The MAK Collection for Occupational Health and Safety

Naled

MAK Value Documentation, addendum – Translation of the German version from 2018

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Keywords: naled; MAK value; maximum workplace concentration; peak limitation; developmental toxicity; increased respiratory volume

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Naled / (1,2-Dibromo-2,2-dichloroethyl) dimethyl phosphate

MAK value documentation

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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 work place (MAK value) and the Pregnancy Risk Group of naled [300-76-5].
Naled is a cholinesterase inhibitor. In an 13-week study in rats at 1 mg/m3 there was a 18% inhibition of the cholinesterase activity in erythrocytes. The calculated lower 95% confidence limit of the benchmark dose (BMDL) for a 30% inhibition, which is regarded as not adverse, was 2 mg/m^3. A MAK value of 1 mg/m3 was established for the inhalable fraction. It is now lowered to 0.5 mg/m^3 taking into account the increased respiratory volume at the workplace (see List of MAK and BAT Values, Sections I b and I c). Since a systemic effect is the critical effect, Peak Limitation Category II is retained and the default excursion factor of 2 confirmed.
For rats, the NOAEL for developmental toxicity was 8 mg/kg body weight and day. Naled was assigned to Pregnancy Risk Group C because the difference between the MAK value and the NOAEL scaled to a concentration in the workplace air was sufficient. There are no new data on developmental toxicity. This classification is retained since now the difference to the MAK value is twice as high.

Keywords

Naled; (1,2-dibromo-2,2-dichloroethyl) dimethyl phosphate; peak limitation; prenatal toxicity; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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Naled

[300-76-5]

Supplement 2018

MAK value (2017)	**0.5 mg/m³ I (inhalable fraction)**
Peak limitation (2002)	**Category II, excursion factor 2**
Absorption through the skin (2006)	**H**
Sensitization (2006)	**Sh**
Carcinogenicity	**–**
Prenatal toxicity (2006)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value (1985)	**reduction of the cholinesterase activity to 70% of the reference value in erythrocytes**

In 2016, the Commission began using a revised approach for assessing substances with a MAK value based on systemic effects and derived from inhalation studies in animals or studies with volunteers at rest; this new approach takes into account that the respiratory volume at the workplace is higher than under experimental conditions. However, this does not apply to gases or vapours with a blood:air partition coefficient < 5 (see List of MAK and BAT Values, Sections I b and I c). As naled was investigated as an aerosol, the increased respiratory volume needs to be taken into account. This supplement evaluates whether the MAK value and the Pregnancy Risk Group for naled need to be re-assessed as a result of the higher respiratory volume at the workplace.

Manifesto (MAK value/classification)

Naled is a direct inhibitor of cholinesterase activity both in humans and in animals.

MAK value and peak limitation. In a 13-week inhalation study in rats, exposure to naled at a concentration of 1 mg/m³ led to inhibition of the cholinesterase activity in plasma and in erythrocytes by 16% and 18%, respectively, but did not inhibit the cholinesterase activity in the brain. The BAT value for acetylcholinesterase inhib-

itors is based on a 30% inhibition of cholinesterase activity in erythrocytes. Given the BAT value for cholinesterase inhibitors and the fact that adverse effects are not expected at 30% inhibition of cholinesterase activity, a MAK value of 1 mg/m³ has been established (documentation "Naled" 2007, available in German only).

For a more precise determination of the NAEC (no adverse effect concentration), the data from the 13-week study were used to carry out a benchmark dose calculation for 30% and 20% inhibition of the cholinesterase activity in erythrocytes and in the brain, respectively. The level of cholinesterase inhibition that is considered tolerable for the brain is lower because the inhibition of cholinesterase activity in the brain is toxicologically more relevant than that in erythrocytes. For both effects, the lower 95% confidence limit of the benchmark dose (BMDL) was about 2 mg/m³ and the inhibition of acetylcholinesterase activity did not increase with an increase in the duration of exposure. The values for cholinesterase inhibition in erythrocytes were calculated separately for males and females; half of the animals of each sex (n = 6) were examined on day 90, the other half on day 91.

Acetylcholinesterase inhibition in erythrocytes, benchmark response: 70% of the control activity (Figures 1–4):

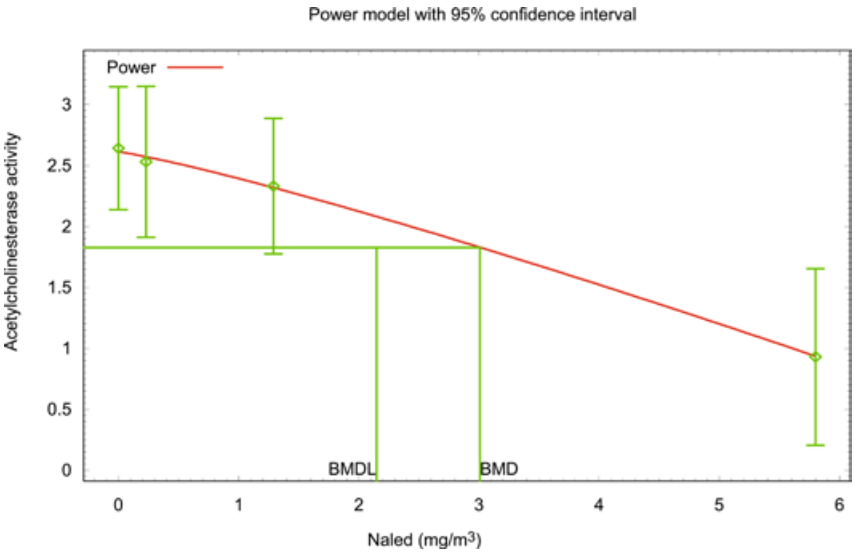

Figure 1 Male animals, day 90, BMDL: 2.15 mg/m³

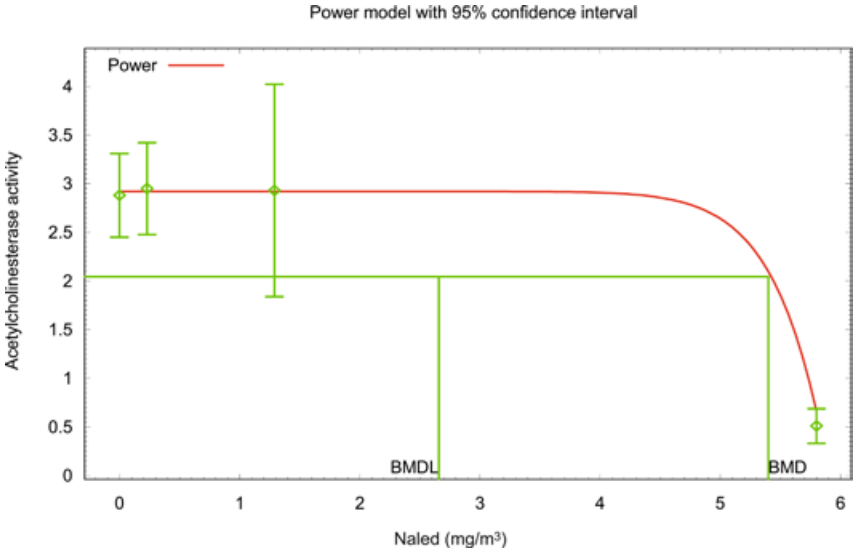

Figure 2 Male animals, day 91, BMDL: 2.65 mg/m³

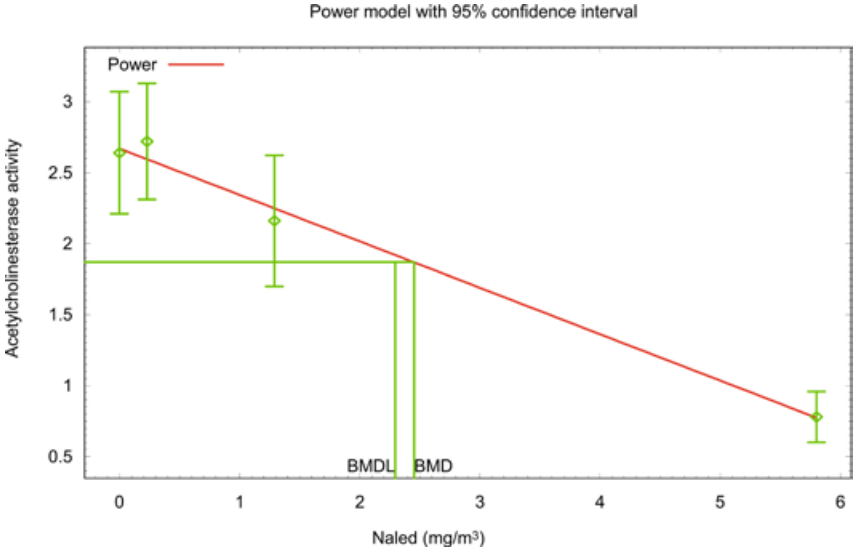

Figure 3 Female animals, day 90, BMDL: 2.3 mg/m³

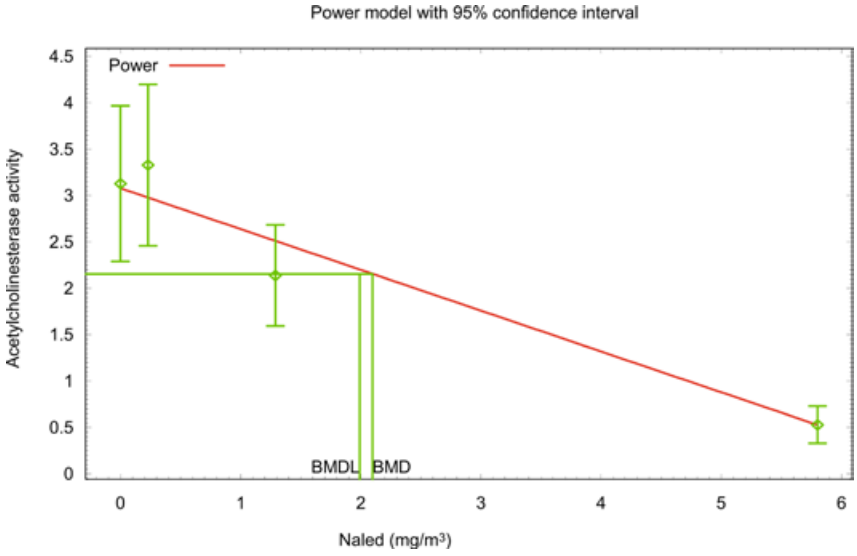

Figure 4 Female animals, day 91, BMDL: 2.0 mg/m³

Acetylcholinesterase inhibition in the brain, benchmark response: 80% of the control activity (Figures 5 and 6):

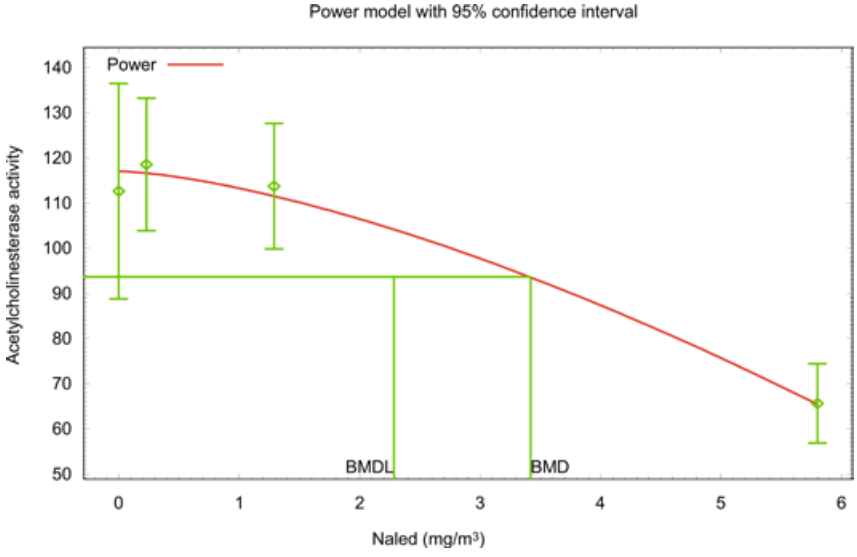

Figure 5 Male animals, BMDL: 2.3 mg/m³

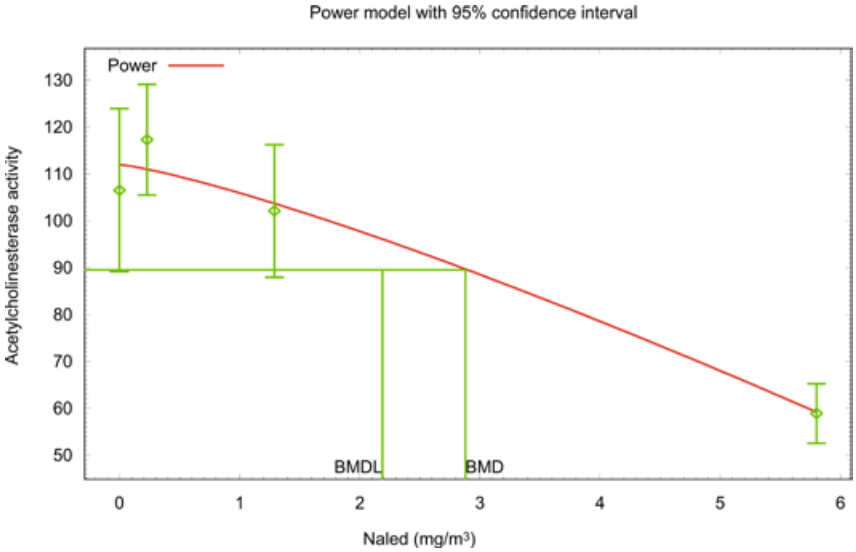

Figure 6 Female animals, BMDL: 2.2 mg/m³

There are no studies available for the interspecies and intraspecies variability of acetylcholinesterase inhibition after exposure to naled. The inhibition of plasma butylcholinesterase activity in dogs and humans was investigated after exposure to chlorpyrifos. The study found that the dose-response relationship is largely identical in humans and dogs and intraspecies variability is slight (Zhao et al. 2006). Therefore, it can be concluded that the standard margin (1:2) is sufficient for the extrapolation of the data from animal studies to humans also in the case of naled.

On the basis of the BMDL of 2 mg/m³, both for the inhibition of cholinesterase in erythrocytes and in the brain of exposed rats, and after extrapolation of the data from animal studies to humans (1:2) and taking into consideration the higher respiratory volume at the workplace in comparison with test animals, the MAK value has been lowered to 0.5 mg/m³ I.

As the primary effect of naled is systemic and there are no half-life data available, Peak Limitation Category II with an excursion factor of 2 has been retained.

Prenatal toxicity. On the basis of the adequate 23-fold margin between the concentration of the substance in air calculated using the NOAEL for developmental toxicity of 8 mg/kg body weight and day and the MAK value of 1 mg/m³ I and the absence of any greater sensitivity in the offspring regarding cholinesterase inhibition, Pregnancy Risk Group C was confirmed for naled in 2011 (supplement "Naled" 2012, available in German only). Lowering the MAK value to 0.5 mg/m³ I to account for the higher respiratory volume (1:2) doubles the margin to the MAK value; Pregnancy Risk Group C has therefore been retained.

References

Zhao Q, Dourson M, Gadagbui B (2006) A review of the reference dose for chlorpyrifos. Regul Toxicol Pharmacol 44: 111–124

completed December 7, 2016