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Tri-n-butyl phosphate

Assessment Values in Biological Material – Translation of the German version from 2018

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Tri-n-butyl phosphate

BAT Value Documentation

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area evaluated tri-n-butyl phosphate [CAS No.126-73-8] in 2016 and derived a biological reference value ("Biologischer Arbeitsstoff-Referenzwert", BAR) for dibutyl phosphate in urine. Available publications are described in detail.
In a study with persons of the general population occupationally not exposed to tri-n-butyl phosphate a 95th percentile of 0.67 µg dibutyl phosphate/l urine was measured. Further studies with non-exposed individuals resulted in maximum levels of 0.45 µg and 0.26 µg dibutyl phosphate/l urine.
Taking these results together with other investigations into consideration, a BAR for tri-n-butyl phosphate of 0.5 µg dibutyl phosphate/l urine was established. Sampling time is at the end of exposure or the end of the working shift.

Keywords

tri-n-butyl phosphate; phosphoric acid tributyl ester; celluphos 4; TBP; BAT value; BAR; toxicity

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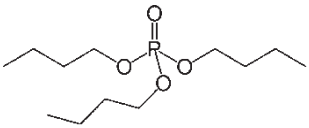
Tri-n-butyl phosphate

BAR (2016)	**0.5 µg dibutyl phosphate/L urine**
	Sampling time: end of exposure or end of shift
MAK value (2000)	**1 mL/m³ ≙ 11 mg/m³**
Peak limitation (2000)	Category II, excursion factor 2
Absorption through the skin (2000)	H
Sensitization	–
Carcinogenicity (2000)	Category 4
Prenatal toxicity (2000)	Group C
Germ cell mutagenicity	–
Synonyms	Phosphoric acid tributyl ester Celluphos 4 TBP
Chemical name	Tri-n-butyl phosphate
CAS No.	[126-73-8]
Formula	 $C_{12}H_{27}O_4P$
Molecular weight	266.32 g/mol
Melting point	–79 °C
Boiling point at 1013 hPa	293 °C
Density at 20 °C	0.98 g/cm³
Vapour pressure at 20 °C	0.008 hPa
Log P_{OW}	4.0

The non-volatile compound tri-n-butyl phosphate (phosphoric acid tributyl ester, TBP) is a polar solvent used in the manufacture of plastics, as a flame-retardant component of aircraft hydraulic fluid, as a cooling lubricant, an extractant in nuclear fuel reprocessing and as a solvent extractant of rare earth metals. Besides, it is used as a defoamer additive for concrete plasticizers, as a wetting agent in the textile dyeing

industry, as a flame retardant and plasticizer. For instance, TBP is employed in both rigid and flexible polyurethane foams (Schindler 2009). It can enter the hydrosphere through the manufacture and release from plastic products. The annual production volume of TBP was estimated to amount to 5.000 tonnes in 2001 (OECD 2001). TBP does not occur naturally in the environment. Background exposure of the general population to TBP thus solely results from the introduction of industrial products (e.g. of flame retardants) into the environment. Various studies have shown the presence of organophosporous flame retardants, including TBP, in environmental matrices (soil, water, house dust, air) (Andresen and Bester 2006; Andresen et al. 2004; Fries and Püttmann 2001, 2003; Ingerowski et al. 1997; Kersten and Reich 2003; Martinez-Carballo et al. 2007; Nagorka and Ullrich 2003; Reemtsma et al. 2008).

1 Metabolism and Toxikokinetics

1.1 Absorption and Distribution

The general population can be exposed to TBP by oral, dermal or inhalation routes. Animal studies have shown that TBP is readily absorbed orally. Dermal uptake is a relevant route of human exposure (designation with an "H"). There are no meaningful data available on absorption by inhalation (Schindler 2009).

Seven days after oral and intraperitoneal administration of ^{14}C-labelled TBP to rats, concentrations are found to be highest in muscle, skin and fatty tissue with a residual radioactivity of less than 1% in any tissue and 1.5% in the rest of the body. A relevant accumulation of TBP in the body is thus unlikely (Greim 2000, translated).

1.2 Metabolism

TBP is almost completely metabolized. Less than 1% of TBP is excreted unmetabolized in urine and faeces (Greim 2000, translated). After intraperitoneal administration of ^{14}C-labelled TBP to rats, 70% of the applied dose is found as metabolites in urine, 7% in faeces and 4% in exhaled air within one month. In total, 90% of the applied dose is excreted within 5 days (Suzuki et al. 1984).

Metabolites of TBP include dibutyl phosphate (DBP), monobutyl phosphate (MBP) and butyl-bis-(3-hydroxybutyl) phosphate (Suzuki et al. 1984).

2 Critical Toxicity

Target organs of TBP toxicity identified in animal studies are mainly the urinary bladder and liver (Greim 2000, translated; Hartwig 2012). Acute toxicity is low (Mitomo 1980). Following 4-hour exposure, the LC_{50} is below 1991 mL/m^3 for mice and approximately 380 mL/m^3 for rats (Greim 2000, translated). Persons occupationally exposed to TBP at a dose of 15 mg/m^3 complained of nausea and headache (ACGIH 2013). This observation, however, has only been documented as personal communication without any further data and is therefore difficult to assess. In addition, irritation to skin, eyes and respiratory tract has been observed (Greim 2000, trans-

lated). Moreover, in animal studies TBP has proved to be carcinogenic and toxic to reproduction (Greim 2000, translated; Hartwig 2012). For further and more detailed information on the metabolism and toxicity of TBP, please refer to the MAK Value Documentation (Greim 2000, translated; Hartwig 2012).

3 Selection of Indicators and Methodology

Di-n-butyl phosphate (DBP) is one of the main metabolites of TBP in humans (Schindler 2009; Schindler et al. 2009). GC-MS/MS methods are available for the determination and detection of DBP in biological material (urine) (Mach 2014; Schindler 2009). The limits of detection range from 0.1 µg DBP/L urine (Dodson 2014; Mach 2012, 2014) to 0.25 µg/L urine (Schindler et al. 2009).

4 Background Exposure

A group randomly selected from the general population of Southern Germany (n = 25; 12 women, 13 men) who were not occupationally exposed to TBP was investigated in the studies by Schindler (2009) and Schindler et al. (2009) in order to determine the environmental background exposure of Germany's general population to flame retardants. The study subjects in this group were aged 41 years on average, one of them was a smoker. Dibutyl phosphate (DBP) as a metabolite of TBP could only be determined in one sample with a value above the limit of detection (LOD) (maximum: 0.26 µg/L urine). The 95th percentile of the random sample was below the LOD of 0.25 µg/L urine.

In another study by this working group (Mach et al. 2012), urine samples from 47 employees at Friedrich-Alexander University Erlangen-Nürnberg who were not occupationally exposed to flame retardants (30 women, 17 men; age: 19–69 years (median: 40 years); 11 smokers) were analysed. The limit of quantitation for DBP was 0.1 µg/L. The median value was 0.22 µg DBP/L and the 95th percentile was 0.67 µg DBP/L urine, with a measuring range of < 0.1 µg/L to 1.03 µg/L for the urinary metabolite (Mach et al. 2012).

The thesis by Mach (2014) yielded a median value of 0.23 µg DBP/L and a 95th percentile of 2.5 µg DBP/L urine for the same group of subjects, with a measuring range of < 0.1 µg/L to 4.08 µg/L urine for the urinary metabolite. There was no statistically significant difference in metabolite excretion between men and women or smokers and non-smokers, although metabolite concentrations measured in the urine of smokers tended to be higher (95th percentile: smokers: 2.10 µg/L, non-smokers: 1.55 µg/L). Besides, the thesis by Mach (2014) specifies the 95th percentile in a group of mother-child pairs (45 mothers). The 95th percentile for urinary concentration of DBP was 1.92 µg/urine among mothers, while it was 1.72 µg/L urine among children.

In a study by Dodson et al. (2014), samples from 16 non-smoking adults living in northern California (sampling in 2011) were analysed using the method (GC-MS/MS) described by Schindler (2009). The limit of detection in this study was 0.08 µg/L urine. DBP was detected in 56% of the samples. The median value was 0.11 µg DBP/L

urine, the mean value was 0.16 µg DBP/L urine and the maximum value was 0.45 µg DBP/L urine.

Another study from Germany (Fromme et al. 2014) investigated the uptake and excretion of metabolites of organophosphate flame retardants in children (sampling in 2011) visiting a day-care centre using the GC-MS/MS method described by Mach (2014) (limit of detection for DBP: 0.1 µg/L). The group of subjects was composed of 312 children from 63 day-care centres in Bavaria, Berlin and North Rhine-Westphalia. Given an external exposure of the children to TBP that was two times higher compared to other measurements, the results for DBP were as follows: A DBP concentration exceeding the limit of detection was found in 71% of the samples. The median value was 0.2 µg DBP/L, the mean value was 0.3 µg DBP/L and the 95th percentile was 0.9 µg DBP/L.

5 Occupational Exposure

A pilot study by Schindler et al. (2014) assessed the occupational exposure of five aircraft maintenance technicians to organophosphates used in hydraulic fluids and turbine oils. The pre-shift values of DBP ranged from 11.0 to 37.2 µg/L urine (median: 12.5 µg/L urine) while the post-shift values of DBP ranged from 6.0 to 51.6 µg/L urine (median: 23.5 µg/L urine).

6 Evaluation

The studies presented in Section 4 show that dibutyl phosphate (DBP), a major urinary metabolite of TBP, is an excellent biomarker of the general population's exposure to tri-n-butyl phosphate. Suitable detection methods using GC-MS/MS are available for the determination of the metabolite.

The reference value for background exposure is influenced by a number of factors, including sex, social status, living environment and lifestyle factors (smoking). Some of the studies mentioned in Section 4, however, do not substantiate any sex-specific or smoking-specific difference. As the ubiquitous occurrence of TBP in the environment may depend on regional and economic characteristics (building regulations, degree of industrialisation), mainly measured values from study participants from Germany or countries with a similar degree of industrialisation are taken into account for the derivation of the BAR. In the present case, the studies by Schindler (2009), Mach et al. (2012), Mach (2014), Dodson et al. (2014) and Fromme et al. (2014) are eligible for consideration.

In the study by Schindler (2009), the 95th percentile of the TBP metabolite dibutyl phosphate was below the limit of detection of 0.25 µg/L urine for this method. The maximum value was 0.26 µg/L urine. The study by Dodson et al. (2014) yielded a median value of 0.11 µg DBP/L urine, a mean value of 0.16 µg DBP/L urine and a maximum value of 0.45 µg DBP/L urine, given a sample size of n = 16 (limit of detection: 0.08 µg/L). In the study by Mach et al. (2012) (n = 47, 86% of the samples above the limit of detection of 0.1 µg/L urine), the 95th percentile of the TBP metabolite dibutyl phosphate was 0.67 µg/L urine, while the median value was 0.22 µg DBP/L urine

and the maximum value was 1.03 µg DBP/L urine. Fromme et al. (2014) observed a 95th percentile of 0.9 µg DBP/L urine in a group of n = 312 children. Although the analyses performed by Fromme et al. (2014) are based on a group of children aged 20 to 80 months, they confirm the data available.

In the thesis by Mach (2014), the 95th percentile was 2.1 µg/DBP/L urine in smokers and 1.6 µg/L urine in non-smokers where n = 47 persons of the general population, while in another group the 95th percentile was 1.9 µg DBP/L urine in 45 women. These measurement results are high compared to the other data published. As contradictory results were published, these are not taken into account for the derivation of the BAR value.

The BAR is thus based on the studies by Schindler (2009), Mach et al. (2012) and Dodson et al. (2014). The results obtained by Fromme et al. (2014) substantiate these data.

For tri-n-butyl phosphate, a

BAR of 0.5 µg dibutyl phosphate/L urine

has been set.

Sampling is performed at the end of exposure or at the end of the shift.

7 Interpretation of the Data

The pre-shift median value of DBP in persons occupationally exposed to tri-n-butyl phosphate was 12.5 µg/L urine, while the post-shift median value was 23.5 µg/L urine (Schindler et al. 2014).

The above-mentioned BAR relates to normally concentrated urine, in which the creatinine concentration should be in the range of 0.3–3.0 g/L (WHO 1996). As a rule, where urine samples are outside the aforementioned limits, a repetition of the measurement in normally hydrated test persons is recommended.

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