
Executive summary

Background

At the request of the Minister of Social Affairs and Employment, the Dutch Expert Committee on Occupational Safety (DECOS), a committee of the Health Council of the Netherlands, recommends health-based occupational exposure limits for airborne substances to which people are exposed in the workplace. These recommendations serve as a basis in setting legally binding occupational exposure limits by the Minister. In this report, the Committee considers the implications of exposure to endotoxins and recommends a health-based occupational exposure limit for these substances.

This report has been compiled in collaboration with the *Nordic Expert Group for criteria documentation of health risks from chemicals*. It updates an earlier Health Council report, published in 1998, which set out the Council's initial evaluation of the health implications of exposure to endotoxins. The present report consists of a brief summary of the earlier report, plus information gleaned from literature published since 1998. The committees' conclusions reflect the content of scientific publications that have appeared prior to January 2010.

Physical and chemical properties

Endotoxins are substances found in the outer membranes of gram-negative bacteria. They consist of proteins, lipids and lipopolysaccharides. Lipopolysaccha-

rides (LPSs) from gram-negative bacteria are hydrocarbons that are free of protein and other cell wall materials. They are responsible for most of the biological effects of bacterial endotoxins. LPSs are soluble in water. The LPS molecule is a stable combination of a lipid component and a polysaccharide component. It is the lipid component, known as 'lipid A', that is responsible for the toxicity of LPSs. The composition of lipid A is remarkably similar in a wide variety of species of bacteria. By contrast, the composition of the hydrophilic polysaccharide LPS component varies considerably.

The presence of endotoxins in ambient air is related to the presence of gram-negative bacteria or cell wall fragments from such bacteria in airborne organic dust particles. Such bacteria-containing particles originate mainly from animal faeces and contaminated plant material. Occupational exposure to endotoxins consequently occurs principally in the agricultural industry and related sectors.

Monitoring

There are no generally accepted standards for the air sampling and extraction procedures. For the determination of endotoxin concentrations in the air, the Committee recommends using the NEN-EN14031 method, with adjustments by Spaan *et al.* (2007).

Exposure limits

To date, no occupational exposure limits have been defined for airborne endotoxins, either in the Netherlands or elsewhere.

Kinetics and toxic effect mechanism

Endotoxins that enter the upper respiratory tract are expelled by means of mucociliary transportation. It is believed that endotoxins that penetrate further into the respiratory tract are rendered harmless by macrophages and polymorphonuclear leukocytes. The effects that these substances can have on lung function are in all probability induced by inflammatory responses in the lungs. The systemic effects that occur are attributable to cytokines that find their way into the blood; it is not thought that inhaled endotoxins themselves enter the bloodstream.

Effects

In humans, the inhalation of endotoxins may cause the following acute symptoms: dry cough, dyspnoea accompanied by diminished lung function, fever and general malaise. After several hours, the following symptoms may develop: bronchoconstriction, headache and aching joints. The acute effects have been observed in the context of research with volunteers and reported in the context of epidemiological research amongst occupationally exposed people. It has been demonstrated that, in asthma sufferers and people with inflammations of the nasal mucosa, exposure to LPSs can lead to bronchial obstruction, accompanied by increased reactivity. Epidemiological research has produced evidence to suggest that prolonged exposure to endotoxins may lead to chronic bronchitis and diminished lung function. It is highly likely that both the acute and the chronic effects are induced by inflammatory reactions in the lungs, in the context of which the macrophages in the alveoli play a key role.

No evidence of mutagenic, reproduction toxic or cardiovascular effects has been reported following exposure to endotoxins. The findings of research into the risk of cancer following exposure to endotoxins in the textiles industry suggest a negative relationship between lung cancer and endotoxin exposure. No convincing explanation for this relationship has been provided. Recent research results also suggest that exposure to endotoxins protects against the development of atopy and hay fever, which are less prevalent in children who grow up on farms (where exposure to endotoxins and other substances can occur). On the other hand, occupational exposure to endotoxins is a risk factor for the development of bronchial sensitivity and dyspnoea. Furthermore, asthma-related conditions are more common in endotoxin-exposed workers.

Evaluation and recommendations

Diminished lung function is regarded as the critical effect of both short and long-term inhalatory exposure to endotoxins. Changes in lung function are best measured by measuring the FEV₁ (forced expiratory volume in one second, i.e. the amount of air that can be forcibly exhaled in the space of a second). Divergence between the pre-exposure and post-exposure FEV₁ over a single day is indicative of acute effects, while change in the baseline FEV₁ or decline in the annual FEV₁ is indicative of chronic effects.

The exposure limit recommended by DECOS is based upon an acute study, in which healthy volunteers were exposed to endotoxins from cotton, a cross-sec-

tional study of the chronic effects on the lung function of animal feed mill workers and a five-year follow-up study of such workers.

On the basis of a study of the effects of six-hour exposure to endotoxins in volunteers, DECOS regards an exposure level of 90 EU/m³ as a NOEL (no observed effect level). DECOS regards the volunteers used in the study as a sensitive group, because they were selected on the basis of their sensitivity to endotoxins. Hence, DECOS does not believe that an extrapolation factor is necessary to take account of variations in individual sensitivity. On the basis of this study, DECOS' health-based recommended exposure limit is 90 EU/m³ (eight-hour time-weighted average).

DECOS has additionally considered whether the health-based recommended exposure limit referred to above affords adequate protection against the effects of prolonged exposure to endotoxins. According to the findings of the cross-sectional study of animal feed mill workers, exposure to 90 EU/m³ for forty years would result in an additional reduction of 120 ml in the average worker's FEV₁. A study of cotton workers indicated a less pronounced effect on lung function (smaller FEV₁ reduction). DECOS does not consider an additional FEV₁ reduction of 120 ml to constitute an adverse effect; a reduction of this size is not generally associated with other health effects (e.g. cardiovascular effects).

Hence, DECOS takes the view that a health-based recommended exposure limit of 90 EU/m³ (eight-hour time-weighted average) affords adequate protection against the effects of both acute and chronic exposure to endotoxins.

DECOS has also established that, subject to certain modifications, the test methods currently described in NEN-EN are more sensitive than the exposure measurement methods used in the past. Nevertheless, DECOS does not believe it is possible to specify a standard conversion factor that is applicable in all circumstances. Furthermore, in more recent studies, which used more recent methods to measure exposure, respiratory effects were observed in subjects who were exposed to concentrations higher than 100 EU/m³. DECOS does therefore not propose the use of a standard factor to correct for differences in the sensitivity of older and newer methods for measuring exposure.

Health-based recommended exposure limit

DECOS proposes a health-based recommended exposure limit (HBROEL) of 90 EU/m³ (eight-hour time-weighted average) for endotoxins in the workplace. Fur-

thermore, DECOS recommends using the method currently described in NEN-EN 14031, modified as suggested by Spaan *et al.* (2007), to measure exposure to endotoxins.