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n-Heptane – Addendum: derivation of a 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 n-heptane [142-82-5] in 2020 and derived a biological tolerance value (BAT value) considering heptane-2,5-dione in urine to characterise the internal exposure. The BAT value is based on the correlation between external and internal exposure and represents an equivalent of the maximum workplace concentration (MAK value) of n-heptane in biological material, taking into account central nervous effects and peripheral neurotoxicity as critical systemic effects.

Mainly data from two human experimental exposure studies were used to derive the BAT value. In a more recent study, 20 non-smoking test persons were exposed at rest to n-heptane up to 500 ml/m^3. Data on renal excretion of the n-heptane metabolite heptane-2,5-dione were similar to those obtained by another working group. The few available workplace studies were not suitable to derive a BAT value. An analysis of the pooled data from both experimental studies resulted in an extrapolated urinary concentration of 235 µg heptane-2,5-dione/l urine after eight hours of exposure to the current MAK value of 500 ml/m^3. Due to a blood:air partition coefficient < 5 for n-heptane, no adjustment for physical workload has to be considered. Therefore, a BAT value of 250 µg/l urine was established. Samples must be taken at the end of exposure or at the end of the working shift.

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BAT value (2020)	**250 µg heptane-2,5-dione/l urine** Sampling time: end of exposure or end of shift
MAK value (1958/1995)	**500 ml/m³ ≙ 2100 mg/m³**
Peak limitation (2000)	Category I, excursion factor 1
Absorption through the skin	–
Carcinogenicity	–
Prenatal toxicity (1995)	Pregnancy Risk Group D

In the 2006 BAT documentation (translated in Csanády 2010), the possibility of deriving a biological tolerance value (BAT value) for n-heptane was investigated. Due to the limited data available, a BAT value was not established at that time. In the meantime, data from an extensive experimental study on the relationship between external and internal exposure have been published and can be used to derive a BAT value.

1 Metabolism and Toxicokinetics

Detailed information on the absorption, distribution, metabolism and elimination of n-heptane after inhalation exposure can be found in the MAK Value Documentation (translated in Greim 1998). In the BAT documentation published in 2006 (Csanády 2010), the metabolism of the substance was again presented in summarised form.

The findings available until then were confirmed and extended by a more recent inhalation study with 20 test persons (Rossbach et al. 2012, 2018). Immediately after a three-hour exposure to 500 ml/m³ n-heptane at rest, the keto compounds heptane-2-one, heptane-3-one and heptane-4-one as well as the unconjugated isomeric hydroxy compounds heptane-1-ol, heptane-2-ol and heptane-3-ol were detected **in the blood** of the test persons in addition to n-heptane. Heptane-2-one was the main metabolite, heptane-3-one and heptane-2-ol were found in about 10-fold lower concentrations, heptane-4-one, heptane-1-ol and heptane-3-ol in 25–50-fold lower concentrations. Heptane-4-ol, on the other hand, was not detected in the blood of the exposed persons (Rossbach et al. 2012). From the data of the study, initial elimination half-lives of 18 minutes for n-heptane and 54 minutes for heptane-2-one were determined in the blood (Rossbach et al. 2010 a). The initial elimination of n-heptane from the blood thus takes place in a similarly rapid manner as the elimination of the homologous compound n-hexane, for which an initial half-life of 12 minutes is given (Greim 2000).

In urine samples from the same 20 test persons, the three isomeric keto compounds heptane-2-one, heptane-3-one and heptane-4-one, the diketone heptane-2,5-dione and all four isomeric monohydroxy derivatives heptane-1-ol, heptane-2-ol, heptane-3-ol and heptane-4-ol of heptane were found at the end of exposure (500 ml n-heptane/m³, 3 hours) in this inhalation study (Rossbach et al. 2018). Among the compounds mentioned, heptane-2-ol and heptane-3-ol were the main metabolites excreted in approximately equal amounts. For the metabolites heptane-2-one, heptane-2,5-dione and heptane-4-ol, about 5–10-fold lower concentrations were determined compared with the ω–1- and ω–2-hydroxy compounds. Heptane-3-one, heptane-4-one and heptane-1-ol were excreted in even lower concentrations, but were still detectable in all samples. However, the excretion of heptane-4-one was not associated with the exposure. The compound was found in higher concentrations before the start of exposure than at the end of exposure. A relationship with the external exposure in the sense of a decrease in excretion at lower air concentrations (in addition to the exposure to 500 ml n-heptane/m³, three-hour exposures to 333 and 167 ml n-heptane/m³ also took place) was not discernible. Comparative analyses of urine samples with or without prior enzymatic hydrolysis indicated – as already described in animal experiments (Bahima et al. 1984) – an extensive conjugation of the resulting monohydroxy compounds with glucuronic acid and/or sulfate.

When considering the time course of elimination up to 21 hours after the end of exposure, the maximum excretion for most metabolites was at the end of exposure. The only exceptions were heptane-2-one and heptane-2,5-dione, whose excretion maxima were reached with a delay of about two and one hour, respectively. The excretion of the metabolites was multiphasic with initial half-lives between 1.5 and 2.9 hours and half-lives between 7.8 and 9.7 hours in a second elimination phase starting about seven hours after the end of exposure. In a period up to 12 hours after the start of exposure, 70 to 90% of the metabolite amount recorded over the entire observation period was excreted, depending on the metabolite. However, within 24 hours after the start of exposure, the baseline level before the start of exposure was not reached again for most of the parameters considered (Rossbach et al. 2018). The elimination times determined for heptane-2,5-dione showed good agreement with the data of an experimental inhalation study with six test persons (Filser et al. 1996; Störmer 1997), which was described in detail in the BAT documentation (Csanády 2010).

In an earlier workplace study by Sturaro et al. (1997), the metabolites heptane-2-one, heptane-2-ol, heptane-3-ol, heptane-2,5-dione as well as γ-valerolactone were detected in urine samples of workers from shoe production (n = 10) at the end of a working day. The mean concentration of n-heptane at the workplaces was 11 ml/m^3 air (range: 3.7–22 ml/m^3). Apart from γ-valerolactone, which was detected in comparatively large amounts but is a non-specific metabolite that also occurs after exposure to n-hexane (Bolt and Fedtke 1994), the other compounds were found in very similar concentrations. Accordingly, no n-heptane-specific major metabolite was demonstrated in this study.

The metabolism of n-heptane is shown in Figure 1 with particular reference to the metabolites detected in the urine of exposed workers or test persons.

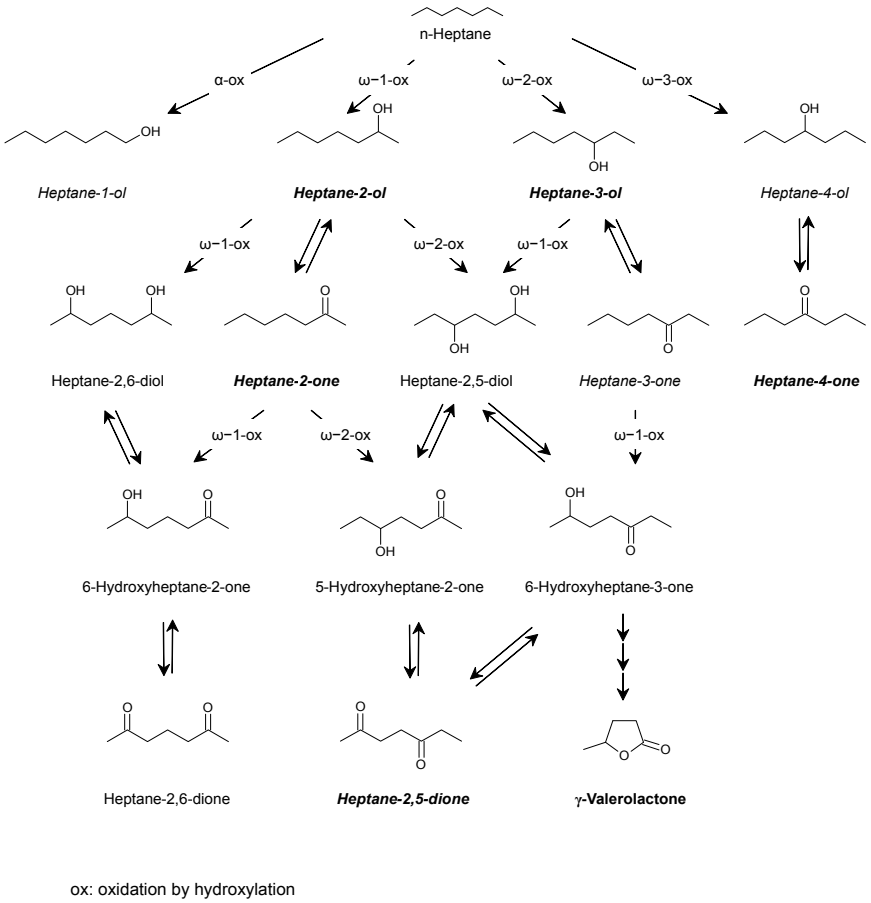

Fig. 1 Proposed metabolic pathway for n-heptane according to data from Bahima et al. (1984) and Perbellini et al. (1986)
italic: urinary metabolites detected in experimental human studies, **bold**: metabolites detected in the urine of exposed workers (Figure according to Rossbach et al. (2012), reprinted by permission of Elsevier http://www.elsevier.com)

2 Critical Toxicity

Acute central nervous effects may occur after inhalation of n-heptane, which are typical of lipophilic solvent vapours. The derivation of the MAK value was based on the respiratory irritation of the substance (Greim 1998). The γ-diketone heptane-2,5-dione formed metabolically from n-heptane induced peripheral polyneuropathy in animal experiments after repeated administration (O'Donoghue and Krasavage 1979). However, results from animal experiments and a toxicokinetic human study with n-heptane led to the conclusion that, if the MAK value is observed, the extent of heptane-2,5-dione formation is too low to cause peripheral neurotoxicity (Greim 1998).

3 Exposure and Effects

3.1 Relationship between external and internal exposure

In a human study, the relationship between external exposure and the formation or renal excretion of the neurotoxic metabolite heptane-2,5-dione was examined in detail (Filser et al. 1996; Störmer 1997). Four female and two male test persons were exposed to constant n-heptane concentrations of 0, 100, 250 and 500 ml/m^3 in a total of seven experiments. From 16 to 24 hours before exposure to 75 hours after exposure, all urine samples were collected from the test persons and analysed for heptane-2,5-dione. As shown in the BAT documentation (Csanády 2010), a baseline excretion of 5.5 µg heptane-2,5-dione/l urine on average was found before exposure. Toxicokinetic calculations showed that after exposure only 0.009% of the metabolised n-heptane amount was excreted as heptane-2,5-dione. The mean elimination half-life of the metabolite was 2.9 hours. The data obtained in the four-hour experiment were extrapolated to an eight-hour exposure under MAK conditions. Accordingly, after an eight-hour exposure to 500 ml n-heptane/m^3, a concentration of 240 µg heptane-2,5-dione/l would be expected in the post-shift urine. Under additional physical workload (50 W), this could rise to 340 µg/l. Based on toxicokinetic considerations, a concentration of 0.02 mmol n-heptane/l blood (2.00 mg/l) was also derived for exposure to 500 ml n-heptane/m^3.

The relationship between external exposure to n-heptane and the level of n-heptane and its metabolites in blood was examined in an experimental study in humans (Rossbach et al. 2012). Here, a total of 20 test persons were exposed to n-heptane concentrations of 167, 333 and 500 ml/m^3 for three hours each. Immediately after the end of exposure, n-heptane (0.297–2.903 mg/l) and heptane-2-one (0.017–0.495 mg/l) were detected in all blood samples. Detection of further monoketo metabolites or (unconjugated) monohydroxy metabolites was mostly possible only after exposure to 500 or 333 ml n-heptane/m^3. For the parameter n-heptane, a linear relationship between external and internal exposure was found, with the regression line running approximately through the origin of the coordinate system (Figure 2). According to results from exposure studies with the homologous compound n-hexane, it is assumed that with constant inhalation exposure to aliphatic solvents, a steady state concentration is reached in the blood after about 90 minutes, which continues to exist until the external exposure is discontinued (Greim 2000). During inhalation of n-heptane, a corresponding concentration plateau was reached after about 60 minutes (Rossbach et al. 2010 a). Thus, it can be assumed that the n-heptane concentrations in the blood determined at the end of the three-hour exposure represent steady state concentrations that are not subject to any significant changes even if the exposure continues. Therefore, the relationship between external and internal exposure shown in Figure 2 is valid even after exposure over an entire work shift. An eight-hour exposure to 500 ml n-heptane/m^3 at rest should therefore result in an average internal burden of 1.6 mg n-heptane/l blood. The experimentally determined value thus shows good agreement with the exposure theoretically derived by Csanády (2010).

In contrast to the parameter n-heptane in blood, no constant linear increase of the metabolite concentration with increasing external exposure was found for the parameter heptane-2-one. A disproportionate increase in the concentration of this metabolite with increasing external exposure seems to indicate that heptane-2-one is increasingly formed especially at higher external exposure concentrations, presumably due to the saturation of alternative elimination pathways (Rossbach et al. 2010 b).

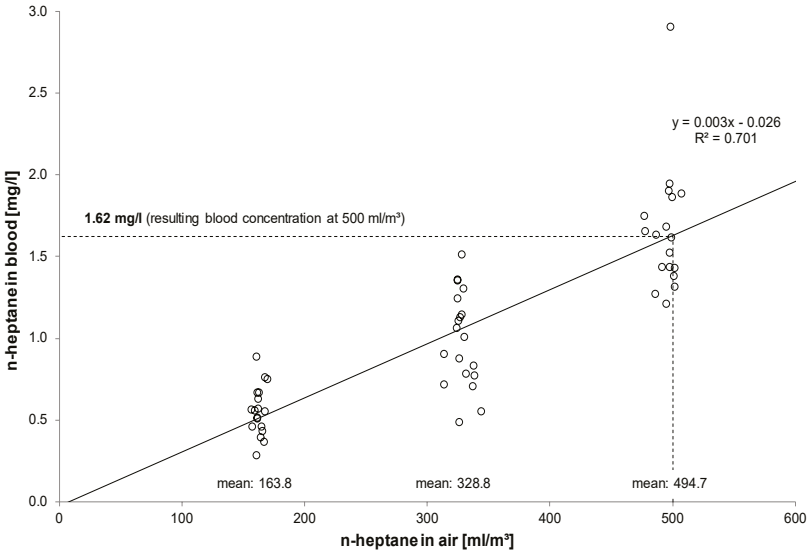

Fig. 2 Linear correlation between the concentrations of n-heptane in air and blood ($p < 0.001$, $n = 55$; figure according to Rossbach et al. (2012), reprinted by permission of Elsevier http://www.elsevier.com)

The experimental study in humans by Rossbach et al. (2018) also provided comprehensive data on the relationship between external exposure and the excretion of heptane metabolites in urine. For most heptane metabolites, no linear relationship to the concentration of n-heptane in air was observed. In contrast, the mean excretion of heptane-2-ol (related to creatinine) increased in a linear fashion with cumulative external exposure ($y = 1.42136x - 5.6$; $R^2 = 0.998$, $p < 0.01$). The regression equation given for the main metabolite heptane-2-ol was used to estimate its concentration in urine after cumulative exposure to 4000 ml n-heptane/$m^3 \times h$, corresponding to 500 ml/m^3 over 8 hours. Accordingly, a concentration of approx. 5700 µg heptane-2-ol/g creatinine would be expected in urine samples at the end of the shift (Figure 3).

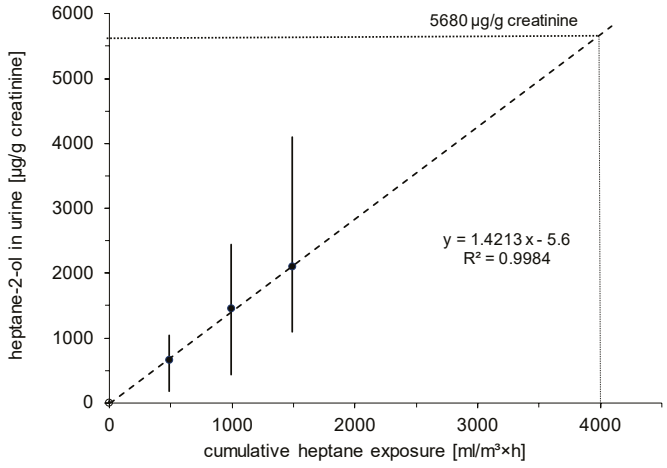

Fig. 3 Relationship between cumulative external n-heptane exposure and mean creatinine-related excretion of heptane-2-ol in urine immediately after a 3-hour exposure and extrapolation to an 8-hour exposure to 500 ml n-heptane/m^3 (Figure according to Rossbach et al. (2018) reprinted by permission of Elsevier http://www.elsevier.com)
●: mean value after exposure; ○: mean value before exposure; vertical bars: value ranges

The data for the parameter heptane-2,5-dione in urine from the study by Rossbach et al. (2018) agree well with the data from the study by Filser et al. (1996) and Störmer (1997). A regression analysis based on the data available from

both studies resulted in a power function that was used to estimate the concentration of heptane-2,5-dione in urine after cumulative exposure to 4000 ml n-heptane/m³ × h to be 235 µg heptane-2,5-dione/l (only data from Rossbach et al. (2018): 193 µg heptane-2,5-dione/l, see Figure 4).

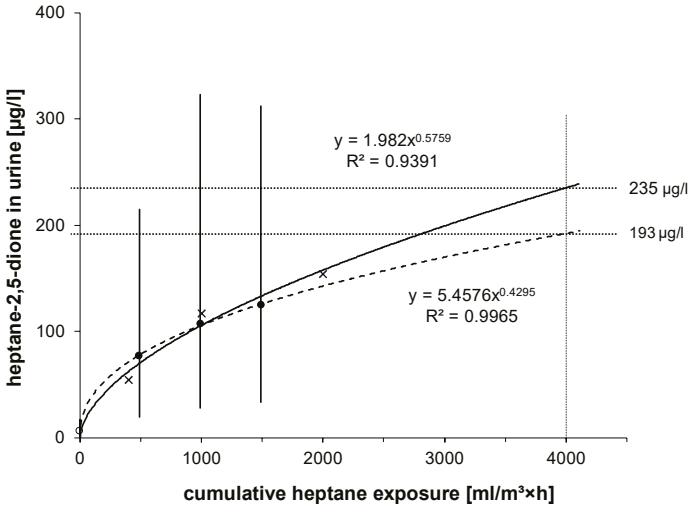

Fig. 4 Relationship between cumulative external exposure to n-heptane and the mean creatinine-related excretion of heptane-2,5-dione in urine immediately after a 3-hour and 4-hour exposure, respectively, and extrapolation to an 8-hour exposure to 500 ml n-heptane/m³ (Figure according to Rossbach et al. (2018) reprinted by permission of Elsevier http://www.elsevier.com);
●: mean value after exposure; ○: mean value before exposure; vertical bars: value ranges; x: data from Störmer (1997);
- - - : Regression function based on the data from Rossbach et al. (2018); —: Regression function based on the pooled data from Rossbach et al. (2018) and Störmer (1997)

In the workplace study by Sturaro et al. (1997), a mean concentration of 197 µg heptane-2,5-dione/g creatinine (range: 77–400) was measured in the urine of 10 workers from the shoe industry after a mean inhalation exposure to n-heptane of 11 ml/m³ (range: 3.7–22) at the end of the shift. In comparison with the experimental studies available, it is striking that the concentration of heptane-2,5-dione in urine is in a range that would correspond to approx. 500 ml n-heptane/m³ air, although the concentrations reported in the study were significantly lower. For heptane-3-ol, heptane-2-one and heptane-2,5-dione, regression parameters describing the relationship between internal and external exposure are given in the publication, whereas no significant relationship was found for heptane-2-ol. In the case of exposure to an n-heptane concentration of 500 ml/m³, however, according to the regression equations, metabolite concentrations would be expected at the end of the shift, which would be below the mean values given for exposure to 11 ml/m³ based on measured values and are thus not plausible. The results of this workplace study and the earlier workplace study by Perbellini et al. (1986) thus do not appear to be sufficiently reliable.

3.2 Relationship between internal exposure and effects

There are no data available on the relationship between internal exposure and effects.

4 Selection of Indicators

In addition to general data on the metabolism of n-heptane, most information that can be used quantitatively is available for the parameters n-heptane in blood and heptane-2,5-dione in urine. This information comes mainly from two human experimental studies in which test persons were exposed to n-heptane concentrations between 100 and 500 ml/m³ at rest. The duration of the exposures was three and four hours, respectively, so that an extrapolation to an exposure duration of eight hours had to be made.

In the case of the parameter n-heptane in blood, the concentration theoretically derived by Csanády (2010) for an exposure to 500 ml/m^3 could be verified experimentally (Rossbach et al. 2012). Assuming that a steady state is reached after a sufficiently long exposure period (approx. 90 minutes), the heptane concentration after eight hours of exposure can be inferred from concentrations determined in the blood after three hours of experimental exposure. However, the very short half-life of n-heptane in blood (approx. 20 minutes) is disadvantageous for the use of this parameter for exposure monitoring.

For the parameter heptane-2,5-dione, data determined in human experimental studies are available (Filser et al. 1996; Rossbach et al. 2018; Störmer 1997), so that an equivalent to the MAK value can be derived.

Other heptane metabolites can be used to assess internal exposure. In particular, the main metabolite heptane-2-ol may be suitable for this purpose, for which a linear relationship to external exposure was demonstrated in the study by Rossbach et al. (2018). An advantage of the parameter heptane-2-ol is its approximately 20-fold higher renal excretion compared with heptane-2,5-dione. The determination of heptane-2-ol should therefore allow sensitive detection of even lower n-heptane exposures. Data from two earlier workplace studies (Perbellini et al. 1986; Sturaro et al. 1997) do not fundamentally contradict the described relationship, but due to methodological differences concerning sample hydrolysis and comparatively low external exposures to < 30 ml n-heptane/m^3 they are hardly suitable, especially for quantitative derivations in the range of the MAK value. When using this parameter, the hydrolysis of the sample before the actual instrumental analytical determination is of decisive importance (see Section 5). In addition, relating the metabolite concentration to creatinine proved to be essential for the significance of the exposure marker. However, due to insufficient data, no assessment value can be derived for this parameter at present. A simultaneous determination of heptane-3-ol, which is also excreted in relatively large amounts under exposure to n-heptane, can be used for a plausibility check.

5 Analytical Methods

The determination of n-heptane in whole blood can be carried out by means of gas chromatographic vapour space analysis (headspace GC, HS-GC), coupled for example to a mass selective detector (HS-GC/MS). If necessary, headspace enrichment methods (for example SPME, SPDE) can also be used (Chambers et al. 2008; Rossbach et al. 2012).

The determination of heptane-2,5-dione in urine can either also be carried out using a headspace enrichment method (Rossbach et al. 2018) or by GC/MS after liquid-liquid extraction (Störmer 1997). A corresponding headspace procedure is currently being examined by the Commission. Due to the low volatility of the analyte, the determination of heptane-2,5-dione places lower demands on sampling, so that an immediate transfer of the samples into crimp seal vials after extraction can be omitted.

6 Background Exposure

Only little information is available on background exposure to n-heptane. With regard to the parameter heptane-2,5-dione in urine, very similar values were determined in the two human experimental studies available to date, indicating a background exposure in the low µg/l range. In samples obtained before the controlled exposures to n-heptane in each case, mean and median heptane-2,5-dione concentrations of 5.5 and 5 µg/l, respectively, were found (Filser et al. 1996; Rossbach et al. 2018). In the study by Rossbach et al. (2018), the values were in the range from < 0.6 to 16.6 µg heptane-2,5-dione/l; the compound was detected in 53 of 55 urine samples (n = 20 test persons).

7 Evaluation of a BAT Value

For the assessment of exposures to n-heptane by biomonitoring, the parameter heptane-2,5-dione in urine is particularly suitable, as explained above.

According to the results of two experimental studies in humans, an eight-hour exposure to n-heptane at the currently valid MAK value of 500 ml/m^3 corresponds to a urinary concentration of 250 µg heptane-2,5-dione/l urine.

Therefore, a BAT value of 250 µg heptane-2,5-dione/l urine is established.

Sampling takes place at the end of exposure or at the end of shift.

8 Interpretation

In the study by Rossbach et al. (2012, 2018), the test persons were exposed under resting conditions. Due to a blood:air partition coefficient of < 5 for n-heptane, no adjustment for physical workload has to be considered when deriving the BAT value.

When using the parameter heptane-2,5-dione in urine, the creatinine concentration of the sample should be included in the considerations. This can reduce possible diuresis-related distortions of analytical results. It is recommended to use only urine samples with creatinine concentrations of 0.3–3 g/l for substance analyses and evaluations of individual tests (translated in Bader et al. 2016). If the MAK value is observed, the exposure to heptane-2,5-dione is too low to induce observable neurotoxic effects. The parameter is therefore not to be interpreted as an indicator of critical toxicity but as a marker of exposure.

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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