Recommendation from the Scientific Committee on

Occupational Exposure Limits

for 2-Ethoxyethanol and 2-Ethoxyethyl acetate

8-hour TWA:	2 ppm
	8 mg 2-ethoxyethanol/m^3
	11 mg 2-ethoxyethyl acetate/m^3
STEL (15 mins):	--
Additional classification:	"skin"
BLV:	50 mg 2-ethoxyacetic acid/l urine
	(40 mg 2-ethoxyacetic acid/g creatinine)

SUBSTANCES

2-Ethoxyethanol

Synonyms : Ethyl glycol
             Ethylene glycol monoethyl ether
EINECS : 203-804-1
CAS : 110-80-5
Mwt : 90.1
Conversion factor (20°C, 101 kPa): 1 ppm = 3.68 mg/m3; 1 mg/m3 = 0.272 ppm
EU-Classification: R10   Flammable.
              Repr. Cat. 2; R60-61   May impair fertility; May cause harm to the unborn child.
              Xn; R20/21/22   Harmful by inhalation, in contact with skin and if swallowed.

2-Ethoxyethyl acetate

Synonyms : Ethylene glycol ethyl ether acetate
EINECS : 203-839-2
CAS : 111-15-9
Mwt : 132.2
Conversion factor (20°C, 101 kPa): 1 ppm = 5.494 mg/m^3; 1 mg/m^3 = 0.182 ppm
EU-Classification:
              Repr. Cat. 2; R60-61   May impair fertility; May cause harm to the unborn child.
               Xn; R20/21/22   Harmful by inhalation, in contact with skin and if swallowed.

It is known from in vitro experiments and from human data that 2-ethoxyethyl acetate is rapidly deacetylated by esterases to 2-ethoxyethanol. The two substances have been found to be of similar toxicity in animal experiments. Numerous in vitro and in vivo studies have shown the toxicity of the two substances to be caused by the same metabolite, 2-ethoxyacetic acid (Henschler and Lehnert 1994). Both substances are therefore evaluated together in this document.

OCCURRENCE AND USE

2-Ethoxyethanol is produced by reaction of ethylene oxide with ethanol under increased pressure and increased temperature in the presence of an alkaline catalyst and subsequent purification by distillation. The compound is used as solvent in numerous products of the chemical industry, mainly of the varnish industry, in particular for packaging varnishes (varnishes for metals, e.g. for the inner coating of cans) and for coil-coating (stoving varnishes for metal-band varnishes). Also in the printing-dye sector and in the plastics industry, it can be assumed that these compounds are continuing to be used, for example, as solvents for resins and as plastisols. 2-Ethoxyethanol serves as solvent for varnishes, waxes, artificial resins and alkyde resins. After the sperm-damaging properties of these substances were publicized, a substitution process ensued through which 2-ethoxyethanol, as varnish solvent, was completely supplanted from the consumption sector and mostly displaced from the industrial field (BUA 1995).

2-Ethoxyethyl acetate is produced via an esterification of ethoxyethanol and acetic acid, acetic acid anhydride, or acetic chloride. It is mainly used in automobile lacquers to retard evaporation and impart high gloss. It is used as a solvent for oils, resins, and nitrocellulose. It retards 'blushing' in lacquers and varnish removers. It is used in wood stains, leather and cosmetic ingredients. It is also used in the semiconductor industry (Australian Government 2005).

HEALTH EFFECTS

Toxicokinetics

Evidence from studies in experimental animals and in humans indicates that 2-ethoxyethanol is rapidly absorbed via the respiratory tract, the skin and the gastrointestinal tract. In humans under sedentary conditions, 64% of the inhaled 2-ethoxyethanol is taken up by the lung.

In five volunteers dermally exposed to vaporised and liquid 2-ethoxyethanol, mean absorption rate of 2-ethoxyethanol vapour was 19±6 cm/h and of liquid 2-ethoxyethanol 0.7±0.3 mg/cm^2·h. Vaporised and liquid 2-ethoxyethanol are therefore readily absorbed through the skin. In the combined inhalatory and dermal exposure when whole body surface is exposed to vapour, the uptake through the skin is estimated to be 42% of the total uptake 2-ethoxyethanol. Dermal uptake resulting from skin contact of both hands and forearms (about 2000 cm^2) with liquid 2-ethoxyethanol for 60 minutes would exceed inhalatory uptake of the eight hour occupational exposure limit (about 5 ppm) by 20 times (Kezic et al. 1997).

2-Ethoxyethyl acetate is metabolized to 2-ethoxyethanol. The main metabolic pathway for 2-ethoxyethanol is oxidation to 2-ethoxyacetic acid, which is further metabolised to its glycine conjugate N-ethoxyacetylglycine. Numerous in vitro and in vivo studies have

shown the toxicity of 2-ethoxyethanol to be caused by the metabolite 2-ethoxyacetic acid (Henschler and Lehnert 1994) which is also the critical metabolite for 2-ethoxyethyl acetate. Ethanol inhibits the 2-ethoxyethanol degradation.

2-Ethoxyethanol is excreted primarily in the urine, with a very small percentage of the dose exhaled via the lung as CO_2. In sedentary human subjects, 23-35 % of the absorbed 2-ethoxyethanol was excreted in the urine as 2-ethoxyacetic acid. At all times after exposure, the amount of 2-ethoxyacetic acid eliminated was proportional to the 2-ethoxyethanol dose. 2-Ethoxyacetic acid is excreted in free form in the urine. According to results on individuals occupationally exposed to 2-ethoxyethanol, the half-life for the elimination of 2-ethoxyacetic acid lies between 50-60 hours; in volunteers with 4 hour exposure half-life was published with 21-24 hours. For rats half-lives of ca. 7 hours were determined (BUA 1995).

Physiologically based pharmacokinetic (PBPK) models for 2-ethoxyethanol and 2-ethoxyethyl acetate in pregnant rats and humans have been developed. PBPK models of Gargas and coworkers (Gargas et al. 2000) were used with data from developmental toxicity studies with pregnant rats (Doe 1984) and from volunteer studies (non-pregnant) with 4 hour exposure to 2-ethoxyethanol or 2-ethoxyethyl acetate (Groeseneken et al. 1986, a, b, 1987 a, b; see below). The models considered 5 compartments, rapid hydrolysis from 2-ethoxyethyl acetate to 2-ethoxyethanol, metabolism from 2-ethoxyethanol to 2-ethoxyacetic acid and its elimination in urine. Physiological parameters for an average pregnant woman were used to calculate human-equivalent NAEL (no adverse effect level) estimates, based on internal concentrations in rats exposed at previously determined NOELS for developmental toxicity (50 ppm). For both substances the NAEL was estimated to be 25 ppm. The authors proposed an 8-h OEL of 2 ppm by dividing the human-equivalent NAEL of 25 ppm by default uncertainty factors (2.5 for interspecies, 3.16 for interindividual variability and 1.8 for intraspecies pharmacokinetic differences) (Sweeney et al. 2001).

In a compartmental based toxicokinetic model, exposure of workers 8 hours/day, 5 days/week was simulated until steady-state was reached. Physical activity was set at 50 W for 12 hours (the 8 hours of work and the 4 following followed by a 12-hour rest period). This was achieved by modifying the value of some physiological parameters (cardiac output, alveolar ventilation, and organ blood flow) (no further details given). For an exposure level of 18 mg 2-Ethoxyethanol/m³ (about 5 ppm), a BEI (95% limit value) of 110 µmol/mmol creatinine (about 100 mg 2-ethoxyacetic acid/g creatinine or 120 mg/l urine, assuming 1,2 g creatinine/l urine) was calculated (Truchon et al. 2006).

Systemic toxicity from a single exposure

2-Ethoxyethanol exhibits low toxicity in animals (rats, mice, guinea pigs, rabbits) in acute toxicity studies after oral, intravenous, intraperitoneal, subcutaneous and dermal application and inhalative exposure. The intoxication symptoms observed were: dyspnoea, somnolence, ataxia, abdominal lateral position, convulsions, paresis and haematuria. Target sites of 2-ethoxyethanol induced acute toxicity include the haematopoietic system, liver, kidneys and spleen (ECETOC 1994).

A 44-year old woman accidentally drank ca. 40 ml 2-ethoxyethanol, whereby unconsciousness set in. Symptoms of intoxication occurred such as cyanosis, pulmonary oedema and chronic toxic-clonic convulsions as well as an acetone odour of the breath. The woman recovered to a wide extent after about 44 days (BUA 1995).

Irritancy

2-Ethoxyethanol was non-irritating to the skin of female rabbits (Jacobs et al. 1987) but moderately irritating to the eye of rabbits (BUA 1995).

No data on irritation in humans are available.

Sensitisation

In a maximization test with guinea pigs according to Magnusson and Kligman, 2-ethoxyethanol showed no sensitising potential (BUA 1995).

Effects of repeated exposure

In oral and inhalation subacute, subchronic and chronic studies in rats, mice, dogs and rabbits the target organs of 2-ethoxyethanol toxicity are mainly haematogenic and lymphatic organs, the germ epithelium of the testes as well as the kidney and the liver (ECETOC 2005).

In a 13-week inhalation study, rats and rabbits were exposed whole-body to 25, 100 or 400 ppm 2-ethoxyethanol for 6 hours per day. Both species exhibited an increased incidence of lacrimation and mucoid nasal discharge, but the response was not consistently dose-related. Rats showed no compound-related effects except for a decrease in relative pituitary weight for high-dose males and a decrease in absolute and relative spleen weight for all females with no pathological changes in these organs. In rabbits, the more sensitive species, mean body weights were decreased in low and high-dose, but not in mid-dose animals. In the high-dose group absolute and relative testicular weights were decreased and the seminiferous tubules showed minimal to slight focal degeneration (see "Fertility"). In this high-dose group haematocrit, haemoglobin concentration and erythrocyte count were also decreased in male and female rabbits. The NOAEL derived for rats was 400 ppm, the NOAEL for rabbits 100 ppm (Barbee et al. 1984).

Based on the results of a 13-week oral study via drinking water in mice, mice appear to be less sensitive than rats to 2-ethoxyethanol-induced toxic effects (NTP 1993). In this study based on effects on thymus, testes, prostate gland and blood, a NOAEL of 109 mg/kg body weight per day was determined for male rats. For female rats a LOAEL of 122 mg/kg body weight per day was determined. A NOAEL of 2003 mg/kg body weight and day was determined for male mice and 722 mg/kg body weight for females.

After long-term exposure to solvents (including ethyl and methyl glycol) slight changes in the differential blood count were determined in parquet-layers compared to unexposed individuals (Denkhaus et al. 1986).

Haematological effects were also described in another study in which anaemia and granulocytopenia were diagnosed respectively in 10% and 5% of the examined painters with exposure to glycol ether. The mean concentration of 2-ethoxyethanol was 2.6 ppm with a maximum of 21.5 ppm. These findings did not appear in the control group (Welch and Cullen 1988). Bone marrow hypoplasia was also observed in a survey of seven printers exposed to 2-ethoxyethanol and other substances (Cullen et al. 1983). The authors assume that air levels have been occasionally, perhaps often, higher than the concentrations reported and skin absorption occurred. As no biological monitoring was performed the data cannot be used for a quantitative evaluation.

In a cross-sectional study (Kim et al. 1999), effects on white blood cells, suggestive of bone marrow depression, were observed in a group of 57 painters exposed to mixed solvents containing 2-ethoxyethyl acetate. Exposure concentrations (geometric means) measured for 2-ethoxyethyl acetate were 3.0 ppm (maximum 18.3 ppm) in the high-exposure groupA and 1.8 ppm (maximum 8.1 ppm) in the low-exposure group B. Concentrations of 2-ethoxyacetic acid in urine were 9.2±5.6 mg/g creatinine (11.0±6.7 mg/l urine, assuming 1.2 g creatinine/l urine) with a maximum of 227 mg/g creatinine (272 mg/l urine) in the high-exposure group and 0.6±11.3 mg/g creatinine (0.7±13.6 mg/l urine) with a maximum of 15.1 mg/g creatinine (18.1 mg/l urine) in the low-exposure group. Co-exposure was to toluene (group A: geometric mean 12 ppm, maximum 154 ppm), xylene (group A: geometric mean 28 ppm, maximum 250 ppm) and methyl isobutyl ketone (group A: geometric mean 4.6 ppm, maximum 159 ppm). White blood cell and granulocyte counts were statistically significantly reduced in the high-exposure group (6033 cells/l; statistically significant) compared to the control group (7031 cells/µl). In the low-exposure group there was a slight but statistically non significant reduction (6325 cells/µl)., The authors considered the decreases in the high exposure group not to be clinically significant but 5/30 workers in group A and 1/27 workers from group B were leucopenic. The authors also noted that mean corpuscular volume was increased in the high-exposure group; they suggest that 2-ethoxyethyl acetate might be toxic to bone marrow. The concentration of 2-ethoxyacetic acid in urine ranged from not detectable up to 227 mg/g creatinine (272 mg/l urine), indicative of particularly high dermal exposure. No analysis was performed of the concentrations of 2-ethoxyacetic acid in urine in workers with clinically significant haematological findings. Therefore, the data do not allow identification of the threshold for the effects on bone marrow.

Mutagenicity

2-Ethoxyethanol was not mutagenic in Salmonella typhimurium, Escherichia coli and CHO-cells. 2-Ethoxyethanol induced a slightly positive effect in the mouse-lymphoma test. In CHO cells 2-ethoxyethanol caused a concentration-dependent increase of sister chromatid exchanges and of chromosome aberrations without metabolic activation. The clastogenic effect in CHO cells was reduced or eliminated in the presence of metabolic activation. No mutagenic effect was detected in mice (micronucleus test) and in Drosophila melanogaster (SLRL-test) (NTP 1993, BUA 1995). Workers occupationally exposed to glycol ethers in a varnish production plant did not show cytogenetic effects (sister chromatid exchange, micronucleus test). Concentrations of 2-ethoxyethanol, 2-ethoxyethyl

acetate, and 2-butoxyethanol in air averaged 2.9, 0.5, and 0.5 ppm, respectively, on Monday, and 2.1, 0.1, and 0.6 ppm, respectively, on Tuesday. The mean urinary 2-ethoxyacetic acid and 2-butoxyacetic acid concentrations were 53.2 and 0.2 mg/l on Monday preshift and 53.8 and 16.4 mg/l on Tuesday postshift (Söhnlein et al. 1993).

Carcinogenicity

No valid data on the carcinogenicity of 2-ethoxyethanol are available.

Groups of 50 rats and 50 mice of both sexes were administered 2-ethoxyethanol by gavage in a 2-year study at dose levels of 0, 500, 1000 or 20000 mg/kg body weight. Testicular atrophy was observed in male rats that died early in this study and in the medium- and high-dose male mouse groups. Gross lesions noted at necropsy indicate that chronic treatment of rats with 2-ethoxyethanol at dose levels of 500 or 1000 mg/kg body weight caused an apparent enlargement of the adrenal gland in male rats and interfered with the development of spontaneous lesions of the spleen (males and females), pituitary (males and females), testis (males), and subcutaneous tissue in the mammary gland region (females) that commonly occur in the aging Fischer 344/N rat. Histopathological data of this study were not reported (Melnick 1984). NTP never finalized this 2-year study; conclusions for carcinogenicity can therefore not be derived.

Reproductive toxicity

In animal experiments, exposure to 2-ethoxyethanol leads to changes of the reproductive organs and to developmental effects in rats and mice. Reduced testis weight, diminished spermatocyte count, slight degeneration of the seminiferous tubules as well as an increased fraction of anomalous spermatocytes occurred in rats and rabbits.

Fertility

Inhalation studies with 2-ethoxyethanol yielded a NOEL of 100 ppm for changes in the reproductive organs of rabbits after inhalation exposure for 13 weeks (6 hours/day). Minimal to slight focal degeneration of seminiferous tubules was noted in rabbits at 400 ppm (Barbee et al. 1984).

In an inhalation study on the effects of 2-ethoxyethanol on reproductive ability, no effects on mating behaviour or fertility were observed in female rats exposed to up to 649 ppm for 3 weeks prior to mating with unexposed males (Andrew and Hardin 1984).

A NOAEL of 900 mg/kg body weight and day was determined for mice in a multi-generation study with application of 2-ethoxyethyl acetate via the drinking water (Gulati et al. 1985).

Reductions in testicular or epididymal sperm counts or alterations in sperm motility or morphology in male rats mated twice a day were noted at oral (gavage) doses as low as 150 mg/kg body weight per day when administered for 6 weeks or longer. In non-mated rats, these effects were observed at 300 mg/kg body weight (Hurtt and Zenick 1986).

Reduction in testicular or epididymal weights or alterations in sperm parameters were also observed in mice orally exposed to 2-ethoxyethanol or 2-ethoxyethyl acetate for 5 weeks or longer (NTP 1993, Chapin and Sloane 1997), although this species appears to be less sensitive than rats. The LOAEL was 10000 mg/kg bw per day and the NOAEL 500 mg/kg bw.

Although not as extensively investigated as in males, exposure to 2-ethoxyethanol in the drinking water for 13 weeks induced effects on the estrous cycle in female rats and mice at doses of 804 and 1304 mg/kg bw per day or more, respectively, with uterine atrophy occurring at higher doses (NTP 1993).

A review study on reproductive assessment by continuous breeding concluded that some ethers of ethylene glycol can be potent and effective reproductive toxicants. Those compounds with the shortest chain lengths are the most toxic. Increasing chain length from monoethyl through monobutyl to monophenyl ethers decreased the degree of effects and increased the doses required to produce an effect on reproduction (Chapin and Sloane 1997).

Sperm analyses of workers of one shipyard exposed to a variety of substances including 2-ethoxyethanol and 2-methoxyethanol indicate that the work-related exposure to ethyl and methyl glycol can influence the sperm count. For non-smokers the proportion of exposed workers with oligospermia was significantly greater among exposed workers (36%) than controls (16%) (Welch and Cullen 1988, Welch et al. 1988). Concentration measurements showed a mean of 2.6 ppm 2-ethoxyethanol (maximum 21.5 ppm) and 0.8 ppm 2-methoxyethanol (maximum 5.6 ppm). No biological monitoring was performed.

The results of a cross-sectional study of 37 men exposed to 2-ethoxyethanol used as a binder slurry in a metal castings process and 38 controls suggest a possible effect of exposure to 2-ethoxyethanol on sperm parameters: the average sperm count per ejaculate was significantly lower after consideration of confounding factors as abstinence, sample age, subject's age, tobacco, alcohol and caffeine use, urogenital disorders, fever, and other illnesses. No significant differences in semen volume, sperm concentration, semen pH, viability, motility, velocity and normal sperm morphology or testicular volume were observed. The proportion of men with oligozoospermia was higher in the exposed group (16.2%) than in the unexposed group (10.5%) but this difference was not statistically significant. Full shift breathing zone exposures to 2-ethoxyethanol ranged from non-detectable to 24 ppm with a geometric mean of 6.6 ppm. Two to three weeks before the survey, the use of 2-ethoxyethanol was suspended in two of the three buildings resulting in much lower exposure during the survey: Building A reduction from 16.9 to 3.0 ppm; Building B almost the same conditions with 10.7 and 14.9 ppm; Building C reduction from almost the same conditions of Building A to 2.4 ppm. Urine measurements of the metabolite 2-ethoxyacetic acid (2EAA) during the survey showed levels ranging from non detectable to 163 mg/g creatinine (about 196 mg/l urine assuming 1.2 g creatinine/l urine). In a subgroup of 10 workers with potentially higher exposure out of hand dippers (35.5±10.9 mg 2EAA/g creatinine), grabber operators (85±31.3 mg 2EAA/g creatinine; corresponding to about 100 mg/l urine), and utility investors, no differences in semen characteristics were observed in a regression analysis compared to workers with lower exposure and unexposed men; however, the number of workers in each exposure group may have been too small to detect an effect. Since the reduction in potential exposure in

two of the three buildings occurred within the average duration of a spermatogenic cycle of about 70 days, an effect on semen quality would probably still be observable at the time of study (Clapp et al. 1987, Ratcliffe et al. 1989), but may not correlate to the current exposure measured during the survey. Therefore, even if no significant effects on sperm parameters were calculated in workers with current exposure up to 85±31.3 mg/g creatinine (100 mg/l urine), the database is insufficient to conclude that no effects occur at this exposure.

In one case-control study of 1019 men with reproductive disorders, ethoxyacetic acid could be detected in the urine of 39/1019 patients (3.8%) and 6/475 controls (1.3%) with concentrations ranging from 1.3 to 71 mg/l. From the 45 subjects with detectable ethoxyacetic acid in the urine, 43 had oligozoospermia and 11 of those showed azoospermia (Veulemans et al. 1993). As no data on time of exposure and time of measurement of 2-ethoxyacetic acid in urine are given, maximal concentrations in urine might have been much higher before. The measured concentrations of 2-ethoxyacetic acid in urine can not be quantitatively correlated to the observed effect.

These epidemiological investigations reveal an association between exposure to 2-ethoxyethanol and the occurrence of toxic effects on reproduction in man (sperm parameters).

In other studies no consistent evidence of effects on reproductive ability (spontaneous abortions) could be detected in association with men or women exposed to 2-ethoxyethanol. However, most of these studies are limited by the lack of analyses for associations with 2-ethoxyethanol specifically (Beaumont et al. 1995, Schenker et al. 1995, Correa et al. 1996)

Developmental Toxicity

In an inhalation study with rats (10, 50, 250 ppm; exposure gestation days 6-15) and rabbits (10, 50, 175 ppm; exposure gestation days 6-18) 50 ppm 2-ethoxyethanol was not teratogenic to rats and rabbits (Doe 1984). Higher concentrations (175 ppm) caused skeletal variations in the offspring of rabbits. This effect was considered to be a marginal effect level for teratogenic effects in rabbits. There was no indication of foetotoxicity at 50 ppm in the rabbits. In rats, statistically significant increased incidences of embryotoxic or foetotoxic effects were observed in all groups (10, 50, 250 ppm); however there was no dose-relation for the effects observed at 10 and 50 ppm. The conclusion drawn by the authors that foetotoxicity was possibly observed at 50 ppm in rats is therefore not supported. Increased incidences of foetuses with minor visceral but especially with minor skeletal defects were found at the high concentration; on a litter basis the increase was not statistically significant. In this study a LOAEL of 250 ppm and a NOAEL of 50 ppm could be identified.

The same research group performed an inhalation teratology study using 2-ethoxyethyl acetate in rabbits at 25, 100 and 400 ppm (gestation days 6-18). There was evidence of teratogenicity (vertebral malformations) at 400 ppm and slight foetotoxicity (reduced body weight, skeletal variations) at 100 ppm; 25 ppm was a NOAEL (Doe 1984). Considering the different concentrations used with 2-ethoxyethanol and 2-ethoxyethyl acetate and the comparable toxicity of both substances, the NOAEL of 50 ppm may also be valid for 2-ethoxyethyl acetate. This is supported by the findings of Tyl et al. (1988).

In another well performed and documented inhalation developmental toxicity study rats and rabbits were exposed on gestational days 6 through 15 (rats) or 6 through 18 (rabbits) for 6 hours a day to 50, 100, 200 or 300 ppm 2-ethoxyethyl acetate. The NOAEL in both species was 50 ppm for maternal and developmental toxicity, including teratogenicity (Tyl et al. 1988). Higher, maternally toxic concentrations of 100 ppm led to skeletal variations in rabbits and 200 and 300 ppm led to an increase in the number of resorptions and malformations in both species.

In a multi-centre case-control study conducted in six regions in Europe, 984 cases of congenital malformation and 1,134 controls were investigated. The exposure to glycol ethers was evaluated by job description. The overall odds ratio of congenital malformations associated with glycol ether exposure was 1.44 (95% confidence interval 1.10-1.90) after adjustment. The association with exposure to glycol ethers appeared particularly strong in three subgroups: neural tube defects, multiple anomalies and cleft lip. In this last subgroup, risk, especially of an isolated defect, tended to increase with level of exposure (Cordier et al. 1997; Ha et al. 1996). This study indicates a potential of glycol ethers for the induction of malformations; in experimental animals 2-ethoxyethanol also induces malformations at high doses. However, the study does not allow a differentiation between individual glycol ethers; in addition, no exposure quantification was performed.

Dermally applied 2-ethoxyethanol or its acetate induced developmental effects, including increased resorptions, reduced number of live foetuses per litter, decreased foetal body weights and increased incidence of visceral malformations and skeletal variants, in rats at all doses tested (i.e. 4000 mg/kg bw per day, a dose that was not or only slightly maternally toxic) (Hardin et al. 1982, 1984).

BIOLOGICAL MONITORING INFORMATION

The respiratory exposure of volunteers to 2.7, 5.3, or 10.7 ppm 2-ethoxyethanol for 4 hours resulted in an excretion of 2-ethoxyacetic acid proportional to the dose (3.2, 6.0, 8.7 mg/l; 2.2, 4.2, 6.9 mg/g creatinine) 4 hours after end of exposure. The exposure to 5.3 ppm under a physical workload of 30 or 60 Watts increased the excretion of 2-ethoxyacetic acid (11.8 and 17.4 mg/l; 9.6, 14.4 mg/g creatinine) (Groeseneken et al. 1986 a, b). Exposure of volunteers to 2.6, 5.1, or 9.8 ppm 2-ethoxyethyl acetate for 4 hours resulted in an excretion of 2-ethoxyacetic acid of 2.2, 4.0, and 6.5 mg/l (2.6, 3.9, and 7.3 mg/g creatinine) 4 hours after the end of exposure. The exposure to 5.1 ppm 2-ethoxyacetic acetate under a physical workload of 30 or 60 Watts increased the excretion of 2-ethoxyacetic acid (7.3 and 13.7 mg/l; 7.8 and 12.8 mg/g creatinine) (Groeseneken et al. 1987 a, b). With equivalent doses, retention of 2-ethoxyethyl acetate was always somewhat lower than retention of 2-ethoxyethanol (Groeseneken *et al*. 1986 a); this was attributed to the slightly lower water solubility of the acetate.

A study of Veulemans et al. (1987) with 5 women daily exposed to 2-ethoxyethanol and 2-ethoxyethyl acetate (3.8 ppm combined exposure expressed as 2-ethoxyethanol) showed that 2-ethoxyacetic acid accumulates in the urine during the working week. An 2-ethoxyacetic acid concentration of 150 mg/g creatinine (180 mg/l urine assuming 1.2 g creatinine/l urine) was found to correspond with repeated 5-day full shift exposure to 5 ppm 2-ethoxyethanol.

19 screen printing workers who were potentially exposed to various glycol ethers including 2-ethoxyethyl acetate were monitored during an 8-hour working day using personal air samplers. The amount of 2-ethoxyacetic acid eliminated during the eight hours was determined by analyzing the urine. Exposure to 2-ethoxyethyl acetate was detected for 8 of the 19 workers. The mean air concentration was 0.9 ppm. 2-Ethoxyacetic acid in urine was about 80 μM (8.3 mg/l or 6.9 mg/g creatinine assuming 1.2 g creatinine/l urine) (Johanson et al. 1989) and therefore within the range that could be expected on the basis of the results of Groeseneken et al. (1987 b) after 5-day constant exposure exclusively by inhalation. The day of the week on which the study was carried out, or the previous exposure to 2-ethoxyethyl acetate, were, however, not stated. It therefore remains unclear whether the systemic dose of 2-ethoxyacetic acid determined in this study can be attributed to accumulation during the working week.

12 persons employed in a paint factory were investigated on the second day of production of a special paint containing glycol ethers to determine their levels of exposure to 2-ethoxyethanol and 2-ethoxyethyl acetate and of excretion of 2-ethoxyacetic acid. The mean 2-ethoxyacetic acid concentration in urine determined before the start of the shift was 128.5 mg/l, which the authors attributed to exposure to ethylene glycol ethers on the previous day and the long half-life of the metabolite 2-ethoxyacetic acid. On the day of the investigation these workers were exposed to average air concentrations of 2-ethoxyethanol and 2-ethoxyethyl acetate of 2.8 and 2.7 ppm, respectively. The highest concentrations observed were 7.8 and 11.1 ppm. At the end of the shift the mean 2-ethoxyacetic acid concentration in the urine of the workers had increased in average to 167.8 mg/l (about 139 mg/g creatinine assuming 1.2 g creatinine/l urine) with a maximum of 497 mg/l. The air concentrations of the two ethylene glycol ethers determined on the day of investigation using personal air monitoring at the individual workplace did not correlate significantly with the 2-ethoxyacetic acid concentrations in urine. The authors conclude from the results that most of the glycol ether was not absorbed by inhalation but through the skin (Angerer et al. 1990).

In another investigation in the same factory with a collective of 19 persons employed in the formulation of paints or their quality control, the exposure levels were measured on Monday and Tuesday after a work-free weekend. The mean air concentrations for 2-ethoxyethanol on the two days were 2.0 and 1.4 ppm, for 2-ethyxoethyl acetate 0.4 and 0.1 ppm. The concentration of 2-ethoxyacetic acid in the urine of the workers on Monday before the start of the shift was 37.8 mg/l, on Tuesday after the end of the shift 35.9 mg/l (31.5 and 29.9 mg/g creatinine assuming 1.2 g creatinine/l urine). The metabolite concentrations found in the urine were on average at least four times the values expected from the data from Groeseneken et al. (1986 a, b, 1987 a, b) for the air concentrations measured for 2-ethoxyethanol and 2-ethoxyethyl acetate. In the opinion of the authors this result is due to the fact that the glycol ethers are readily absorbed by the intact skin and this is the main route of absorption at most workplaces (Angerer et al. 1991).

RECOMMENDATION

2-Ethoxyethyl acetate and 2-ethoxyethanol show similar toxicity in animal experiments due to metabolism to the same critical metabolite (2-ethoxyacetic acid). As both substances may be used at the same time, it is necessary to limit exposure of the common critical metabolite. Evaluation of both substances together is therefore necessary.

The critical effects of 2-ethoxyethanol and 2-ethoxyethyl acetate are on reproduction and the blood, which are detected in experimental animals and in humans. As humans are more sensitive than animals, only human studies (even if they are of limited validity) are used for deriving an OEL.

For effects in humans on hematopoesis, effect levels of 2.6 ppm (maximum 21.5 ppm; Welch and Cullen 1988) and 3.0 ppm (maximum 18.3 ppm) and a level of no significant effects of 1.8 ppm (maximum 8.1 ppm) (Kim et al. 1999) were derived. Effects on sperm parameters were observed in workers exposed to about 17 ppm 2-ethoxyethanol with exposure being reduced during the study to 6.6 ppm (Ratcliffe et al. 1989). In the light of significant uncontrolled dermal uptake of 2-ethoxyethanol, which is expected to contribute to a high extent to internal exposure, as well as additional exposure to 2-methoxyethanol (which elicits the same effects), the concentrations of 2-ethoxyethanol reported in the air only account for inhalational uptake; if dermal uptake is avoided, concentrations in the air might be higher until effects occur.

If dermal absorption is avoided, an 8-h TWA of 2 ppm should protect from effects on hematopoesis and fertility. This TWA is consistent with the 8-h TWA of 1 ppm for 2-methoxyethanol, an analogous glycol ether with stronger hematotoxic and reproductive effects.

Since there is significant dermal uptake of 2-ethoxyethanol biological monitoring of the toxic metabolite 2-ethoxyacetic acid is the preferred measure to control exposure.

Statistically but not clinically relevant effects on white blood cells were observed in workers with concentration of 9.2 mg 2-ethoxyacetic acid/g creatinine (11 mg/l urine) (Kim et al. 1999). In workers with about 100 mg 2-ethoxyacetic acid/l urine no differences in semen characteristics were observed (Ratcliffe et al. 1989). However, due to methodological limitations of the study, effects cannot be excluded. Considering this, the SCOEL concluded that 50 mg/l urine is sufficiently protective. Based on the toxicokinetic model of Truchon et al. (2006) an 8-hour exposure of 2 ppm corresponds to 50 mg 2-ethoxyacetic acid/l urine (about 40 mg/g creatinine). SCOEL proposes these values as BLV, measured at the end of the work week.

The TWA will prevent from developmental toxicity (NOAEL 50 ppm), provided that dermal exposure is avoided and the biological limit value is observed. This is in accordance with the proposal by Sweeney et al. (2001) who used a different approach based on developmental toxicity.

Sufficient data are not available to recommend a STEL (ACGIH 2001 a, b).

A "skin" notation is recommended as dermal absorption can contribute substantially to the total body burden.

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