

# Addendum to Nitroglycerin

## BLW (2007)

## Not established

Sampling time: end of exposure or end of shift

## MAK value (2005)

## Not established\*

Absorption through the skin (1978)

H

Carcinogenicity (2005)

Carcinogen Category 3 B

\* No longer valid. For updated values/classifications please refer to <http://onlinelibrary.wiley.com/book/10.1002/9783527695539>

In 2005, due to its carcinogenicity in the rat and its uncertain genotoxicity in vitro, nitroglycerin was classified in carcinogen category 3 B and the MAK value of 0.005 ml/m<sup>3</sup> valid up to then was withdrawn (Greim 2006). The BAT values of 0.5 µg 1,2-glycerine dinitrate/l plasma and 0.5 µg 1,3-glycerine dinitrate/l plasma (see Documentation 1996, translated) have therefore also been withdrawn. This addendum summarizes the scientific data on nitroglycerin gained since 1995, and thus complements the BAT documentation of 1996.

## 10 Metabolism and Toxicokinetics

Since the BAT documentation of 1996, more recent studies are available for metabolism and toxicokinetics (Ademola and Maibach 1995; Auclair et al. 1998; Santoro et al. 2000). These support the previously drawn conclusions and show that nitroglycerin has a high potential for absorption through the skin. Unlike inhalation or ingestion, dermal absorption is the main route by which nitroglycerin is taken up at the workplace. This makes clear the importance of biological monitoring to estimate the internal exposure after occupational contact with nitroglycerin and also the necessity to derive a “Biologischer Leitwert” (BLW) for interpretation of the analytical results obtained.

On the basis of the metabolism of nitroglycerin, a number of metabolites are principally available for biological monitoring. These are 1,2-glycerine dinitrate and 1,3-glycerine dinitrate, glycerine mononitrate, glycerine, nitrite, nitrate and carbon dioxide (see Documentation 1996, translated ) as well as their reaction products

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with amino acids, including tyrosine with the formation of 3-nitrotyrosine (Schwemmer et al. 2000). 3-nitrotyrosine was also proposed as a parameter for demonstrating nitrate tolerance in humans (Skatchkov et al. 1997).

## 11 Critical Toxicity

The toxicity of nitroglycerin is mediated by the metabolic release of nitrogen monoxide (NO), which is of considerable importance in physiological vascular regulation (see Documentation 1996, translated). Thus, nitroglycerin causes a dose-dependent decrease in diastolic and systolic blood pressures as well as cerebral vascular dilation, resulting in headache, dizziness and nausea. The release of NO additionally results in the potential involvement of nitroglycerin in the (vascular) cellular redox equilibrium and in the induction of oxidative stress. As a reaction, together with superoxide ( $O_2^{2-}$ ), NO leads to the formation of peroxynitrite in the cell and the induction of counter-effects, for example a loss in sensitivity to nitro-induced vascular dilation as well as the activation of mechanisms increasing vascular contraction. The nitroglycerin-induced oxidative stress is thus closely linked to the effect of nitrate tolerance observed after administration of nitroglycerin (Daiber et al. 2005; Münzel et al. 2005; Sarr et al. 2005). The intracellular release of NO is at the same time held responsible for the potential mutagenic properties of glycerine trinitrate in the repair-deficient strain *Salmonella typhimurium* TA1535 (single base exchange, C→T-transitions) and of hypoxanthine-guanine phosphoribosyl transferase (hprt) mutations in murine cell lines (Birnboim and Privora 2000; Margos et al. 1993; Sandhu and Birnboim 1997).

## 12 External and Internal Exposure and Effects

In addition to the procedure for detecting nitroglycerin and its dinitro metabolites (1,2-glycerine dinitrate and 1,3-glycerine dinitrate) in plasma described above (Carlin et al. 1990; see Documentation 1996, translated), methods for the determination of 1,2-glycerine dinitrate and 1,3-glycerine dinitrate in urine (Akrill and Cocker 2002) as well as 3-nitrotyrosine in urine (Tsikas et al. 2005) and plasma in humans (Söderling et al. 2003; Tsikas and Caidahl 2005) have also been described in the literature in the meantime. The determination of 1,2-glycerine dinitrate and 1,3-glycerine dinitrate in urine (total glycerine dinitrate) was applied in biological monitoring at two workplaces producing explosives and one workplace handling nitroglycerin in the pharmaceutical industry (Akrill et al. 2002). The concentrations determined in these cases were between 0 and 18.0  $\mu\text{mol/mol}$  creatinine (0–28.9  $\mu\text{g/g}$  creatinine) for total glycerine dinitrate in the explosives workers, and between 0 and 0.9  $\mu\text{mol/mol}$  creatinine (0–1.5  $\mu\text{g/g}$  creatinine) in the pharmaceutical workers. In spite of the potentially available methods to detect total glycerine dinitrate in urine and

plasma as well as 3-nitrotyrosine in the urine of workers exposed to nitroglycerin, no studies on the relationship between external (nitroglycerin in the air at the workplace) and internal exposure are available. There are also no studies available for the relationship between exposure and effect parameters.

## 13 Evaluation

Owing to the classification of glycerine trinitrate in carcinogen category 3 B, the BAT value has been withdrawn.

**From the studies available to date, there is no possibility to derive a “Biologischer Leitwert” (BLW) for nitroglycerin.**

Sampling time shall be at the end of exposure or end of shift.

The production of nitroglycerin in the pharmaceutical industry, its use in commercial explosives production and its absorption at the workplace being mainly through the skin, as well as the fact that no organic nitrates occur naturally in the environment, make it highly desirable for the future to obtain the relevant data necessary to derive a BLW.

## 14 References

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