
Executive summary

1 Scope

At the request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands recommends health-based occupational exposure limits for the concentration of toxic substances in air at the workplace. These recommendations are made by the Council's Dutch Expert Committee on Occupational Standards (DECOS). They constitute the first step in a three-step procedure that leads to legally-binding limit values. Based on the consequences of occupational exposure to n-, iso-, sec-, and tert-butyl acetate the DECOS recommends a health-based occupational exposure limit.

The present report on n-, iso-, sec-, and tert-butyl acetate was prepared in co-operation with the Swedish Criteria Group, which advises the Swedish government. The committees' conclusions are based on scientific publications prior to January 1997. Scientific publications between 1997 and 2000 were no reason for both committees to adjust their conclusions.

2 Physical and chemical properties

The butyl acetates are colourless, flammable liquids with a fruity odour. They are slightly soluble or insoluble in water, and soluble in ethanol and ether.

The butyl acetates occur in natural and food products, but are also produced chemically. The main use of butyl acetates is as solvents in paints and lacquers.

3 Monitoring

Methods for the determination of the butyl acetates have been described by the National Institute for Occupational Safety and Health (NIOSH, USA), and are based on gaschromatographic (GC-FID) analysis.

Methods for personal air sampling using diffusive samplers have also been reported.

4 Limit values

In The Netherlands and the UK, the current occupational exposure limits are 700 and 710 mg/m³ (150 ppm) for n- and isobutyl acetate, respectively, and 950 mg/m³ (200 ppm) for both sec- and tert-butyl acetate. In the USA, the American Conference of Governmental Industrial Hygienists (ACGIH) has recommended threshold limit values of 713 mg/m³ (150 ppm) for n- butyl acetate, 152 mg/m³ (50 ppm) for iso- butyl acetate, and 303 mg/m³ (100 ppm) for both sec- and tert-butyl acetate. Scandinavian countries and Germany have one occupational exposure limit for all isomers varying from 355 mg/m³ (75 ppm) in Norway to 950 mg/m³ (200 ppm) in Germany.

5 Kinetics

The committees could not retrieve quantitative data on the absorption of butyl acetate isomers.

Butyl acetates are quickly metabolised in the body in acetic acid and their respective butanols. The half-life time for n-butyl acetate is less than 1 minute and for n-butanol a few minutes in rats, whereas the half-life time for tert-butyl acetate is much longer (up to 70 min). When added to blood samples from men and rats, half-life times measured were respectively 4 and 12 minutes for n-butyl acetate and respectively 300 and 270 minutes for tert-butyl acetate.

When rats were exposed to 34,000 mg/m³ (7,000 ppm; 1 hour) or to 4,800 mg/m³ (1,000 ppm; 5 hours) n-butyl acetate via a tracheal canula, a steady-state blood level of the compound and its metabolite (n-butanol) was rapidly reached. Similar experiments in rats with tert-butyl acetate showed continuously increasing blood levels of both the parent compound and the metabolite (tert-butanol). After ending exposure, tert-butyl acetate was eliminated in two phases ($t_{1/2}$ 5 and 70 min), while tert-butanol levels continued to increase or remained constant depending on exposure conditions.

Acetic acid is oxidised via the citric acid cycle to carbon dioxide and water. Generally, butanols are readily metabolised by alcohol and aldehyde dehydrogenases

to their respective aldehydes or ketones, their acids, and finally to carbon dioxide. Only tert-butanol is very slowly metabolised by dehydrogenases. Ethanol inhibits or retards butyl acetate metabolism.

The parent compounds and their metabolites were identified in urine and exhaled breath. However, no validated methods for biological monitoring are available.

6 Effects

Studies, in which volunteers were exposed for four hours to concentrations of 700 mg/m³ (≈150 ppm), indicate that n-butyl acetate is only minimally irritating to humans. It may occasionally cause allergic contact dermatitis. Isobutyl acetate probably has no sensitising properties. In animal experiments, n-butyl acetate had no skin irritant properties and did not act as a sensitiser. n-Butyl acetate appeared to be at most slightly irritating to the eyes of rabbits.

The committees could not find any case-control or epidemiological studies in which systemic effects could be attributed to exposure to butyl acetates.

Mortality data from animal experiments with acute inhalatory exposure to n-butyl acetate are conflicting. However, the committees consider n-butyl acetate, as well as isobutyl acetate, to be of low toxicity via the inhalatory, oral, and dermal route. Acute exposure to non-lethal n-butyl acetate levels of 3,700-7,300 mg/m³ (800-1,575 ppm) for four to six hours resulted in transient effects on the eyes and behaviour.

Subchronic exposure to up to 14,520 mg/m³ (3,000 ppm) n-butyl acetate for 13 weeks (6 hrs/day, 5 days/week) did not induce persistent neurotoxic effects in rats. Exposure to 7,260 mg/m³ (1,500 ppm) caused growth retardation, minimal reduced activity on the nervous system, and minimal to mild olfactory epithelial necrosis. No effects were observed at 2,662 mg/m³ (550 ppm).

The committees did not find long-term and carcinogenicity studies concerning butyl acetates. n-Butyl acetate did not induce mutations in bacteria and yeast nor showed clastogenic effects in Chinese hamster fibroblasts. With respect to the other isomers, the committees did not find data on genotoxicity.

In a study, in which pregnant female rats and rabbits were exposed to 7,260 mg/m³ (1,500 ppm) n-butyl acetate according to a number of exposure schemes, minor developmental effects in the fetuses and minor reproductive effects in mothers were observed, in both species. Since only one concentration was tested, the committees consider these results to be inconclusive with respect to developmental toxicity induced by n-butyl acetate.

7 Evaluation and advice

DECOS takes the subchronic rat study as a starting point in deriving a health-based recommended occupational exposure limit (HBR-OEL). In this study, acute transient effects on the nervous system, effects on body weight and on the olfactory epithelium were found following exposure to n-butyl acetate concentrations of 7,260 mg/m³ (1,500 ppm) for 13 weeks. No effects were observed at 2,662 mg/m³ (550 ppm), which is considered to be a NOAEL.

For the assessment of a HBR-OEL, DECOS has taken the following considerations into account: a factor of 3 for intraspecies variation, a factor of 3 for interspecies variation, and a factor of 2 for the extrapolation from a subchronic to chronic situation. Application of this overall uncertainty factor of 18 and assuming that the dose inhaled by rats is equivalent to the dose inhaled by humans, a HBR-OEL of 150 mg/m³ (≈30 ppm) for n-butyl acetate is recommended. This level is considered to protect workers against systemic effects and irritation.

DECOS considers the available data to be insufficient to recommend an HBR-OEL for iso-, sec- and tert-butyl acetates. As an additional consideration, DECOS assumes that iso- and sec-butyl acetate show comparable toxicity as n-butyl acetate. Tert-butyl acetate is, however, broken down more slowly, which may lead to higher concentrations in the body and, therefore, may result in more hazardous effects.

8 Health-based recommended occupational exposure limit

The Dutch Expert Committee on Occupational Standards recommends a health-based occupational exposure limit for n-butyl acetate of 150 mg/m³, as an eight-hour time weighted average.

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