Executive summary

Scope

At the request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands sets health-based recommended occupational exposure limits for chemicals 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 which leads to legally-binding limit values.

In the present report the committee discusses the consequences of occupational exposure to ethanol. The committee's conclusions are based on scientific publications prior to January 2006.

Occurrence, physical and chemical properties

Ethanol (CAS registry number 64-17-5) is a clear, colourless liquid with a pleasant characteristic odour. The odour threshold is about 95 mg/m^3. Ethanol is miscible with water and organic solvents. It has a high vapour pressure.

Ethanol is currently one of the largest-volume organic chemicals utilised in industrial and consumer products, primarily as an intermediate in the production of other chemicals (ie acetaldehyde, ethylacrylate and ethylchloride) and as a solvent. In addition, ethanol is is present in alcoholic beverages.

Besides, ethanol is present endogenously in humans, which leads to a blood alcohol concentration of 0.27 ($^{+}/_{-}$ 0.17) mg/l.

Monitoring

Methods for the determination of ethanol in air have been described by NIOSH* and OSHA**, and are based on GC-FID.

A method for analysing ethanol in blood by GC-FID has been described by NIOSH. In addition, ethanol can be determined in human breath samples as well.

Limit values

The current occupational exposure limit in the Netherlands and Sweden is 1000 mg/m^3 (500 ppm), whereas in Germany the limit is 960 mg/m^3 (500 ppm). In the UK, Denmark, and the USA the occupational exposure limit is about 1900 mg/m^3 (1000 ppm).

Short-term exposure limits have been set in Germany at 4800 mg/m^3 (2500 ppm; 30-min value) and Sweden 1900 mg/m^3 (1000 ppm; 15-min value). In Germany, ethanol has been assigned in Category 5 for carcinogenic effects (*i.e.* the genotoxic carcinogenic potential is so low that the MAK*** value (500 ppm) will not represent an unacceptable risk level), in Group C for genotoxic effects (*i.e.* the substance is shown to be genotoxic in studies performed in mammals), and Group 2 for reproduction toxic effects (*i.e.* no need for concern at exposure levels at/lower than the MAK level).****

Kinetics

Inhaled ethanol is absorbed by the lungs for about 60%. Exposure to 1900 mg/m^3 by inhalation for 4 hours, results in blood concentrations of approximately 2 mg ethanol/l (at rest). As a worst case estimate, a penetration rate of 0.7 mg/cm^2/h can be used to calculate the internal dose after dermal exposure.

Orally consumed ethanol is efficiently absorbed (>90%). The blood ethanol concentration is influenced by a number of factors of which food intake and gender are the most important. Consuming two alcoholic beverages (~20 gram etha-

* National Institute for Occupational Safety and Health
** Occupational Safety and Health Administration
*** Gas chromatography with flame ionization detector
**** Maximale Arbeidsplatzkonzentration

nol) results in a maximal blood concentration of approximately 300 mg ethanol/l; the maximal concentration in blood is reached within a hour, but the concentration is decreased rapidly and the blood ethanol concentration has reached endogenous levels after several hours.

Inhalatory exposure to 1900 mg/m^3 ethanol (corresponding to 11 gram ethanol per day[*]) results in a maximal ethanol concentration in blood which is 10 to 100 times lower than the maximal blood ethanol concentration after drinking one alcoholic beverage (approximately 11 gram ethanol). Most effects are related to the maximal ethanolconcentration in blood. In that case DECOS is of the opinion that the health risks after oral exposure to ethanol will overestimate the risk of inhalatory exposure to comparable levels of ethanol. For the genotoxic carcinogenic effects, however, the total internal exposure[**] is the relevant exposure estimate. The total internal exposure (or AUC) after drinking one glass of beer is comparable with the AUC after eight hour exposure to 1900 mg/m^3 ethanol.

The human liver is the main site of ethanol oxidation. Ethanol degradation occurs in two steps, first the formation of acetaldehyde with a subsequent formation of acetic acid.

Ethanol and acetaldehyde are oxidized by a wide range of enzymes and each of these enzymes may occur in different isoenzymes. Overall, ethanol and acetaldehyde are efficiently metabolized in Caucasians. A healthy subject is considered to metabolize between 6 and 9 g ethanol per hour. The significance of the first-pass metabolism is most likely limited.

Effects

Human data

Short-term inhalatory exposure to ethanol for one hour will not cause irritation or other effects below concentrations of 1900 mg/m^3 (1000 ppm). Concentrations higher than 3000 mg/m^3 might result in transient cough, dry throat and tickling of the nose. Levels over 40,000 mg/m^3 (21,000 ppm) are suffocating.

In concentrated form, ethanol is very irritating to the eyes. Non-occlusive, repeated dermal exposure to 95% ethanol does not cause skin irritation, but may

* Assuming that 10 m^3 air is inhaled per 8-hour working day and a lung retention of 60 percent.

** the total internal exposure is the product of the bloodalcoholconcentration (BAC) times the period present in the body, (*i.e.* the Area Under the Curve AUC).

cause dry skin due to defatting. Occlusive contact, in contrast, may induce erythema and induration (thickening/hardening of the skin). It may also induce irritant contact dermatitis and non-immunologic urticaria.

Most human data on the effects of long term exposure to ethanol concern the consumption of alcoholic beverages. Several epidemiological studies reported that the dose-effect curve for ethanol and overall mortality appears to be U- or J-shaped; beneficial effects due to the consumption of low levels of ethanol are observed, like a reduced risk of coronary heart disease.

The most critical non-carcinogenic effects in humans appear to be liver cirrhosis and effects on the development of offspring and fertility. Epidemiological studies suggest that consumption levels below 10-12 grams of ethanol per day, will probably not cause liver cirrhosis. However, the Committee on Alcohol consumption and reproduction concluded that at these consumption levels effects on fertility and development have been reported. Even long term oral exposure to levels of 1-12 gram ethanol per day might result in effects on the development (like increased incidence of spontaneous abortion, foetal death, pre-term delivery and decreased length of gestation) and fertility, according to the Committee on Alcohol consumption and reproduction.

With respect to carcinogenicity the most relevant types of cancers appear to be breast and colorectal cancer. All the available data concern the association of the consumption of alcoholic beverages and these cancer types. Pooled studies or meta-analyses can be used to estimate the cancer risk in a quantitative way. Adequate studies are only available for breast cancer, resulting in a RR of 1.1 per each 10 grams of ethanol per day consumed. Such studies are not (yet) available for colorectal cancer.

Animal studies

The lowest lethal dose by inhalation is 55000 mg/m^3 in mice (7 hrs exposure) and 25000 mg/m^3 in rats (22 hrs). In one study, behavioural depression occurred in rats inhaling 385 mg/m^3 for 45 minutes.

The lowest reported lethal dermal dose for rabbits is 20 g/kg body weight. In rabbits acute occluded exposure to 95% ethanol caused mild irritation. 96% ethanol is mildly irritating to the eyes of the rabbit.

Available animal studies with repeated inhalatory exposure were only limited in design. From the available data it may be concluded that at high concentrations

(*i.e.* resulting in blood alcohol concentrations > 1700 mg/l), only slight toxicity was observed.

After repeated oral administration to animals, ethanol appears to affect all organs with the liver as main target organ. Increased hepatic concentrations of fatty acid and triglycerids were observed after a 30-day administration of a liquid diet containing ethanol.

No long-term inhalation carcinogenicity studies in animals have been found. Because in the long-term oral exposure studies in rats and mice the MTD was not reached, these studies are of limited value to evaluate the carcinogenic potential of ethanol.

There is no convincing evidence that ethanol is genotoxic. In a limited number of *in vitro* as well as *in vivo* genotoxicity tests, however, ethanol gave positive results. Because a role for one of the major metabolites of ethanol, *i.e.* acetaldehyde (a known genotoxic carcinogen) can not be excluded, the committee on the Evaluation of the carcinogenicity of chemical substances of the Health Council concluded that ethanol should be considered a genotoxic carcinogen.

According to the Committee on Alcohol consumption and reproduction of the Health Council, exposure of rats by inhalation to concentrations upto 30,400 mg/m^3 ethanol, resulting in blood alcohol levels of about 500 mg/l, did not cause changes in male fertility. Oral intake of ethanol (ca. 10 g ethanol/kg bw/day or higher), in contrast, resulted in decreased reproductive performance, decreased serum testosterone levels, decreased testicular weight and testicular atrophy in rats. An oral study in male mice at levels up to 0.6 g ethanol/kg bw/day) did not influence mating behaviour and pregnancy success. Other studies into the fertility effects of ethanol have shown that oral intake of high ethanol doses (> 2 g/kg bw/day) before and during pregnancy had no influence on mating behaviour of females.

In addition, the Committee on Alcohol consumption and reproduction concluded that exposure of female rats by inhalation during pregnancy to concentrations upto 38,000 mg/m^3 ethanol, resulting in blood alcohol levels up to about 2500 mg/l, did not cause developmental toxicity although maternal toxicity was observed. Exposure of male rats to concentrations up to 30,400 mg/m^3 did not show changes in paternal offspring. Teratogenic effects, however, were observed in rats and mice following oral intake of large amounts of ethanol during pregnancy, resulting in blood alcohol levels of about 2000-6000 mg/l. No teratogenic effects were observed in mice after oral intake of ethanol resulting in blood alcohol levels of about 200 mg/l.

Health based occupational exposure limit

In this report, DECOS evaluates the effects of occupational exposure to ethanol. Although the committee acknowledges the fact that drinking alcoholic beverages might be a more important source of ethanol exposure, this exposure is not taken into consideration for the assessment of the effects after occupational exposure.

Recommendation of an HBROEL, 15-min TWA (STEL)

Although the human data are limited, the committee is of the opinion that inhalatory exposure to 1900 mg/m^3 ethanol for one hour will probably not cause local or systemic effects in man. Exposure to higher concentrations will result transient cough, dry throat and tickling in the nose. In conclusion, DECOS is of the opinion that exposure to 1900 mg/m^3 for 15 minutes will be low enough to protect workers for effects after short term exposure. DECOS therefore recommends a short term exposure limit of 1900 mg/m^3.

Recommendation of an HBC-OCRV

The committee considers the development of breast cancer after exposure to ethanol as the critical effect. Based on the advice of the Committee Evaluation of Carcinogenic substances that ethanol is known to be carcinogenic to humans (comparable to EU category 1) and that a genotoxic mechanism cannot be excluded, DECOS calculates occupational cancer risk values for ethanol.

From the available meta-analysis and pooled studies, the committee concluded that drinking of one glass of alcoholic beverage (~10 gram ethanol) per day would increase the risk for breast cancer with 7-10%. From a RR of 1.1, DECOS calculates the following HBR-OCRVs:

- 4×10^{-5} for 40 years of occupational exposure to 13 mg/m^3
- 4×10^{-3} for 40 years of occupational exposure to 1300 mg/m^3.

However, ethanol is present in the human body of non-drinkers as well, which results in a total internal ethanol dose for lifetime (80 years) of 21.6 (±13.6) (mg/l)×year. On the other hand, occupational ethanol exposure to 13 mg/m^3 (corresponding to a extra cancer risk of 4×10^{-5}) gives an internal dose of approximately 0.2 (mg/l)×year. DECOS is of the opinion that an internal dose of 0.2 (mg/l)×year as a result of occupational exposure to 13 mg/m^3 is negligible as compared to the internal dose due to the endogenous ethanol concentration in

blood ((22 mg/l)×year). Consequently, the committee considers the relevance of the calculation of an HBC-OCRV corresponding to a risk of 4×10^{-5} doubtful.

Therefore, DECOS estimates the HBC-OCRV of 1300 mg/m^3 corresponding to an additional breast cancer risk of 4×10^{-3}.

Subsequently, the committee evaluated whether this HBC-OCRV of 1300 mg/m^3 is low enough to protect workers against other toxic effects. According to the Committee on Alcohol consumption and reproduction, first signs of developmental toxicity and effects on fertility manifest after drinking one alcoholic consumption per day or less (<10 gram ethanol per day). However, for these effects DECOS is of the opinion that the blood alcohol concentration (BAC) is the relevant exposure parameter. Considering the fact that the maximal alcohol concentration in blood after one (oral) drink is approximately 10-100 times higher than the ethanol concentration in blood after inhalatory exposure to1300 mg/m^3, the committee is of the opinion that a HBC-OCRV of 1300 mg/m^3 is low enough to protect against these effects. Other toxic effect manifest after exposure to higher exposure levels.

Skinnotation

At request of the minister of Social Affairs and Employment, the committee judged wheteher for ethanol is skin notation is needed. As dermal exposure can substantially contribute to the body burden of ethanol, DECOS recommends a skin notation.

Health based calculated occupational cancer risk value

DECOS calculates an HBC-OCRV of 1300 mg/m^3, resulting in a breast cancer risk of 4 additional death cases per 1000 ($4*10^{-3}$) deaths for 40 years.

In addition, DECOS recommends a short term exposure limit (STEL) of 1900 mg/m^3 twa 15 minutes and a skin notation.