of sampling (Chou et al. 2004; Cox et al. 1998; Nishiwaki et al. 2004; Omae et al. 1998; Takebayashi et al. 2003, 2004). As a result, the correlation published by Drexler et al. (1994), which was used for the last re-evaluation, continues to present the best basis for the derivation of the BAT value (Figure 1 in Drexler 2010). This correlation is supported by the values for external carbon disulfide exposure and TTCA excretion published by Korinth et al. (2003) and Shih et al. (2003). For the derivation of the BAT value via the correlation to external exposure, according to the new definition of the BAT value, the mean, specifically the corresponding pair of values on the regression curve, is to be used. In correlation to the MAK value of 5 ml/m$^3$ established in 1997,

**a BAT value of 2 mg TTCA/g creatinine**

is derived. Sampling time is at the end of exposure or end of shift.

Studies on the correlation between internal exposure and effects confirm that no adverse health effects are observed at this level of exposure (Greim 2005).

### Interpretation

Since the BAT value is defined as the mean value of several biomonitoring investigations on a single person, individual values above the BAT value do not necessarily indicate an exceedance of the assessment value. In these cases, however, it is important to ensure that these individual values do not reach the level of acute toxic effects. For carbon disulfide, the inhibition of oxidative xenobiotic-metabolising enzymes of the liver is the most sensitive effect of acute exposure. This inhibition was detected in subjects during 6-hour inhalation at 20 ml/m$^3$ (Greim 2005; Henschler 1975). With regard to the correlation reported by Drexler et al. (1994), a TTCA excretion of 7 mg/g creatinine corresponds to a concentration of 20 ml/m$^3$ in workplace air. As a result, no acute toxic effects are expected at individual TTCA values less than 7 mg/g creatinine.

With a half-life of 2 to 8 hours directly after exposure, the urinary TTCA concentration displays rapid excretion behaviour, so that an accumulation over a working week is not to be expected. Consequently, the elimination kinetic does not justify any limitation for the time period until next sampling.

Additional factors which should be considered when interpreting anomalous TTCA concentrations are given in Section 9.3 of Drexler (2010).

The BAT value refers to normally concentrated urine in which the creatinine content should be in the range of 0.3–3.0 g/l. As a rule, for urine samples outside the above limits, it is generally recommended to repeat the measurement on normally hydrated individuals (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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