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Di-*n*-butyl phosphate and its technical mixtures

MAK Value Documentation, supplement – Translation of the German version from 2020

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di-*n*-butyl phosphate; irritation; carcinogenicity; bladder; tri-*n*-butyl phosphate

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the maximum concentration at the workplace (MAK value) and the carcinogenicity classification of di-*n*-butyl phosphate [107-66-4] and its technical mixtures.

Di-*n*-butyl phosphate is irritating to the forestomach and the bladder of rats, causing epithelial hyperplasia, degeneration and ulceration of the bladder mucosa.

No carcinogenicity study has been performed with di-*n*-butyl phosphate. The bladder carcinogenicity of tri-*n*-butyl phosphate may be caused by the irritant effects of its metabolite di-*n*-butyl phosphate. Therefore, di-*n*-butyl phosphate and its technical mixtures are classified in Category 3B for suspected carcinogens.

No inhalation study has been performed with di-*n*-butyl phosphate. The MAK value of tri-*n*-butyl phosphate cannot be applied to di-*n*-butyl phosphate because di-*n*-butyl phosphate is a stronger irritant. Therefore, no MAK value can be derived for di-*n*-butyl phosphate and its technical mixtures.

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MAK value	–
Peak limitation	–
Absorption through the skin	–
Sensitization	–
Carcinogenicity (2019)	**Category 3 B**
Prenatal toxicity	–
Germ cell mutagenicity	–
BAT value	–
CAS number	107-66-4
1 ml/m³ (ppm) ≙ 8.722 mg/m³	**1 mg/m³ ≙ 0.115 ml/m³ (ppm)**

"Di-*n*-butyl phosphate and its technical mixtures" were classified in 2009 in category 3 A for carcinogens (Hartwig 2014). This supplement re-evaluates this classification. New data for genotoxicity and carcinogenicity are not available.

Technical di-*n*-butyl phosphate is irritating to the skin and corrosive to the eyes of rabbits (Hartwig 2014).

Di-*n*-butyl phosphate is not genotoxic in vitro in bacteria and mammalian cells. There are no in vivo studies of its genotoxicity or carcinogenicity (Hartwig 2014).

When di-*n*-butyl phosphate was administered to rats by gavage over a period of approximately 6 weeks, hyperplasia, erosion and ulceration of the mucosa in the stomach and bladder were found to occur in a dose-dependent manner at doses of 63 mg/kg body weight and day and above; these findings are attributable to the irritant effect of di-*n*-butyl phosphate. In contrast, the structurally similar tri-*n*-butyl phosphate, which is metabolized to di-*n*-butyl phosphate, had no such effects in the stomach even after the administration of up to 140 mg/kg body weight and day with the diet for 2 years. However, a dose-dependent carcinogenic effect occurred in the urinary bladder of the rat. Hyperplasia, papillomas and transitional cell carcinomas were observed (Hartwig 2014).

After oral administration of tri-*n*-butyl phosphate, di-*n*-butyl phosphate was found to be the main metabolite (20%) in the urine of rats, whereas the mother substance accounted for only 1%. Di-*n*-butyl phosphate is significantly more irritating than tri-*n*-butyl phosphate. It is therefore assumed that the acidity of the metabolite di-*n*-butyl phosphate is responsible for the carcinogenic effects on the bladder after the administration of tri-*n*-butyl phosphate. However, there are no data to support this (Hartwig 2014).

Rats are much more sensitive to bladder stones and acidic effects in the bladder than are mice and humans. However, since it cannot be completely excluded that these findings are of relevance for humans, tri-*n*-butyl phosphate was classified in Carcinogen Category 4 (see Greim 2002). Di-*n*-butyl phosphate was evaluated in analogy to tri-*n*-butyl phosphate, but was assigned to category 3 A due to a lack of data for the derivation of a MAK value (Hartwig 2014).

No new data are available on the basis of which the carcinogenicity of di-*n*-butyl phosphate could be evaluated or a MAK value could be derived.

Manifesto (MAK value/classification)

The critical effect is the strong irritant effect of di-*n*-butyl phosphate, which is suspected of being responsible for the bladder carcinogenicity. There is no evidence of this in animals or humans.

MAK value. No inhalation studies with di-*n*-butyl phosphate are available. Since the irritant effect of di-*n*-butyl phosphate is significantly stronger than that of tri-*n*-butyl phosphate, the MAK value of tri-*n*-butyl phosphate cannot be adopted. It is therefore still not possible to derive a MAK value for di-*n*-butyl phosphate and its technical mixtures.

Carcinogenicity. In the evaluation of tri-*n*-butyl phosphate (see Greim 2002) it was assumed that the acidity of its main metabolite di-*n*-butyl phosphate was responsible for its bladder carcinogenicity after oral administration. There are no long-term studies of the carcinogenicity of di-*n*-butyl phosphate. However, as hyperplasia and degeneration of the mucosal epithelium of the bladder occurred after administration for 6 weeks and the substance is suspected of being the cause of bladder carcinomas in the case of tri-*n*-butyl phosphate, di-*n*-butyl phosphate and its technical mixtures are assigned to Carcinogen Category 3 B.

References

Greim H (ed) (2002) Tributyl phosphate. MAK Value Documentation, 2000. In: Occupational Toxicants, vol 17. Wiley-VCH, Weinheim, 285–314. Also available from DOI: https://doi.org/10.1002/3527600418.mb12673e0017

Hartwig A (ed) (2014) Di-n-butylphosphate and its technical mixtures. MAK Value Documentation, 2009. In: The MAK-Collection for Occupational Health and Safety. Part I: MAK Value Documentations. Wiley-VCH, Weinheim. DOI: https://doi.org/10.1002/3527600418.mb10766kske4714