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Tricresyl phosphate, sum of all ortho-isomers – Evaluation of study results in biological material

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 evaluated tricresyl phosphate, sum of all ortho-isomers [78-30-8]. The available data did not allow the derivation of assessment values in biological material.

The internal exposure to tri-o-cresyl phosphate is considered to be characterised by the quantification of its metabolite di-o-cresyl phosphate in urine. Di-o-cresyl phosphate is also one of the metabolites of o,o,m- and o,o,p-tricresyl phosphate, but not of the mono-o-tricresyl phosphates.

In an analysis of 2666 spot urine samples collected from a random one-third subset of 2013–2014 NHANES (National Health and Nutrition Examination Survey) participants' di-o-cresyl phosphate levels were determined. Even 95th percentiles were below the limit of detection of the analytical method (0.05 µg/l urine) for both males and females as well as for all age and ethnic groups analysed.

In another study, a total of 332 urine samples of pilots and cabin crew members in common passenger airplanes, who reported fume/odour during their last flight, were analysed. None of the samples contained di-ortho-isomers of tricresyl phosphate metabolites above the limit of detection of 0.5 µg/l urine.

Thus, in spite of the availability of methods for biomonitoring of ortho-isomers of tricresyl phosphate, guidance or reference values cannot be determined.

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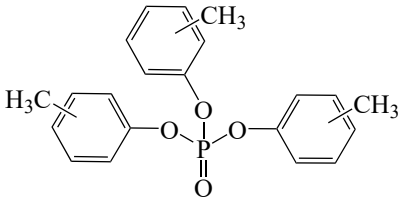
BAT value (2020)	**not established**
BAR (2020)	**not established** Sampling time: end of exposure or end of shift
MAK value (2019)	**0.001 ml/m³ (ppm) ≙ 0.015 mg/m³ for the sum of all o-isomers**
Absorption through the skin (2019)	H
Carcinogenicity (2019)	Category 3
Synonyms	Tri-ortho-cresyl phosphate Tri-2-methylphenyl phosphate Tris(methylphenyl) phosphate o-Tritolyl phosphate Tri-o-tolyl phosphate ToCP
CAS numbers	78-30-8 for the tri-o-isomer, 1330-78-5 for all tricresyl phosphate isomers
Formula	 o-o-o, o-o-m, o-o-p, o-m-m, o-m-p, o-p-p $C_{21}H_{21}O_4P$
Molar mass	368.37 g/mol
Melting point	Tri-o-isomer: 11 °C (IFA 2020)
Boiling point	Tri-o-isomer: 410 °C (IFA 2020)
Vapour pressure at 25 °C	Tri-o-isomer: < 0.0001 hPa (IFA 2020)
Density at 20 °C	Tri-o-isomer: 1.18 g/cm³ (IFA 2020)

The term o-tricresyl phosphates is used here to describe tricresyl phosphates in which at least one cresyl residue has a methyl group in the ortho position. Tricresyl phosphates are used as flame retardants, plasticisers and as cooling lubricant additives. Tri-o-cresyl phosphate (often abbreviated ToCP) used to be added as a plasticiser to Igelit (polyvinyl chloride) (Hartwig and MAK Commission 2020).

ToCP is the tri-o-isomer of tricresyl phosphates. Besides ToCP there are two di-o-tricresyl phosphates (o,o,m and o,o,p) and three mono-o-tricresyl phosphates (Winder and Balouet 2002).

1 Metabolism and Toxicokinetics

Metabolism and toxicokinetics are described in detail in Hartwig and MAK Commission (2020).

2 Critical Toxicity

The critical toxicity of ortho-isomers of tricresyl phosphate is neurotoxicity, which manifests itself as organophosphate-induced delayed neuropathy (OPIDN). It is attributed to an inhibition of esterases, in particular cholinesterases and neurotoxic esterases (Winder and Balouet 2002). For further details see Hartwig and MAK Commission (2020). The critical metabolite identified is o-cresyl-saligenin phosphate (2-(2-cresyl)-4H-1,3,2-benzodioxaphosphorin-2-oxide or 2-(o-tolyloxy)-4H-1,3,2-benzodioxaphosphorin-2-oxide, CBDP), which inhibits neurotoxic esterase very potently and is a strong irreversible inhibitor of butyrylcholinesterase and a weak inhibitor of acetylcholinesterase (Hartwig and MAK Commission 2020).

3 Exposure and Effects

There are no studies available on a relationship between external exposure via inhalation and internal exposure or a relationship between internal exposure (metabolites of o-tricresyl phosphate isomers in urine) and effects in terms of neurotoxic damage.

4 Selection of the Indicators

For the biomonitoring of ortho-isomers of tricresyl phosphate, di-o-cresyl phosphate (DoCP) is determined as relevant metabolite of ToCP and as one of the metabolites of o,o,m-TCP and o,o,p-TCP in urine. In addition, di-m-cresyl phosphate (DmCP) and di-p-cresyl phosphate (DpCP), which belong to the metabolite spectrum of o,m,m-TCP and o,p,p-TCP, can be determined (Schindler et al. 2013).

5 Analytical Methods

Various methods for determining dicresyl phosphate in urine have been published. A gas chromatography tandem mass spectrometry method (GC-MS/MS) achieved a limit of detection for DoCP, DmCP and DpCP of 0.5 µg/l urine after solid phase extraction, derivatization and quantification (Schindler et al. 2013). Using UPLC-MS/MS (ultra-performance liquid chromatography coupled with tandem mass spectrometry), the two metabolites DoCP and DpCP were determined as a sum with a detection limit of 0.13 µg/l and a quantification limit of 0.41 µg/l (Kosarac et al. 2016). Using a method with SPE (solid phase extraction) and HPLC-MS/MS (high-performance liquid chromatography coupled with tandem mass spectrometry), a detection limit of 0.05 µg/l was achieved for DoCP (Jayatilaka et al. 2017). In another study, in which sample pre-treatment with SIPTE (solvent induced phase transition extraction) and quantification by UPLC-MS/MS was performed, the two tricresyl phosphate metabolites DoCP and DpCP could not be separated. The limit of detection was 0.032 µg/l, the limit of quantification 0.11 µg/l (Hu et al. 2019).

6 Background Exposure

The NHANES survey (2013/2014) analysed 2666 urine samples for DoCP. For all age groups and ethnic groups examined, as well as for both sexes, the 95th percentile was below the detection limit of the analytical method of 0.05 µg DoCP/l urine (Ospina et al. 2018). This indicates low levels of tri-o- and di-o-tricresyl phosphate exposure. However, dicresyl phosphates with only one cresyl residue in ortho-position are not recorded by this parameter. These can originate from mono-o- or di-o-tricresyl phosphates. Mono-o-tricresyl phosphates have a higher toxicity than di-o-tricresyl phosphates, which in turn have a higher toxicity than tri-o-tricresyl phosphate (Aldridge and Barnes 1961; Henschler 1958).

Analysis of the urine samples of 332 pilots and cabin crew members of passenger aircraft revealed concentrations of DoCP – as a relevant metabolite of the ortho-isomers of tricresyl phosphate – below the method's detection limit of 0.5 µg DoCP/l urine (Schindler et al. 2013).

7 Evaluation

As there are no studies for the ortho-isomers of tricresyl phosphate on the relationship between external and internal exposure or the relationship between internal exposure and effects,

a biological tolerance value (BAT value) cannot be derived.

Since both the 95th percentiles of the urinary DoCP values for the background exposure of an occupationally non-exposed reference population and all values in a study of air crew members were below the detection limit of the respective analytical method,

a biological reference value (BAR) for the ortho-isomers of tricresyl phosphate cannot be derived.

8 Interpretation

Values above the detection limit of 0.05 µg DoCP/l urine in the study by Ospina et al. (2018) can be regarded as evidence of a significantly increased exposure to the ortho-isomers of tricresyl phosphate.

References

Aldridge WN, Barnes JM (1961) Neurotoxic and biochemical properties of some triaryl phosphates. Biochem Pharmacol 6(3): 177–188. DOI: https://doi.org/10.1016/0006-2952(61)90162-9

Hartwig A, MAK Commission (2020) Trikresylphosphat, Summe aller o-Isomere. MAK-Begründung. MAK Collect Occup Health Saf 5(3): Doc050. DOI: https://doi.org/10.34865/mb7830d5_3or

Henschler D (1958) Die Trikresylphosphatvergiftung. Experimentelle Klärung von Problemen der Ätiologie und Pathogenese. Klin Wochenschr 36(14): 663–674. DOI: https://doi.org/10.1007/BF01488746

Hu L, Tao Y, Luo D, Feng J, Wang L, Yu M, Li Y, Covaci A, Mei S (2019) Simultaneous biomonitoring of 15 organophosphate flame retardants metabolites in urine samples by solvent induced phase transition extraction coupled with ultra-performance liquid chromatography-tandem mass spectrometry. Chemosphere 233: 724–732. DOI: https://doi.org/10.1016/j.chemosphere.2019.05.242

IFA (Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung) (2020) o,o,o-Tricresyl phosphate. GESTIS substance database. https://gestis.dguv.de/data?name=510394&lang=en, accessed 25 Jan 2020

Jayatilaka NK, Restrepo P, Williams L, Ospina M, Valentin-Blasini L, Calafat AM (2017) Quantification of three chlorinated dialkyl phosphates, diphenyl phosphate, 2,3,4,5-tetrabromobenzoic acid, and four other organophosphates in human urine by solid phase extraction-high performance liquid chromatography-tandem mass spectrometry. Anal Bioanal Chem 409(5): 1323–1332. DOI: https://doi.org/10.1007/s00216-016-0061-4

Kosarac I, Kubwabo C, Foster WG (2016) Quantitative determination of nine urinary metabolites of organophosphate flame retardants using solid phase extraction and ultra performance liquid chromatography coupled to tandem mass spectrometry (UPLC-MS/MS). J Chromatogr B Analyt Technol Biomed Life Sci 1014: 24–30. DOI: https://doi.org/10.1016/j.jchromb.2016.01.035

Ospina M, Jayatilaka NK, Wong L-Y, Restrepo P, Calafat AM (2018) Exposure to organophosphate flame retardant chemicals in the U.S. general population: Data from the 2013-2014 National Health and Nutrition Examination Survey. Environ Int 110: 32–41. DOI: https://doi.org/10.1016/j.envint.2017.10.001

Schindler BK, Weiss T, Schütze A, Koslitz S, Broding HC, Bünger J, Brüning T (2013) Occupational exposure of air crews to tricresyl phosphate isomers and organophosphate flame retardants after fume events. Arch Toxicol 87(4): 645–648. DOI: https://doi.org/10.1007/s00204-012-0978-0

Winder C, Balouet J-C (2002) The toxicity of commercial jet oils. Environ Res 89(2): 146–164. DOI: https://doi.org/10.1006/enrs.2002.4346