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Criteria Document for Swedish Occupational Standards

Ethylene glycol monomethyl ether and ethylene glycol monomethyl ether acetate

Gunnar Johanson

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Preface

The Swedish Criteria Group for Occupational Standards (SCG) of the Swedish National Institute for Working Life (NIWL) has engaged Professor Gunnar Johanson at NIWL, Sweden, to write this criteria document concerning ethylene glycol monomethyl ether and ethylene glycol monomethyl ether acetate. Based on this document the Criteria Group will present a report to be used as the scientific background material by the National Board of Occupational Safety and Health in their proposal for an occupational exposure limit.

Johan Högberg
Chairman
Criteria Group

Johan Montelius
Secretary
Criteria Group

Abbreviations of glycol ethers and their metabolites

DEGDME	diethylene glycol dimethyl ether
EAA	ethoxyacetic acid
EGEE	ethylene glycol monoethyl ether, 2-ethoxyethanol
EGEEA	ethylene glycol monoethyl ether acetate, 2-ethoxyethyl acetate
EGME	ethylene glycol monomethyl ether, 2-methoxyethanol
EGMEA	ethylene glycol monomethyl ether acetate, 2-methoxyethyl acetate
MAA	methoxyacetic acid
MALD	methoxyacetaldehyde
PGME	propylene glycol monomethyl ether
PGMEA	propylene glycol monomethyl ether acetate

Contents

1. Introduction

Ethylene glycol monomethyl ether (EGME) and ethylene glycol monomethyl ether acetate (EGMEA) belong to the family of so called glycol ethers. The term glycol ethers refers to alkyl derivatives of diols such as ethylene and propylene glycol. The most commonly encountered glycol ethers are colourless liquids with mild ethereal odours.

Previously published criteria documents and toxicity reviews of EGME and EGMEA include those by the Nordic Expert Group for Criteria Documentation (38), the UK Health and Safety Executive (47), the WHO International Programme on Chemical Safety (48), the US National Institute for Occupational Safety and Health (86), and the European Centre for Ecotoxicology and Toxicology of Chemicals (25).

2. Physical and Chemical Properties

2.1. Ethylene glycol monomethyl ether (EGME) (25, 48, 98, 113)

Chemical name	2-methoxyethanol
CAS registry number	109-86-4
Synonyms	methyl cellosolve methyl glycol
Structural formula	$CH_3–O–CH_2–CH_2–OH$
Molecular weight	76.09
Density	0.96 (20°C)
Boiling point	124°C
Freezing point	-85.1°C
Vapour pressure	1.3 kPa (9.7 mm Hg) (20°C)
Evaporation rate	0.5 (butylacetate = 1)
Concentration in saturated air	12 800 ppm (25°C)
Relative density (air = 1)	2.6
Conversion factors	1 ppm = 3.11 mg/m^3 (20°C) 1 mg/m^3 = 0.322 ppm (20°C)

2.2. Ethylene glycol monomethyl ether acetate (EGMEA) (25, 48, 98, 113)

Chemical name	2-methoxyethyl acetate
CAS registry number	110-49-6
Synonyms	2-methoxyethanol acetate methyl cellosolve acetate methyl glycol acetate
Structural formula	$CH_3–O–CH_2–CH_2–O–CO–CH_3$
Molecular weight	118.13
Density	1.005 (20°C)
Boiling point	145°C
Freezing point	-65°C
Flash point	55.6°C (open cup)
Vapour pressure	0.27-0.50 kPa (2.0-3.7 mm Hg) (20°C)
Evaporation rate	0.3 (butylacetate = 1)
Concentration in saturated air	3 100-6 000 ppm (25°C)
Relative density (air = 1)	4.07
Conversion factors	1 ppm = 4.90 mg/m^3 (20°C) 1 mg/m^3 = 0.2 ppm (20°C)

EGME and EGMEA are highly flammable, colourless, volatile liquids at room temperature. They have a mild, sweet, ethereal odour and a bitter taste. These ethers have very good solubility properties and are miscible with water as well as a large number of polar and non polar organic solvents.

EGME is produced by reacting ethylene oxide with methanol. EGMEA is produced from EGME by conventional esterification. Commercial EGME contains up to 0.1% methanol, up to 0.1% diethylene glycol monomethyl ether and up to 0.02% ethylene glycol as impurities (25, 48).

2.3. Occurrence, production and use

EGME and EGMEA do not occur naturally. Internationally, reported areas of use include paints, lacquers, stains, inks and surface coatings, silk-screen printing, photographic and photo lithographic processes, *e.g.* in the semiconductor industry, textile and leather finishing, production of food-contact plastics, and anti-icing additive in hydraulic fluids and jet fuel (Mellan 1977, in (48)). In 1993, EGME was listed in 23 chemical products in Sweden with an estimated use of about 260 tonnes per year. EGME was predominantly used as a solvent, but also as an ingredient in paints and lacquers. EGMEA was not listed (55). By 1997, EGME was listed in 27 products with an annual use of 19 tonnes, with the dominating use as a photoresist in the telecommunications industry. EGMEA was used in 3 products with a total annual use below 0.1 ton (personal communication, the Products Register, Swedish Chemicals Inspectorate). Since 1994, EGME and EGMEA are listed as reproductive toxicants by the European Union and are not

allowed in consumer's products (Directive 94/60/EG from the European Parliament and Council).

3. Occupational Exposure

In a survey of European manufacturing sites, time-weighted averages of 9.3 ppm EGME and 0.9 ppm EGMEA were reported (ECETOC 1985 in (48)). A compilation of ambient air levels during different work tasks in the United States indicated geometric means between 1 and 23 mg/m^3 (0.4-7.4 ppm) EGME and between 0.8 and 2.0 mg/m^3 (0.2-0.4 ppm) EGMEA (US EPA 1987, in (48). Ambient air monitoring in the breathing zone indicated geometric means of 0.1 ppm EGME and 0.01 ppm EGMEA (93).

In a study of 78 Belgian industries with reported use of glycol ethers EGME was detected in 14 and EGMEA in 15 out of 262 air samples. Levels of 4-5 mg/m^3 (0.8-1.0 ppm) EGMEA were measured during printing, 6-137 mg/m^3 (2-44 ppm) EGME during painting, 3-16 mg/m^3 (1-5 ppm) EGME and 2 mg/m^3 (0.4 ppm) EGMEA during car repair, and 0.4-143 mg/m^3 (0.1-29 ppm) EGMEA during other tasks (129).

In an extensive study of glycol ether exposure in 55 French companies covering 18 sectors of activity the highest exposure to EGME was seen in the electronic industry during use of photoresist varnishes in the production of printed-circuit boards. In this activity the average ambient air level of EGME was 2.1 ppm (range 0.1 - 18 ppm). EGME was also detected (<0.1 - 0.2 ppm) in car painting. Presence of the metabolite methoxyacetic acid (MAA) in both pre- and post-shift urine samples from workers engaged in the fabrication of paints and in painting and varnishing furniture strongly suggested exposure to EGME or EGMEA also in these sectors (132).

Personal monitoring of 36 shipyard painters (102 samples) revealed time-weighted averages of between 0 and 18 mg/m^3 (5.8 ppm) EGME with a mean of 2.6 mg/m^3 (0.8 ppm) (114).

4. Toxicokinetics

The chemical structures and solubility properties of EGME and EGMEA suggest that both substances are efficiently absorbed by all routes and rapidly distributed to the different tissues.

4.1. Uptake

In male volunteers exposed at rest to 5 ppm EGME for 4 h the respiratory uptake was 76% of the inhaled amount of EGME (37). In contrast to most other more volatile and less polar solvents, only a negligible fraction is exhaled after exposure has ended. The high relative uptake and negligible post-exposure exhalation may

be explained by the extremely high water:air and blood:air partition coefficients of EGME (53).

The average absorption rate of EGME through isolated, thawed human epidermal preparations *in vitro* was 2.8 mg/h per cm^2 of epidermis with a lag time for penetration of 1-3 h (24). Out of 9 glycol ethers tested EGME had the by far highest percutaneous absorption rate (53).

In an early study human volunteers were exposed to 15 ml EGME via a closed plastic vessel attached to the arm (area 12.5 cm^2). Two hours after application the concentrations of EGME in blood were 200-300 μg/ml, or one order of magnitude higher than recorded in similar experiments conducted with ethanol, acetone, and methylacetate (81). The vessel used for blood sampling was not reported and no quantitative estimates of the percutaneous absorption rate can be made from this study.

In a more recent study five volunteers were exposed to liquid or vaporised EGME (59). Exposure to liquid EGME was performed on the forearm (skin area 27 cm^2, duration 15 min) and the percutaneous absorption rate was obtained by measuring the excretion of the EGME metabolite MAA in urine. The average value 2.9 $mg/cm^2/h$ was very close to that obtained in the previously mentioned *in vitro* study by Dugard et al. (24). Kezic et al. (59) also exposed the hand and forearm (skin area approximately 1000 cm^2) to 4000 mg/m^3 EGME for 45 min. By comparing the two experiments, the authors estimated that, upon whole-body exposure to EGME vapour, dermal absorption accounts for 55% and respiratory absorption for 45% of the total systemic uptake. Percutaneous uptake during contact of both hands and forearms (skin area 2000 cm^2 or 10% of the total body surface area) with liquid EGME for 60 min was estimated to exceed by 100 times the inhalation uptake during an 8-h exposure to 16 mg/m^3 (5 ppm) EGME vapour (59).

4.2. Distribution

EGME appears to be rapidly and evenly distributed in tissues, with the exception of adipose tissue. Thus, the tissue:blood partition coefficients determined *in vitro* using material from mice and rats vary between 0.9 (skin) and 1.9 (extra embryonic fluid). EGME has a low solubility in fat with an olive oil: blood partition coefficient of 0.02. The slightly higher reported adipose tissue: blood partition coefficients of 0.04 and 0.1 can be attributed to the presence of water and other non-fat components in adipose tissue. Judging by partition coefficients, the metabolite MAA also appears to be evenly distributed to the tissue (53).

Whole-body autoradiography in mice showed that, following administration of ^{14}C-labelled EGME, the radioactivity is preferentially localised to the liver, urinary bladder, kidney, bone marrow, and epididymis. Further, the autoradiography studies suggest a rapid distribution to various tissues (2).

4.3. Biotransformation

EGMEA is rapidly and extensively hydrolysed to EGME by carboxyl esterases in the nasal epithelium, liver, kidneys, lungs, and blood, as shown with tissues from mouse, rat, dog, and rabbit (115). Such esterase's are also present in human tissues, as indicated by rapid disappearance of ethylene glycol monoethyl ether acetate (EGEEA) from human blood (54) and the appearance of ethylene glycol monoethyl ether (EGEE) in exhaled breath from humans exposed to EGEEA (36).

The dominating metabolic pathway of EGME is oxidation via methoxyacetaldehyde (MALD) to methoxyacetic acid (MAA). The biological half time of MAA in serum or plasma has been reported to about 6 h in mouse and 20 h monkey. The half time of the decrease in urinary excretion in man was 77 h (53). Testis is capable of metabolising EGME via alcohol dehydrogenase (shown in mouse and rat but neither hamster, guinea pig, rabbit, dog, cat, nor man) and aldehyde dehydrogenase (shown in all these species) to MAA (78).

In addition to MAA, nine EGME metabolites have been identified in mice and rat urine. The most extensive study in this respect was performed by Jenkins-Sumner and co-workers (51), who analysed urine samples from animals dosed with ^{13}C-labelled EGME by two-dimensional nuclear magnetic resonance spectroscopy and identified ethylene glycol, glycolic acid, glycine, methoxyethyl ß-D-glucuronide, methoxyethylsulfate, MAA, methoxyacetyl ß-D-glucuronide, methoxyN-acetylglycine, methoxycitrate and methoxybutenoic acid. Acetate given together with EGME reduced the percentage of EGME metabolites incorporated into intermediary metabolism. These results show that EGME may enter the Krebs cycle via formation of methoxyacetyl-Coenzyme A (51). It has been speculated (73) that this ”false substrate” of Krebs cycle may be related to reproductive effects of EGME described below.

The analyses (51) further show that demethylation of EGME may occur (resulting in ethylene glycol). A case report suggests that demethylation of EGME may also occur in humans. Thus, one of two men who had accidentally ingested about 100 ml EGME developed high oxalate levels in urine in spite of massive treatment with ethanol (87).

4.4. Excretion

EGME is mainly eliminated from the body via excretion of metabolites in urine. In an experiment with male volunteers exposed at rest to 5 ppm EGME for 4 h, the total (extrapolated) amount of MAA excreted in urine was calculated to 86% of the inhaled EGME, on an equimolar basis (37). Due to the extremely high water: air and blood: air partition coefficients of approximately 36000 and 33000, respectively (54), it can be assumed that the amounts of EGME eliminated via exhaled air is negligible.

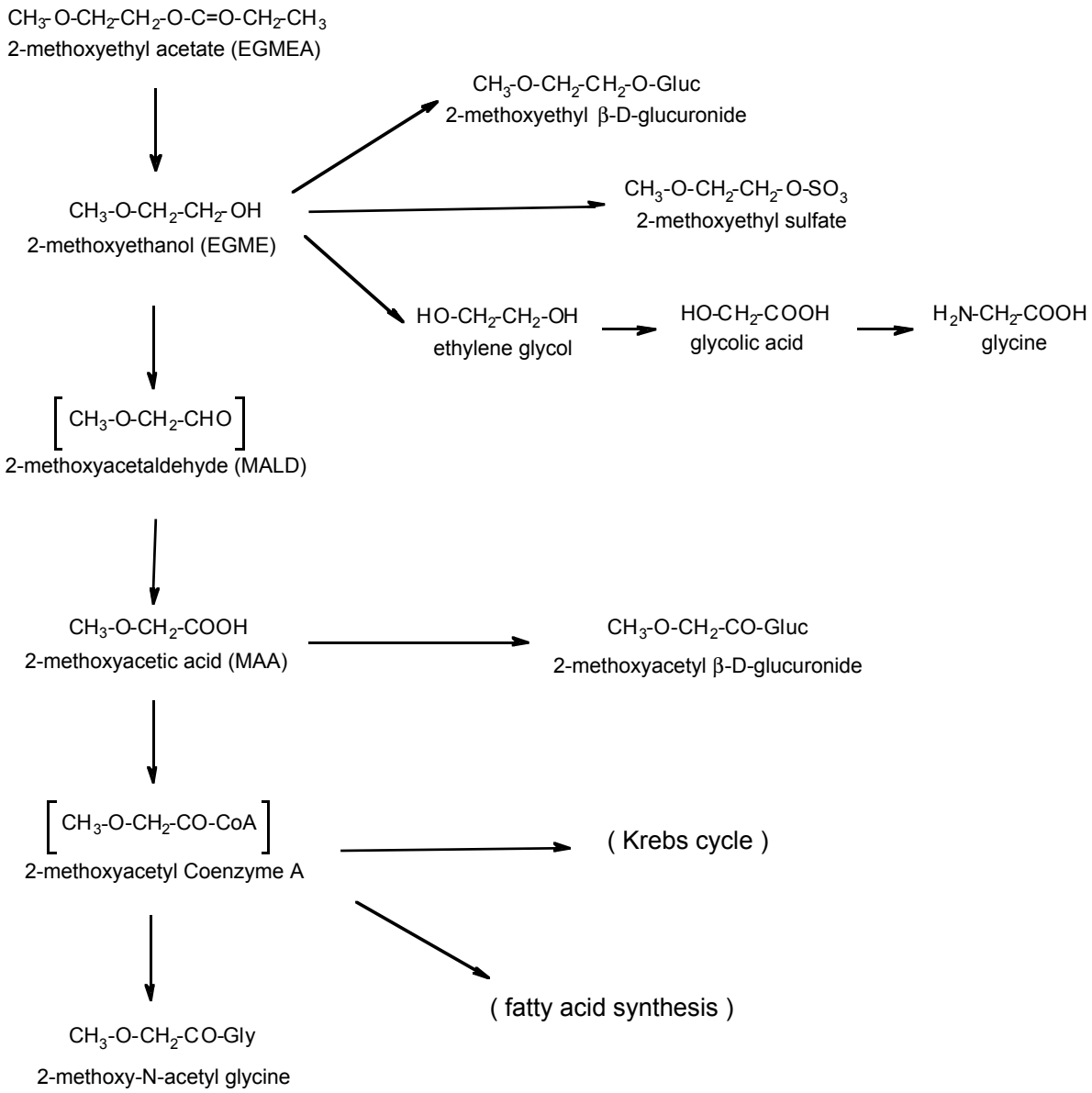

Figure 1. Proposed metabolic pathways of 2-methoxyethyl acetate and 2-methoxyethanol. Modified from Jenkins-Sumner et al. (51). Square brackets denote postulated metabolites.

4.5. Kinetic interactions

Following an intraperitoneal injection of EGME (150 mg/kg) in rats, the rate of elimination of EGME was significantly higher in males (average half time 49 min) than in females (28 min). In contrast, there was no difference in the elimination of MAA (half times 12.6 and 14.1 h) after an intraperitoneal dose of 100 mg/kg EGME (1).

The transformation of EGME to MAA can be inhibited by ethanol, as shown in rat experiments. Thus, in adult female rats exposed for 2 h to 1600 ppm, EGME reached three times higher concentrations in blood after intraperitoneal pre-treatment with ethanol (20 mmol/kg body weight). After co-administration of EGME (10 mmol/kg) and ethanol (20 mmol/kg), EGME in blood reached a higher level and remained constant for several hours, or as long as ethanol levels in blood were above 3 mmol/L (99). The importance of alcohol dehydrogenase was shown by an almost complete inhibition of EGME metabolism in rats treated with pyrazole (79).

It is commonly recommended that glycol ether intoxication should be treated with ethanol. However, in rats orally treated with EGME (10 mmol/kg) co-administration of alcohol (ethanol, n-propanol, or n-butanol, 10 or 30 mmol/kg) did not modify the testicular toxicity, measured as the urinary creatine:creatinine ratios at 24 h and 48 h, nor the 24 h cumulative excretion of MAA. The authors concluded that alcohol treatment merely delays, and does not alter, the metabolism of EGME (76). This interpretation is, however, contra-indicated by the previously referred metabolism study by Jenkins-Sumner (51).

5. Biological Monitoring

It is likely that dermal uptake contributes significantly to, or even dominates, the total uptake of EGME and EGMEA. In addition, inhalation uptake is highly dependent on pulmonary ventilation and thus on physical work load. These considerations point to the need of biological monitoring of exposure (52). The recovery of MAA in urine accounts for about 85% of the inhaled dose of EGME in human experiments (37), pointing towards MAA in urine as the biological indicator of choice.

MAA was detected in both pre- and post-shift urine samples from workers engaged in the manufacture of printed-circuit boards, fabrication of paints and in painting and varnishing of furniture. The study did not present any relation between ambient air levels and urinary MAA (132).

Exposure to ethylene glycol ethers was monitored for an entire work week in 8 silkscreen printers, by personal air sampling and by analysis of urine samples with regards to alkoxyacetic acid metabolites. Linear regression analysis suggested that 5 daily 8-h exposures to 0.5 ppm EGMEA correspond to a urinary excretion of MAA of 3 mmol/mol creatinine 14 - 16 h after the last shift, *i.e.* Saturday morning. No correlation was seen between EGMEA in air and MAA in urine sampled end of shift (64).

Comparable results have been obtained in an experimental study with seven male volunteers exposed at rest for 4 h to 16 mg/m^3 (5 ppm) EGME. The urinary excretion of MAA reached a maximum of about 3 µg/min 2 - 5 h after exposure. The excretion then decreased over time, with a half time of 77 h and reached a rate of about 2 µg/min 20 h later (*i.e.* the next morning).

The relation between exposure to EGME and internal levels of the active metabolite MAA may be deduced from two studies. An intravenous bolus dose of 250 mg EGME per kg body weight and an 8-h continuous subcutaneous infusion of a total dose of 400 mg/kg resulted in the same maximum level of MAA in plasma of 5 mmol/L (118). Simulations performed with a physiologically based toxicokinetic model suggest that daily 8-h exposures to 5 ppm EGME result in plasma MAA levels of about 0.05 mmol/L in mouse, rat, and man (128).

6. Mechanisms of Toxicity

Human erythrocytes were studied *in vitro* by means of electron paramagnetic resonance spin-labelling techniques. MAA increased the protein-protein interactions of cytoskeletal proteins in a concentration-dependent manner in the interval 0-5 mmol/L, whereas EGME was ineffective. Membrane fluidity was not affected. The authors suggest that MAA may give rise to teratologic insult by interacting not with lipid components but with certain, perhaps specific, protein components such as transport proteins, cytoskeleton proteins, or neurotransmitter receptors (67).

A 30-min treatment of cultured myometrial cells with 32 or 63 mmol/L EGME significantly decreased dye transfer to adjacent cells from 90% to 71% and 63%, respectively, suggesting inhibition of gap junctional communication. The effect disappeared after 2 h in the continued presence of EGME. MAA was ineffective at equimolar concentrations (71). The high concentrations required suggest that it is unlikely that gap junctional inhibition is the primary mechanism for developmental effects of EGME.

A number of substances, namely formate, acetate, glycine, glucose, serine, and sarcosine, involved in the synthesis of purine and pyrimidine bases, reduce or eliminates the malformations and testicular damage induced by EGME in laboratory animals. Formate is particularly effective in attenuating the teratogenic effect of EGME. Formate is predominantly metabolised via the folate-dependent 1-carbon oxidation pathway, a source in many biosynthetic pathways including that of purine and pyrimidine. Thus, EGME may interfere with the DNA and/or RNA synthesis and thereby influence normal cell proliferation (74, 75). D-Serine is a more efficient attenuator than L-serine. Both enantiomers delayed the absorption of EGME from the gastrointestinal tract, however, comparison of data from different routes of administration and different dose levels suggests that the protective effect is not only a secondary result of altered toxicokinetics of EGME (15).

In vitro studies show that MAA is an efficient competitive inhibitor of sarcosine dehydrogenase, the enzyme involved in the transformation of sarcosine to glycine. Inhibition constants of 1.8 mmol/L (32) and 0.26 mmol/L (95) have been reported.

mRNA differential display was used to identify gene expression changes in cultured rat germ cells treated with 5 mmol/L EGME or MAA for 24 h. Up-regulation of oxidative stress proteins were found in both pachytene sperma-

tocytes and Sertoli cells, whereas other proteins were down-regulated. The same changes in expression pattern were seen *in vivo* in rats after an oral dose of 250 mg/kg EGME or MAA (117).

7. Effects in Animals and *In Vitro* Studies

7.1. Irritation and sensitisation

Neat EGME or EGMEA were applied on the shaved skin of rabbits for 4 h. Readings of erythema and edema was performed according to the Draize scale up to 72 h after removal of the patch. Both substances were classified as non-irritants according to the EEC Directives (50).

EGME was tested for eye irritancy in rabbits according to the OECD Guidelines of 1981. Neat EGME (100 µl) was applied in the lower conjunctival sac for up to 96 h and the Draize scoring criteria were used. EGME was classified as not irritating to eyes (49).

7.2. Acute toxicity

The acute toxicity of EGME is moderate. LD_{50} values of between 2.1 and 3.4 g/kg body weight have been reported after oral and intraperitoneal administration to mice and rats. The corresponding values in guinea pigs and rabbits are 0.95 and 0.9-1.5 g/kg, respectively. A dermal LD_{50} in rabbit of 1.3 g/kg has been reported. The LC_{50} of inhalation was 4600 mg/m^3 (1480 ppm) in mice (48). A 4-h exposure of male rats to EGME vapours resulted in testicular atrophy at 1000 ppm and spermatid damage at 625 ppm. These effects occurred within 24 h (102).

The acute toxicity of EGMEA is of the same magnitude as EGME. Thus, oral LD_{50} values of 3.9 g/kg in rats and 1.3 g/kg in guinea pigs and a dermal LD_{50} of 5.6 g/kg in rabbits have been reported (48).

For comparison, the oral LD_{50} of MAA in water solution is reportedly between 1 and 1.5 g/kg (25).

7.3. Short-term toxicity

Repeated short-term exposure to EGME or EGMEA via gavage, dermal application, drinking water, or inhalation results in similar effects in several animal species. These effects include reduced organ weights of the thymus, spleen and testes, reduced number of erythrocytes, leukocytes and thrombocytes, lowered hematocrit, depression of bone marrow cellularity, and increased fraction of immature granulocytes. Sperm differentiation is affected in a specific phase, late pachytene, which is later expressed as oligo- or azoospermia. The toxicity pattern is independent of the route of exposure (25, 48). Oral and inhalation toxicity studies are compiled in Tables 1 and 2, respectively.

7.4. Long-term toxicity/carcinogenicity

No cancer studies of either EGME or EGMEA have been reported. McGregor concluded in a carcinogenic evaluation of glycol ethers, based on data published up to 1994, that the only experimental basis for suspicion of carcinogenicity is the Salmonella-positive results (described in the following section) (72).

7.5. Mutagenicity and genotoxicity

With the exceptions itemised in the following, EGME and its metabolite MAA were negative in all genotoxicity assays including the Ames' test for all Salmonella strains tested, with and without addition of metabolising systems (for review see (72)).

After testing with a series of Salmonella strains, with and without metabolic activation, the mutagenicity of EGMEA was judged by two independent laboratories to be weak and questionable, respectively (136).

EGME induced mutations in the *gpt* gene in a Chinese hamster ovary cell line (CHO-AS52), but no mutations in the *hprt* gene in another cell line (CHO-K1-BH4) (5, 14, 70). The intermediary metabolite metoxyacetaldehyde (MALD) was weakly mutagenic in the strain TA 97a and slightly more so after metabolic activation (42). MALD induced mutations, sister chromatid exchanges, and chromosomal aberrations in Chines hamster ovary (V79) cells *in vitro* in the concentration interval 5-40 mmol/L. Chromosomal damage was noted in human lymphocytes following treatment with 40 mmol/L MALD for 1 h or 2.5 mmol/L for 24 h (13). However, no chromosomal damage could be detected *in vivo* in mice given oral doses of up to 1000 mg/kg MALD or up to 2500 mg/kg EGME (6).

A number of glycol ethers and their aldehyde and acid metabolites were tested for genotoxic and epigenetic effects in various short term test systems. The effects sought were gene mutations at the *hprt* locus (V79 cells), sister chromatid exchanges (V79 cells), chromosomal aberrations (V79 cells and human lymphocytes), micronuclei (V79 cells and mouse bone marrow), alterations of the mitotic division and aneuploidy (V79 cells), morphological transformation (Syrian hamster embryo cells), and inhibition of intracellular communication (V79 cells). Reduced cell division was noted in the concentration intervals 100-1000 mmol/L EGME, 1-10 mmol/L MAA and 0.1-1 mmol/L MALD. Mutations were induced at 1-10 mmol/L MALD and sister chromatid exchanges and chromosomal aberrations at 0.1-1 mmol/L MALD. Increased number of micronuclei and mitotic disturbances were seen in V79 cells at 65 mmol/L EGME, 0.12 mmol/L MALD and 3.2 mmol/L MAA. Increased number of morphological transformations in embryonic cells were seen at 0.1-0.3 mmol/L MALD. The authors judged the results to be weakly positive with respect to micronuclei and mitotic disturbances from EGME and MAA and clearly positive with respect to the other endpoints and MALD (27).

Male rats were gavaged with 500, 1000, or 1500 mg/kg EGME. Animals were killed 2 or 5-6 weeks after treatment and bone marrow cells and testes cells were prepared and investigated for DNA damage by the comet assay. A significant dose-dependent increase in DNA damage was seen in the germ cells 2 weeks but not 5-6 weeks after treatment. No effect in bone marrow could be detected (4).

EGMEA was tested for induction of aneuploidy in two *Drosophila melanogaster* systems. Aneuploidy, mainly expressed as chromosome losses, was seen in the oocytes from young adult females exposed to 32000 and 42000 ppm, but not to 3200 and 4200 ppm EGME in the food (89).

7.6. Reproductive and developmental toxicity

A large number of animal studies gives a uniform picture that both EGME and EGMEA cause reproductive toxicity in laboratory animals of both sexes. The effects in male animals include reduced testes weight, histopathological changes in the testes and reduced sperm count. These effects are reversible. At higher doses testicular atrophy and azoospermia are seen. Effects in female animals include reduced fertility, increased number of dead and resorbed foetuses, impaired postnatal survival, and increased number of skeletal variations, malformations of the extremities and visceral malformations. Effects on the offspring are seen at doses with no overt maternal effects. Higher doses cause 100% foetal death. The reproductive effects have been shown in a number of animal species and for all main routes of exposure. The severity of the effects on the foetus is highly dependent on the time of exposure (25, 48). Selected studies are listed in Tables 1 and 2. The most recent reproductive toxicity studies are summarised in the following paragraphs.

7.6.1. Effects in males

Groups of 6-7 rabbits were given EGME via drinking water 5 days/week for 12 weeks (0, 12.5, 25, 37.5 or 50 mg/kg/d). A dose-dependent decrease over time in sperm quality was seen. The effects reached statistical significance at 37.5 and 50 mg/kg/d, the most marked effect being reduced number of sperms per ejaculate. Histological evaluation revealed slightly disturbed spermatogenesis at 25 mg/kg, expressed as a decrease in the number of round spermatids per Sertolic cell. At 37 mg/kg spermatogenesis was markedly disrupted and at 50 mg/kg it was almost completely destructed in 5 of 7 rabbits. No effects on libido or fertility were seen in those rabbits which still had sperm production. The authors concluded that, with respect to spermatogenesis, rabbits are about ten times more sensitive to EGME than mice and rats (9, 31).

Male mice were exposed to EGME by gavage for 5 days (0, 50, 200, 750, or 1500 mg/kg/d) and then mated once a week with unexposed female mice for the next 7 weeks. An aggregation chimera assay was used to examine the transmission of impaired viability in the males to their progeny preimplantation embryos. Prior to their aggregation into pairs, one of the embryos was labelled with a viable fluorescent dye to determine the relative cellular contribution from

each partner embryo when chimeras were dissociated 30-35 h later (2-3 cell cycles). Direct cell-cell contact of embryos derived from exposed males and embryos from control males creates a competitive situation that has been shown to confer a cell proliferation disadvantage to the embryo from an exposed parent. The cell proliferation disadvantage is expressed as the ratio between the number of cells from an experimental embryo and the total chimera cell number. Proliferation ratios were significantly decreased in all embryos fertilised by sperms exposed at week 4, corresponding to the pachytene stage of spermatogenesis. The authors suggest that effects induced in the spermatids are transferred to the embryo via a non-mutagenic process (90).

Testicular response to EGME was compared in rats and guinea pigs. Single doses of 200 or 300 mg/kg caused marked depression in dividing spermatocytes whereas triple doses of 200 mg/kg per day for 3 days caused complete spermatocyte depletion. The effects in guinea pig were less severe and also differed in onset and histological characteristics (62). In a subsequent study the same researchers showed that the spermatocyte degeneration is associated with programmed cell death (apoptosis) (63).

The effects of MAA were studied *in vitro* in cultured rat seminiferous tubules and human testicular tissues. Apoptosis of germ cells was seen in both species at 1 mmol/L MAA but not at lower concentrations. Addition of known calcium channel blockers to the medium prohibited the apoptotic effect of MAA whereas substances acting as inhibitors of calcium mobilisation from intracellular stores were ineffective (68, 69).

Repeated exposure of rats to EGME for 10 days administered in the drinking water at doses corresponding to 43, 87, and 220 mg/kg/d caused significant testicular damage, reduced relative testicular weight, and reduced body weight gain at the highest dose. In contrast, the urinary creatine: creatinine ratio was significantly increased at the high and the mid dose and, on some days, also in the low dose group. The authors suggest that the urinary creatine: creatinine ratio may be a useful marker for chronic testicular damage (12).

7.6.2. Effects in females

Female reproductive toxicity of EGME was studied *in vivo* in rats after oral administration of EGME and *in vitro* in cultured rat luteal cells after addition of the metabolite MAA. Daily gavage of 300 mg/kg EGME resulted in a complete suppression of cyclicity without evidence of systemic toxicity within 3 - 8 days, whereas doses less than 100 mg/kg had no effect. The suppression of cyclicity was associated with inhibited ovulation, hypertrophy of the corpora lutea, elevated serum progesterone, whereas serum estradiol, follicle stimulating hormone, luteinising hormone, and prolactin remained at baseline levels. *In vitro*, elevated progesterone levels were seen already at 1 mmol/L MAA, the lowest concentration tested (19).

MAA was tested in a system with cultured human luteinised granulosa cells *in vitro*. Treatment with 0-5 mmol/L MAA for 6-48 h caused an increase in progesterone that depended on both exposure duration and concentration used. The

effect was significant at 1 mmol/L but tendencies were seen also at 0.1 and 0.5 mmol/L MAA. This implies that EGME has the potential to alter ovarian luteal function in women (3).

Intraperitoneal injections of 250 or 500 mg/kg EGME or its metabolite MAA on day 11 of gestation caused marked congestion, haemorrhages, necrosis and desquamation in the placenta. These lesions signify a disordered maternal circulation which, according to the authors, may play a role in the embryotoxic and teratogenic effects of EGME and MAA (60).

7.6.3. Effects in offspring

Pregnant monkeys (*Macaca fascicularis*) were gavaged during organogenesis (day 20-45) with 0.16, 0.32, or 0.47 mmol/kg EGME, corresponding to daily doses of 12, 24, or 36 mg/kg per day. The treatment caused maternal toxicity, expressed as moderate to markedly reduced appetite and weight loss. The affected animals were given additional nutrients by gavage. Foetuses were collected at day 100 by Caesarean section. At the highest dose level, all 8 pregnancies ended in death of the embryo. One of the embryos lacked a digit on each forelimb, a malformation hitherto not observed in this species. In the mid-dose group 3 of 10 and in the low dose group 3 of 13 pregnancies ended in embryonic death. These frequencies can be compared with those of the untreated control group (0 of 6 pregnancies) and a control group dosed with 0.47 mmol/kg/d ethanol (0 of 3). No malformations were seen in live foetuses. Based on the malformation and the appearance of dead embryos the authors suggested that the effects seen are directly related to exposure to EGME, and not secondary to maternal toxicity. In an additional experiment a dose-related decrease in foetal weight was seen at day 35 but not at day 100 of gestation (105).

Male rats were exposed to 25 ppm EGME (7 h/day, 7 days/week) for 6 weeks and then mated with unexposed females. In addition, female rats were mated with unexposed males and then exposed to 25 ppm EGME on gestation days 7-13 or 14-20. No paternal or maternal effects were seen. Six different behavioural tests revealed significant differences from controls only in avoidance conditioning of offspring of mothers exposed on days 7-13. Neurochemical deviations were seen in brains from 21 days old offspring of both the paternally and maternally exposed groups. These deviations were numerous in the brainstem and cerebrum, and fewer in the cerebellum and midbrain. Thus, acetylcholine was reduced to about one third in all EGME-treated groups, as compared to the controls. Conversely, acetylcholine increased by three-fold in the brainstem. Similar changes were seen for norepinephrine and 5-hydroxytryptamine whereas changes in the opposite direction were seen for dopamine. The mechanism of the neurochemical changes was not addressed (82).

A synergistic teratogenic effect between EGME and radio frequency radiation has been reported. Groups of 18-27 pregnant rats were gavaged with distilled water or EGME (150 mg/kg) on day 13 of gestation with or without concurrent exposure to radio frequency radiation at 10 MHz at an intensity (0.8-6.6 W/kg) selected to cause a 4°C increase in body temperature. The number of malformations per litter

increased from 0% in controls to 14% in EGME only, 30% in radio frequency only and 76% in combined treatment (83). In a follow up study, different dose levels and different dosing days were tested. As in the previous study, a synergistic effect was seen at high EGME doses (75-150 mg/kg), whereas low doses (20 and 40 mg/kg) produced antagonistic effects between EGME and radiation (84, 85).

Daily oral dosing of female rats with 50 mg/kg/d EGME on day 7-13 resulted in prolonged gestation length and reduced litter size, perinatal survival, and postnatal growth. Electrocardiographic changes at 3 and 6 weeks of age, interpreted as a intraventricular conduction delay, were seen in nearly 50% of the offspring. At a slightly higher dose of 75 mg/kg/d there were no survivors beyond 3 days of age (120). Daily doses of 25 mg/kg caused reduced ornithine decarboxylase activity in the heart muscle of the offspring but no other signs of reproductive toxicity (121, 123).

The embryotoxic and teratogenic properties of EGME are highly dependent on the timing of exposure. Thus, single oral doses of 500 mg/kg given to female mice on day 10 through 15 of gestation caused time dependent decreases in embryo lethality, from 100% day 10 to 5% on day 15, as compared to 2% in control animals. A parallel decrease in malformations, from 100% to 0%, was seen (106). Similar results have been obtained in several studies with EGME and MAA. In one study on mice different doses of EGME were given on gestation days 8 or 9, either as an intravenous bolus or as a subcutaneous infusion. The frequency of exencephalies (frequency range 0-48%, dose range 0-606 mg/kg) strongly correlated with the maximum level of MAA, but not with the area under the concentration-time curve (AUC) of MAA, in maternal and embryonal plasma (118). An oral dose of 10 mmol/kg (700 mg/kg) at 10.5, 11 and 11.5 days after conception resulted in different malformation patterns in the extremities. The most pronounced effects were seen after dosage at day 11.5 (96). In a third mouse study, neural development was followed after subcutaneous administration of 250 mg/kg EGME on gestation day 8. Open neural tubes appeared at a higher frequency compared to controls at all days examined (gestation days 9, 10, and 18). The most pronounced effects were seen on day 9, suggesting partial recovery and catch-up in neurolation later during gestation (119).

Teratogenic effects of EGME have been documented in various strains of *Drosophila melanogaster*, including a strain that lacks alcohol dehydrogenase. According to the authors this shows that EGME itself acts as a teratogen (26).

7.7. Immunotoxicity

Male mice were given different intravenous doses of bacterial endotoxin followed by an additional intravenous dose of 950 mg/kg EGME. The EGME treatment caused a 64-fold increase in sensitivity, in that the endotoxin LD_{50} changed from 17 to 0.25 mg/kg (33).

In male rats given human leukaemia cells by subcutaneous injections, all clinical, morphological, and histological signs of leukaemia disappeared when the animals were supplied with 2.5 mg/ml EGME via the drinking water. Addition of

0.25 mg/ml, corresponding to a daily dose of 15 mg/kg, reduced the leukaemia response by 50%. The closely related substance ethylene glycol monoethyl ether (EGEE) also depressed the response, but was ten times less potent than EGME. Seven other glycol ethers were ineffective. Experiments carried out *in vitro* with the same leukaemia cell line showed a concentration dependent reduction in cell count in the interval 1-100 µmol/L EGME. The metabolite MAA was approximately half as effective as EGME, unlike the results of teratogenic or spermatotoxic experiments carried out by other investigators. According to the authors, these observations suggest that cytotoxicity is not solely responsible for the antiproliferative activity of EGME (21).

A markedly atrophic cortex and almost intact medulla were seen in the thymus of mice gavaged with 100 or 500 mg/kg/day EGME for 5 to 10 days. Study of thymocyte surface markers revealed a decrease in immature thymocytes in treated animals (58).

Female rats exposed to 2000 and 6000 ppm EGME in drinking water (corresponding to 161 and 486 mg/kg per day, respectively) for 21 days expressed increased natural killer cell activity and reduced thymus weight, anti-KLH IgG production, splenocyte gamma-interferon production (high dose only), and spleen cell number. Male rats exposed to 1600 and 4800 ppm (200 and 531 mg/kg/d) were similarly affected. In addition, splenocyte gamma-interferon and testis weight reductions were seen at both dose levels and thymus atrophy and depressed interleukin-2 production at the high dose (30).

A single oral dose of 125 mg/kg EGME caused a 3-fold increase and 500 mg/kg an 8-fold increase in apoptotic index (programmed cell death) in the thymus, compared to untreated animals. Pre-treatment with phenobarbital abolished almost completely the apoptotic effect. In parallel, a decreased capacity of the liver to metabolise EGME to MALD and a marked enhancement in the capacity to metabolise MALD to MAA were seen (7).

Immune responses were studied in rats and mice following oral treatment with EGME, EGMEA, MALD, and MAA at daily doses of 50, 100, 200 and 400 mg/kg for 10 days. In rats, the four substances resulted in similar immunosuppression in the rat, expressed as reductions in thymus and spleen weights and antibody plaque-forming cell response. Significant effects were seen already at the lowest dose tested and equal doses resulted in equivalent degrees of suppression. Pre-treatment with the alcohol dehydrogenase inhibitor 4-metylpyrazole blocked the immunosuppressive effects of EGME. Further, pre-treatment with the aldehyde dehydrogenase inhibitors disulfiram or cyanamide blocked the immunosuppression otherwise seen with EGME and MALD. Altogether, these data show that metabolism of EGME and EGMEA to MALD or MAA is required for the development of immunotoxic effects in rats. In a comparative study, immunosuppression was recorded in all rat strains tested but in none of the mouse strains. Not even very high doses of up to 1920 mg/kg/d MAA given subcutaneously via a miniosmotic pump caused immunosuppression in the mouse. This suggests that the observed species differences cannot be explained by differences in bioavailability or MAA biotransformation capacity (97, 107-112).

Further studies *in vitro* showed that the immunosuppressive actions (decrease in polyclonal IgM and IgG antibody responses) of EGME (effective concentrations 0.5-1.0 in mouse and 2.0 mmol/L in rat) and MAA (effective concentrations 12.5 and 25 mmol/L, respectively) were more pronounced in mouse than in rat lymphocytes, whereas MALD was equally effective in both species (effective concentration 0.3 mmol/l in both species). Further, immunosuppression was markedly higher in rat lymphocytes co-cultured with mouse hepatocytes than when co-cultured with rat hepatocytes (61). These results indicate that MALD or some other intermediary metabolite may be the proximate immunotoxicant.

Female mice were gavaged with 100, 150 or 200 mg/kg/d EGME on days 10-17 of gestation and immunology parameters were analysed in the foetuses on day 18. Thymus atrophy, dose dependent reduction in cellularity, and changes in thymocyte pattern, suggesting impairment of thymocyte maturation, were seen in the exposed foetuses. EGME also reduced the percentage of CD45+ leukocytic cells in foetal liver. Addition of 10, but not 1, µmol/L MAA to foetal liver cells *in vitro* impaired the proliferative capacity, expressed as a reduction in ^{3}H-thymidine incorporation. No effect on hepatocyte survival was seen (43).

Immune effects were studied in male rats following occluded dermal applications of 150, 300, 600, 900, and 1200 mg/kg/d EGME for 4 days. Decreases in thymus weight were seen at all dose levels and in spleen weight at the two highest doses. The lymphoproliferative responses to phytohemagglutinin and pokeweed mitogen were enhanced at 1200 mg/kg/d. In a separate experiment, reductions in antibody plaque-forming cell response to either trinitrophenyl-lipopolysaccharide or sheep red blood cells were seen at 600 and 300, but not 150 mg/kg/d. These effects occurred in the absence of body weight losses. Similar effects were seen after oral administration of 25, 50, 100, and 200 mg/kg/d EGME for 4 days (131).

7.8. Other effects

EGME was ineffective whereas 0.5 mmol/L MAA caused increased osmotic fragility in human erythrocytes *in vitro*. Incubation of human erythrocyte membranes (ghosts) inhibited membrane bound acetyl cholinesterase (IC_{50}=5.5 mmol/L) and ATPase (IC_{50}=1.4 mmol/L) activities (77).

Male rats exposed to 75 ppm EGMEA, 8 h per day for 4 weeks expressed changes in serum protein patterns, revealed by two-dimensional electrophoresis. At least 12 unidentified (out of 410) proteins were dramatically changed. Exposure to isobutylacetate caused yet another protein pattern and exposure to a combination of EGMEA and isobutylacetate caused additional changes (134). Oral administration of 100 or 300 mg/kg/d EGME to male rats for up to 4 weeks caused a dose dependent increase in gamma-glutamyltranspeptidase activity in serum, liver and lungs (56). Depressed activities of the enzymes acetyl cholinesterase and delta-aminolevulic acid dehydratase (ALA-D) were seen in erythrocytes, blood and bone marrow from rats 3 days after a peritoneal injection of 200 mg/kg EGME (66).

8. Observations in Man

8.1. Acute effects

Three cases of acute intoxication after ingestion of EGME have been reported. A man who drank half a pint of EGME died with acute haemorrhagic gastritis and degenerative changes in the kidneys, liver and pancreas (133). Two men who consumed approximately 100 ml EGME became mentally confused and complained of weakness and nausea. They became cyanotic and developed hyperventilation, tachycardia, and metabolic acidosis. One of them developed renal failure. Both men recovered within four weeks (87).

8.2. Effects of repeated exposure on organ systems

According to older reports, repeated occupational exposure to EGME presumably at high concentrations affects the central nervous system with symptoms such as headache, fatigue, general weakness, drowsiness, ataxia, and irregular pupils (11, 22, 35, 91).

Six poisonings with pronounced central nervous system effects and, in one man (the only case studied in this respect) hypocellular bone marrow, were reported in the fifties. The men were cleaning machines in a printing shop and the effects appeared after replacement of the cleaner solution from a mixture of heavy aromatics and isopropanol to EGME. At reconstruction of the work procedures ambient air levels of between 61 and 3960 ppm EGME were measured (135).

One report describes a man with apathy, somnolence and prolonged sleep time. The man was engaged in microfilm production and was reportedly exposed to EGME via inhalation as well as via skin. Blood examination revealed reductions in red cell, white cell and thrombocyte counts, and in haemoglobin and haematocrit. Air measurements revealed EGME levels between 18 and 58 ppm. Methyl ethyl ketone and propylene glycol monomethyl ether (PGME) were detected at lower concentrations. All haematologic parameters normalised within a month after terminated exposure (16).

Three young women employed in a frame factory used a mixture of 30% EGME and 70% acetone to glue together cellulose acetate frame components. Periodic examinations revealed abnormally low white blood cell counts with a relative lymphocytosis, macrocytosis with red blood cells, and haemoglobin at borderline values. In two of the women blood values normalised within one year after cessation of exposure. The work area was well ventilated and the authors suggest that exposure occurred predominantly or exclusively via skin (65).

One case report describes two workers preparing screens for use in textile printing. The mandril was cleaned by hand rubbing with acetone. During the energy crisis in the spring of 1974, acetone was replaced by EGME. In August the same year, one worker developed symptoms initially interpreted as encefalopathy, bone marrow depression and pancytopenia. He was replaced by another man who developed similar but less severe symptoms within a month. The two men re-

covered within several weeks and one week, respectively, after exposure was discontinued. Air measurements revealed levels of about 8 ppm EGME at the work site. No protective equipment was used (88).

Ambient air levels of 4-20 ppm and breathing zone levels of 5.4-8.5 ppm EGME (2-h time-weighted averages) were recorded in a cohort of 65 workers engaged in production and packaging of EGME. Non-significant tendencies towards reductions in white blood cell count and haemoglobin were seen in 40 exposed workers, as compared to 25 unexposed controls. A subgroup of 6 exposed and 9 unexposed individuals were examined more thoroughly. Tendencies towards reductions in white blood cell count, haemoglobin, testicular size, sperm count, serum testosterone, and serum FSH along with a tendency towards increased serum luteinising hormone were found. No gross abnormalities or clinically meaningful deviations in haematological or fertility indices were seen (17).

Out of 73 shipyard painters examined, 10% were anaemic and 5% granulocytopenic, compared to 0% in unexposed controls. Exposure levels were 0-5.6 (mean 0.8 ppm, median 0.4) ppm EGME and 0-21.5 (mean 2.6, median 1.2) ppm EGEE. Review of company records documented that most of these abnormalities were acquired during employment. According to the authors there was no exposure to lead or other chemicals known to cause haematological effects (125).

Changes in lymphocyte subpopulations, similar to those seen in immunodeficiency and immunogenetic forms of aplastic anaemia, were detected in nine floorers exposed to organic solvents, as compared to unexposed controls. Solvent exposure included EGME (mean 6.1, maximum 150 mg/m^3), EGEE (mean 4.8, maximum 53 mg/m^3), ethylene glycol monobutyl ether (EGBE), butanol, isobutanol, toluene, xylene, methyl ethyl ketone and methyl isobutyl ketone. Judging by solvent levels in blood, the predominant exposure was EGME (mean 0.4, maximum 9.7 mg/L). Changes in peripheral lymphocytes included decreases in total T cells and T helper cells, and increases in NK cells and B cells, whereas the suppressor cell count was unaffected. In addition, there were tendencies towards decreases in haemoglobin and red blood cell count. According to the authors, it is not known whether the observed change in lymphocyte counts is an indicator of early haematological and/or immunological effects which may eventually cause disorders of the haematopoietic and/or lymphopoetic system (20).

8.3. Genotoxic effects

No studies were found dealing with genotoxic endpoints in humans exposed to either EGME or EGMEA.

8.4. Carcinogenic effects

Acute myeloid leukaemia (198 cases) was studied in a French case-control study. For each case and control, exposure to glycol ethers was assessed in a blinded fashion by an expert in industrial hygiene. The exposure assessment was based on a job description obtained by an interview and a questionnaire. No significantly

elevated odds ratio for any group of glycol ether was seen. The odds ratio for exposure to group I glycol ethers (including EGME, EGMEA, EGEE, EGEEA, and a number of other ethylene glycol methyl and ethyl ethers) was 0.62 (95% CI 0.33-1.15, 26 cases). The only odds ratios above one in group I were those for exposure level 3 (OR 1.12, 95% CI 0.42-3.03) and latency below 11 years (OR 1.26, 95% CI 0.29-5.47) (number of cases not reported). The odds ratios for acute myeloid leukemia of the type FAB M2 (number of cases not reported) were higher than one in all glycol ether groups except group I, although none of the increases were statistically significant (46).

8.5. Reproductive and developmental effects

8.5.1. Effects in men

A case-control study was conducted among first time patients at a clinic for reproductive disorders. The study group consisted of 1019 cases diagnosed as infertile or subfertile and 475 controls diagnosed as normally fertile by spermiograms. Possible exposure to ethylene glycol ethers was assessed by the presence of the urinary metabolites. In total, ethoxyacetic acid (EAA), suggesting exposure to EGEE or its acetate ester, was detected in 39 cases and 6 controls (odds ratio of 3.11, $p = 0.004$). In contrast, MAA was only found in one case and two controls (130). Thus, the study supports an effect of EGEE but is inconclusive with respect to EGME. Whereas the expected latency period between exposure and sperm effects is several weeks, presence of acid metabolite in urine indicates exposure during the last few days. Therefore, exposure misclassification and, hence, underestimation of the true risk is highly probable.

The semen of 73 painters and 40 controls who worked in a large shipyard was examined. Painters had an increased prevalence of oligospermia (10/73 versus 0/40 in the control group) and azoospermia (4/73 versus 0/40) and an increased odds ratio for a lower sperm count per ejaculate (odds ratio 1.9, 95% CI 0.6-5.6), while smoking was controlled. There was no difference in fertility between groups. The industrial hygiene survey revealed exposures to 0-17.7 mg/m^3 EGME with a mean of 2.6 mg/m^3 and 0-80.5 mg/m^3 EGEE with a mean of 9.9 mg/m^3 (time-weighted averages). Urinalysis of EAA suggested extensive dermal exposure (126).

8.5.2. Effects in women

An increased frequency of spontaneous abortions was noted in women employed in semiconductor industry. Spontaneous abortions were assessed by structured interviews, blinded with respect to occupational history. Increased risk was observed in the ”diffusion” (18 pregnancies, 39% abortions, relative risk 2.2, 95% CI 1.1-3.6) and photolitographic (16 pregnancies, 31% abortions, relative risk 1.8, 95% CI 0.8-3.3) processes. The frequency of spontaneous abortions in unexposed controls (398 pregnancies) was 18%. The diffusion process was associated with exposure to arsine, phosphine, and diborane while the photolitographic process involved glycol ethers, xylene, toluene, and hexamethyl disilane. According to the

authors, general population studies have usually reported spontaneous abortion ratios in the 10-20% range (92). Following this report several epidemiologic studies were initiated in the semiconductor industry.

An extensive study of reproductive outcome in the semiconductor industry was published in 1995 (103). In industrial hygiene surveys it was found that 15-20% of the work sites used negative photoresist chemicals containing usually 3% EGME. All personal samples revealed air levels below 10 ppb EGME, whereas the average exposure to other glycol ethers were 22 ppb EGEEA and 8 ppb propylene glycol monomethyl ether acetate (PGMEA, 1-methoxypropyl acetate) (40). Exposure to ethylene glycol ethers was highly correlated with exposure to xylene and n-butylacetate (41).

The risk of spontaneous abortions was studied in a historical cohort covering 904 pregnancies and 113 clinical abortions among 6088 employees in 14 semi-conductor industries. A higher frequency of spontaneous abortions was seen in fabrication (15.0%) compared to non fabrication employees (10.4%) with a relative risk of 1.43 (95% CI 0.95-2.09) after controlling for age, smoking, ethnicity, education, income, year of pregnancy, and stress by logistic regression. The highest risk was seen in masking (17.5% spontaneous abortions, relative risk 1.78, 95% CI 1.17-2.62). Within masking, the highest risk was found in etching-related processes (22.2% spontaneous abortions, relative risk 2.08, 95% CI 1.27-3.19) (8). In a follow-up study, the outcome of 891 pregnancies was examined in relation to exposure factors. Fabrication-room workers exposed to photoresist and developed solvents, including ethylene glycol ethers (EGME, EGEE and their acetates), and fluoride compounds used in etching (mostly so-called buffered-oxide etch, an aqueous solution of hydrofluoric acid and ammonium fluoride) were at greater risk (relative risk 3.21, 95% CI 1.29-5.96), whereas fabrication workers without these exposures showed no increase in spontaneous abortions (116).

In a prospective study at the same companies 403 women were followed for five menstrual cycles. Daily urine samples were analysed to confirm clinical spontaneous abortions and early foetal losses. After control for opportunity to become pregnant, use of oral contraceptive, and age, a significantly reduced fecundability was seen in dopant workers (adjusted fecundability ratio 0.22, 95% CI 0.05-0.96, for clinical pregnancies) and the same tendency in workers exposed to ethylene glycol ethers (adjusted fecundability ratio 0.37, 95% CI 0.1-1.2) (28). Of 19 pregnancies in the cohort, 12 (63%) ended in spontaneous abortion compared to 33 pregnancies and 15 abortions (46%) among controls. Logistic regression to control for smoking, ethnicity, income, education, and previous pregnancies and abortions demonstrated that this increase was statistically significant. Among women exposed to ethylene glycol ethers all 3 pregnancies ended in spontaneous abortion (relative risk 2.0, 95% CI 1.5-2.8) (29). In a parallel study, the menstrual cycle of 402 women was followed by means of questionnaires, diaries and daily urine sampling for assay of reproductive hormones. Thin film and ion implantation workers had significantly longer menstrual cycles (36.1 days) than non fabrication workers (32.0 days). In addition,

thin film, ion implantation and photolitography workers had significantly higher variability in cycle length (34).

In an overview of the semiconductor industry study, Schenker and colleagues concluded that the association between spontaneous abortions and fabrication work is strengthened by the fact that similar findings were obtained in different populations and in historical as well as prospective cohorts. The findings are also consistent with that of other investigators. Further, the historical cohort suggested an association with fluorides and photoresist or developer chemicals (ethylene glycol ethers, n-butyl acetate, and xylene). Exposure to these chemicals was highly correlated limiting the ability to analyse the outcome of exposure to any single substance. Another important finding was the absence of an independent association of spontaneous abortions with dopant gases (arsenic, phosphorous, boron, antimony), cleaning solvents (acetone, isopropanol, methanol), electromagnetic fields, or radio frequency radiation (104).

In a study of 454 past pregnancies among 1368 semiconductor employees, tendencies towards increased risk of spontaneous abortions were seen in wafer fabrication (odds ratio 1.6, 95% CI 0.8-3.4) and in nonfabrication but chemically exposed women (odds ratio 2.0, 95% CI 0.9-4.7) after control for age, alcohol during pregnancy and salary type. The risk of stillbirth showed a similar tendency. According to the authors, wafer fabrication is associated with exposure to ethylene glycol ethers as well as other organic solvents, the most common being xylene, n-butylacetate, acetone, and 1,1,1-trichloroethane. However, no hygienic measurements were conducted in this study (94).

Reproductive outcome was studied in a cohort of female employees (561 pregnancies) and spouses of male employees (589 pregnancies) in two semiconductor manufacturing plants. Increased risks of spontaneous abortion (22 pregnancies, relative risk 2.8, 95% CI 1.4-5.6) and subfertility (more than one year of unprotected intercourse to conceive, relative risk 4.6, 95% CI 1.6-13.3) were seen among the female employees with the highest potential for exposure to ethylene glycol ethers. Both of these risks exhibited a significant dose-response relation with potential ethylene glycol ether exposure. A tendency towards subfertility was seen among spouses of male employees (relative risk 1.7, 95% CI 0.7-4.3). Glycol ethers specifically mentioned were diethylene glycol dimethyl ether (DEGDME) and EGEEA, with levels below 0.2 ppm in the high exposure group. No increases in risk were seen in women exposed to n-butylacetate, N-methyl-2-pyrrolidon, or xylene without concurrent potential exposure to glycol ethers (18).

A common characteristic of the semiconductor industry epidemiologic studies is that data on air levels of contaminants are scarce. The few available data indicate exposure to ethylene glycol ethers in the sub-ppm range. In a separate study, analysis of about 400 air samples revealed average levels of 0.1 ppm EGME and 0.01 ppm EGMEA (93). Another common feature is that no exposure to reproductive toxicants, other than ethylene glycol ethers, could be demonstrated.

8.5.3. Teratogenic effects

A woman was exposed to EGMEA by dermal contact and probably also by inhalation during two pregnancies. Both children suffered from hypospadia. The family history and medical examination showed no overt risk factor other than the EGMEA exposure. The risk for isolated hypospadia is reportedly between 1 in 300 and 1 in 800 whereas that of repeated hypospadia (the risk when hypospadia has already occurred in a sibling) is 1 in 24 (10).

A total of 44 patients in Matamoros, Mexico, had a peculiar phenotype with facial and musculoskeletal malformations and mental retardation. All were born 1971-1977. Based on this finding, a case-control study was performed, considering the 44 patients as cases and healthy siblings as controls. Another control group was formed by 90 patients in the same region with other malformations or mental retardation. In all cases, but in none of the controls, the mother had been working in the same factory during pregnancy. The factory manufactured radio and television capacitors and was operating between 1970 and 1977. Work practices included dipping the hands in a solution mainly consisting of EGME and ethylene glycol. No other chemical exposures were mentioned by the authors. Ventilation was absent and gloves or breathing masks were not used. No quantitative data on exposure are available. Work was associated with signs of acute intoxication, fatigue, vertigo, nausea, and vomiting. Of the 44 patients, 32 were the only sibling affected in the family. In none of these 32 cases were there any family history of malformations or any familiar relationship between cases. A closer investigation of 28 patients revealed that all had facial malformations and musculoskeletal defects in the spine, hands, and feet and that about one half also expressed ocular and otological defects (100, 101).

Congenital malformations were studied in a European collaborative case-control study (991 cases, 1144 controls) by combining six registers in four countries. Based on structured interviews on occupational history, potential exposure to different types of glycol ethers were assessed for each trimester by occupational hygienists. According to a preliminary report, there was a significant excess of mothers exposed to glycol ethers during the first trimester in the groups of oral clefts (odds ratio 2.0, 95% CI 1.1-4.1), central nervous system malformations (odds ratio 1.8, 95% CI 1.1-3.3) and musculoskeletal malformations (odds ratio 1.6, CI 0.9-2.8) were noted (Ha et al. 1996). The results are remarkable, considering the high level of uncertainty in exposure categorisation which tends to decrease the odds ratios. Notably, as many as 20% of the controls and 27% of the cases were classified as exposed to glycol ethers during the first trimester. However, only one of the cases was considered exposed to type 1 glycol ethers, *i.e.* EGME, EGEE or their acetates.

9. Dose-Effect and Dose-Response Relationships

Impaired cell division has been demonstrated in mouse foetal liver cells *in vitro* after addition of 10 µmol/L MAA (43). According to a toxicokinetic model (128) this concentration would correspond to 8 h exposure at 1 ppm EGME.

Dose-effect and dose-response relationships in laboratory animals are illustrated by Tables 1 and 2.

The first effects occurring at low doses after oral administration are as follows. In a single study in monkey, increased embryo lethality was reported after oral exposure to 12 mg per kg and day during gestation (105) (Table 1). An immuno stimulating effect was observed in rat at 15 mg/kg/d (21). At 25 mg/kg/d, testes and sperm defects were seen in rabbit (9, 31) and prolonged gestational time, reduced litter size, and increases in malformations in rat (121, 123, 124). Doses of 50 mg/kg/d resulted in thymus alterations, immunosuppression, foetal toxicity, and malformations in rodents and completely disrupted spermatogenesis in rabbits. Doses around 100 mg/kg/d induced similar but more severe effects and, in addition, bone marrow depression, impaired haematopoiesis, and reduced fertility.

Neurochemical deviations were seen in the offspring of female as well as male rats exposed to 25 ppm EGME during gestation and prior to mating, respectively (Table 2). These deviations were seen in the absence of overt maternal or paternal toxicity. Inhalation exposure of pregnant rodents to 50 ppm EGME resulted in foetal toxicity, skeletal variations, and malformations in parallel with reduced maternal weight gain. Notably, most of these effects are seen in all species and all exposure routes examined and at approximately the same exposure levels. Based on the inhalation data in Table 2, a no observed effect level (NOEL) of 10 ppm for rats and mice and of 3 ppm for rabbits may be deduced (Hanley 1984), cited by (25). The oral gavage data in Table 1 suggest a NOEL of 12 mg/kg/d for male rabbits, whereas no NOELs can be identified for monkeys, rats, and mice.

Abnormal peripheral blood picture, disturbed haematopoiesis, reduced testes size, and oligospermia have been observed after occupational exposure to EGME at air levels between 0.4 and 10 ppm EGME and with additional dermal exposure (Table 3). The observed effects are in good agreement with those seen in laboratory animals at somewhat higher air levels of EGME and are most likely due to EGME, even if other exposure factors cannot be completely ruled out in each case.

Female reproductive effects, expressed as disturbed menstrual cycle, subfertility, and increased frequency of spontaneous abortions, have been demonstrated in women working in the semiconductor industry. Also these effects are in agreement with the findings on EGME in animal experiments. Furthermore, ethylene glycol ethers have been attributed by the investigators as the most plausible agent and EGME appears to be the most potent reproductive toxin among the glycol ethers. Still, the importance of EGME in relation to other exposure factors is unclear. The exposure levels of EGME in the semiconductor industry were apparently in the sub-ppm range.

Table 1. Selection of oral toxicity studies illustrating the dose-effect relationship for EGME

Dose, mg/kg/d	Exposure duration	Species	Animals per dose group	Observed effects	References
12	Day 20-45 of gestation	Monkey	8-14 females	4/14 (29%) dead or resorbed fetuses	105
24				4/11 (36%)	
36				8/8 (100%)	
12	5 d/wk, 12 wk	Rabbit	6-7 males	No observed effects	9, 31
25				Reduced testes weight, impaired sperm quality and spermatogenesis	
38				Idem + severely disrupted spermatogenesis	
50				Nearly completely disrupted spermatogenesis in 5 of 7 rabbits	
15	60 d	Rat	8-10 males	50% reduction in leukemia response after s.c. injection of human leukemia cells	21
150				No leukemia response	
25	4 d	Rat	6 males	No observed effects	131
50				Reduced thymus weight, reduced PFC response	
100				Idem	
200				Idem + reduced spleen weight, increased lymphoproliferative response	
25	Day 7-13 of gestation	Rat	8-11 females	Reduced litter size, cardiovascular and other malformations, abnormal ECG	124
50				Idem, effects more pronounced	
25	Day 6-12 of gestation	Rat	8 females	Prolonged gestation	121
50				Idem + reductions in litter size, birth weight, and embryonic ornitindekarboxylase activity	
75				Idem, effects more pronounced	
25	Day 7-13 of gestation	Rat	13 females	Prolonged gestation, reduced neonatal ornitindekarboxylase activity	123
	Day 13-19			No observed effects	

continued

Table 1 (continued)

Dose, mg/kg/d	Exposure duration	Species	Animals per dose group	Observed effects	References
31	Day 7-14	Mouse	21-24 females	Delayed ossification, skeletal variations(82%)	80
62	of gestation			Idem + skeletal variations(91%), skeletal malformations (9%)	
125				Idem + reduced fetal weight, skeletal variations(100%) and malformations (44%), tendency to serious malformations (3%)	
250				Idem + reduced maternal weight gain, reduced number of live born fetuses (47%), skeletal (100%) and serious (37%) malformations	
500				0.3% live born	
1000				No live born fetuses	
43	10 d	Rat	5-6 males	Dose-dependent increase in creatine: creatinine ratio, significant at all dose levels	12
87				Occasional testicular damage (depletion of tubules, spermatids, spermatocytes)	
220				Reductions in body weight gain and relative testicular weight, marked testicular tubular damage	
50-400	10 d	Rat	6 males	Dose-dependent immuno supression, significant at all doses	97, 112
		Mouse		No immunology effects	
50	Day 7-13	Rat	14-21 females	Prolonged gestation, reduced litter size, increased perinatal mortality, slower postnatal growth, abnormal ECG in offspring	123
75	of gestation			100% pre- and perinatal mortality	
50	Day 9-15	Rat	12-14 females	Reductions in implantation, litter size and fetal weight, 58% malformed fetuses, changes in calcium and vitamin D turnover (secondary effect?)	122
100	of gestation			No live fetuses	

continued

Table 1 (continued)

Dose, mg/kg/d	Exposure duration	Species	Animals per dose group	Observed effects	References
50 100 250-500	11 d	Rat	36 males	No observed effects Testicular degeneration Idem + reduced testes weight	Foster 1983, cited by (25)
50 100-200	5 d	Rat	20 males, 40 untreated females	Reduced sperm count, mild testicular effects Idem + marked testicular effects, abnormal sperms, impaired fertility, reduced litter size	Chapin 1985, cited by (25)
50 100 200	10 d	Rat	6-8 males	Immunosuppression Idem Reduced testes weight, increased serum testosterone	Smialowicz 1991, cited by (25)
50 100 200	4 d	Mouse	7-10 females, 7-10 males	Reductions in granulopoetic stem cells and white cell count (males) Idem + bone marrow hypocellularity, reductions in red cell count, hemoglobin, and erythropoetic stem cells (females) Idem + reduced testes weight, degeneration of germinal epithelium (males)	44
50 200 750 1500	5 d	Mouse	20-49 males	Significant dose-dependent reduction in proliferation of embryonic cells stemming from exposed males (chimera assay)	90
62.5 125 250 500-1000 2000	5 d/wk, 5 wk	Mouse	5 males	No observed effects No observed effects Testicular atrophy Idem + reductions in red and white cell counts and hematocrit All animals died	Nagano 1979, cited by (25)

continued

Table 1 (continued)

Dose, mg/kg/d	Exposure duration	Species	Animals per dose group	Observed effects	References
62.5-500	5 d/wk, 5 wk	Hamster	4 males	Dose-dependent reductions in testes weight, significant at all dose levels	Nagano 1984, cited by (25)
100 150 200	Day 10-17 of gestation	Mouse	5 females	Offspring: dose-dependent hypocellularity in thymus (all dose levels), reduction in CD45 positive cells in liver (not examined at lowest dose)	43
100 300	20 d	Rat	5-6 males	Marked, dose-dependent increases in γ-glumly transpeptidase activities in serum, liver and lungs	56
100 300	20 d	Rat	5-6 males	Tendency to increased ADH activity in liver cytosol Increased ADH activity in liver cytosol	57
100 300	20 d	Rat	4 males	Reduced body, thymus, and testes weights Idem + reduced liver, kidney, spleen, and heart weights, marked decrease in number of lymphocytes in thymus	Kawamoto 1990, cited by (25)
100 500	4 d	Rat	24 males	Reductions in leukocyte, neutrophil, and lymphocyte counts, thymus weight, and extramedullar hemato-poesis Idem, marked effects + reductions in red cell count, hemoglobin and hematocrit, and testes weight, transient bone marrow hyperplasia	Grant 1985, cited by (25)
100 175 250 300 400-500	Day 11 of gestation	Mouse	9-11 females	Dose-dependent reduction in fetal weight (significant from 250 mg/kg) Malformed limbs in approx. 30% of fetuses Idem, approx. 70% Idem, approx. 77.5% Idem 100%	45
100 250 350	Day 11 of gestation	Mouse	2-3 females per observation	No observed effects No observed effects Signs of cytotoxicity in forelimb buds 2 h after dosage, maximum effect after 6 h, without overt maternal toxicity	Greene 1987, cited by (25)

continued

Table 1 (continued)

Dose, mg/kg/d	Exposure duration	Species	Animals per dose group	Observed effects	References
100 175 250 300 350-500	Day 11 of gestation	Mouse	16-18 females	No observed effects 12% of fetuses had malformed forelimb buds Idem, 42% Idem, 73% Idem, 83-93%	Greene 1987, cited by (25)
125 500	Single dose	Rat	4 males	3-fold increase in thymic apoptosis 8-fold increase in thymic apoptosis	7
158 315	Day 12 of gestation	Rat	6 females	19% dead, 45% malformed fetuses 15% dead, 100% malformed fetuses	Ritter 1985, cited by (25)
150	1, 2, 4, 7, 10 d	Rat	5-6 males	Progressive spermatocyte degeneration from day 1 and on Reduced testicular weight from day 2	Chapin 1984, cited by (25)
250 500-1000	5 d/wk, 2 wk	Mouse	10 females	No observed effects Reductions in white blood cell count, thrombocyte count, and hematocrit, thymic atrophy	House 1985, cited by (25)
250	Day 7-9, 8-10, 9-11, or 7-14 of gestation	Mouse	9-12 females	In all groups: malformed extremities, reduced fetal weight, embryonic deaths	Horton 1985, cited by (25)
250 500	5 d/wk, 5 wk	Guinea pig	3 males	Both dose groups: testes weight reduced by 75% white blood cell count reduced by 50%	Nagano 1984, cited by (25)
304	Day 11 of gestation	Mouse	16 females	Malformed extremities in 68% of offspring (88% of litters) without overt maternal toxicity	Hardin 1987, cited by (25)
500	Day 9, 10, 11, 12 or 13 of gestation	Mouse	9-12 females	Malformed extremities. Most pronounced in group dosed on day 11 (100% of offspring), no effects in group dosed on day 13	45

Table 2. Selected animal inhalation studies on EGME

Exposure level, ppm	Exposure duration	Species	Animals per dose group	Observed effects	References
3 10 50	6 h/d, day 6-15 of gestation	Rat	28-30 females	No observed effects No observed effects Reduced maternal weight gain, skeletal variations in offspring	Hanley 1984, cited by (25)
3 10 50	6 h/d, day 6-18 of gestation	Rabbit	22-30 females	No observed effects Increased resorption judged to be unrelated to exposure, delayed ossification Idem + reduced maternal weight gain, increased resorption, skeletal and soft tissue variations, malformations in 91 of 145 fetuses	Hanley 1984, cited by (25)
10 50	6 h/d, day 5-17 of gestation	Mouse	23-32 females	No observed effects Reduced maternal weight gain, indications of slight fetotoxicity, skeletal variations	Hanley 1984, cited by (25)
25	6 h/d, day 7-16 of gestation	Rat	25 females	Maternal toxicity: increased liver weight, reduced food consumption. Decreased fetal weight. Skeletal variations: ruimentary lumbar ribs, wavy ribs	23
25	7 h/d, day 7-13 Day 14-20	Rat	15 females	Neurochemical deviations and impaired learning ability in offspring without overt maternal toxicity. Neurochemical deviations in offspring without overt maternal toxicity	82
25	7 h/d, 7 d/wk for 6 wk prior to mating	Rat	18 males	No paternal toxicity. Neurochemical deviations in offspring	82
30 100 300	6 h/d, 5d/wk, 13 wk	Rat	20-30 per sex	No observed effects No observed effects Impaired fertility in males, partially reversible	Rao 1983, cited by (25)

continued

Table 2 (continued)

Exposure level, ppm	Exposure duration	Species	Animals per dose group	Observed effects	References
30 100 300	6 h/d, 5 d/wk, 13 wk	Rat	10 per sex	No observed effects No observed effects Reductions in white cell count, thrombocyte count, hemoglobin, and plasma levels of total protein, albumin and globulin. Thymic and testicular atrophy	Miller 1983, cited by (25)
30 100 300	6 h/d, 5 d/wk, 13 wk	Rabbit	5 per sex	Reduced testis size (2/5), degenerative changes in germinal epithelium (1/5) Idem (4/5) and (3/5), respectively Reductions in white cell count, thrombocyte count, and hemoglobin. Thymic and testicular atrophy	Miller 1983, cited by (25)
50 100 200	7 h/d, day 7-15 of gestation	Rat	11-38 females	Increased resorptions, skeletal and cardiavascular malformations Idem Complete resorptions	Nelson 1984, cited by (25)
100 300 1000	6 h/d, 9 d	Rat	5-10 per sex	Reduced leukocyte count (males) Idem both sexes + reductions in red blood cell count and hemoglobin (females), reduced thymus weight Idem both sexes + reduced hematocrit	Miller 1981, cited by (25)
100 300	6 h/d, 10 d	Rat	10 males	No observed effects Semeniferous tubular atrophy, reduced testis weight, reductions in white and red blood cell counts, hemoglobin and hematocrit	Doe 1983, cited by (25)
100 300	6 h/d, day 6-17 of gestation	Rat	20 females	Prolonged gestation, reduced number of litters and number, weight and viability of pups Reduced maternal weight gain, no litters delivered	Doe 1983, cited by (25)

continued

Table 2 (continued)

Exposure level, ppm	Exposure duration	Species	Animals per dose group	Observed effects	References
150 300 625 1250-5000	4 h	Rat	20 males	No observed effects No observed effects Damage on maturing spermatids Idem + reductions in testis weight and semeniferous tubular damage	Samuels 1984, cited by (25)
750	6 h/d, 5 d/wk, 13 wk	Dog	2	Reductions in number of red blood cells, hemoglobin, hematocrit and lymphocytes. Increases in osmotic fragility and number of immature granulocytes	Werner 1943, cited by (25)
1000 2000	4 h	Rat	6 females	No effects on osmotic fragility in red blood cells Increased osmotic fragility	Carpenter 1956, cited by (25)

Table 3. Dose-effect relationship, occupational exposure to EGME

Exposure level, ppm	Exposure conditions	Number of people	Observed effects	References
mean 0.8 median 0.4	Shipyard painters, pronounced dermal exposure, also exposed to 2.6 ppm EGEE (time-weighted average)	73 men	10% anemia, 5% granulocytopenia (0% in non-exposed controls), reduced sperm count, no effect on fertility	125-127
mean 2 max 48	Parquet makers, predominantly exposed to EGME but also EGEE and several other solvents	9 men	Increased neutrophilic band, total lymphocyte, NK and B cell counts. Reduced eosinophilic, segmented neutrophilic segmented, total T, and T helper cell counts. Tendencies towards reductions in red blood cell count and hemoglobin.	20
5-9	Production and packaging of EGME	65 men	Tendencies towards reductions in testis size, sperm count, white blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, and testosterone and FSH in serum.	17
approx. 8	Manual cleaning, dermal exposure	2 men	Bone marrow depression, pancytopenia	88
18-58	Microfilm production	1 man	Increases in sleep time, body weight, and fatigue. Decreased appetite. Abnormal low levels of red blood cell, white blood cell, thrombocyte counts, hemoglobin and hematocrit	16
60-4000 (experimental reconstruction) 10-37 (plant redesign)	Cleaning of floor and printing machines. No protective equipment.	6 men	Personality changes, nervousness, anxiousness, fatigue, somnolence, anorexia, hearing loss, stuttering, ataxic walk, slurred speech, tremor, alteration in taste, impotency. Hypocellular bone marrow (only examined in one man). No further intoxication after plant redesign.	135

10. Conclusions

Based on experiences from occupational exposure as well as animal data the critical effect of ethylene glycol monomethyl ether (EGME) may be impairment of reproduction or haematopoiesis.

EGME and its acetate ester (EGMEA) are efficiently absorbed by inhalation as well as via dermal penetration. Dermal absorption may contribute substantially to the total uptake following skin contact with liquids or vapours containing EGME or EGMEA. EGMEA is rapidly converted to EGME in the body and the two substances are equally toxic in animals. Therefore, EGME and EGMEA should be considered as equally hazardous to man.

Effects on peripheral blood, haematopoiesis, testes, and sperm have been reported at exposure levels of EGME ranging between 0.4 and 10 ppm, and with additional, possibly substantial, dermal exposure. In addition, severe malformations and disturbance of blood formation have been linked with exposure to EGME or EGMEA at unknown, probably high, levels. Embryonic deaths in monkeys, disturbed immune system in rats, and impaired spermatogenesis in rabbits have been reported after daily oral doses of 12, 15, and 25 mg per kg body weight, respectively.

In several studies, increased frequency of spontaneous abortions, disturbed menstrual cycle, and subfertility have been demonstrated in women working in the semiconductor industry. The contribution of EGME in relation to other exposure factors is unclear.

11. Summary

Johanson G. Criteria Document for Swedish Occupational Standards. *Ethylene glycol monomethyl ether and ethylene glycol monomethyl ether acetate*. Arbete och Hälsa 1999:13;1-43.

Ethylene glycol monomethyl ether (EGME) and its acetate ester (EGMEA) are highly flammable, colourless, volatile liquids with very good solubility properties. They are used in paints, lacquers, stains, inks and surface coatings, silk-screen printing, photographic and photo lithographic processes, *e.g.* in the semiconductor industry, textile and leather finishing, production of food-contact plastics, and as an anti-icing additive in hydraulic fluids and jet fuel.

EGME and EGMEA are efficiently absorbed by inhalation as well as via dermal penetration. Dermal absorption may contribute substantially to the total uptake following skin contact with liquids or vapours containing EGME or EGMEA. EGMEA is rapidly converted to EGME in the body and the two substances are equally toxic in animals. Therefore, the two substances should be considered as equally hazardous to man.

Effects on peripheral blood, testes, and sperm have been reported at occupational exposure levels ranging between 0.4 and 10 ppm EGME in air, and with additional, possibly substantial, dermal exposure. Severe malformations and disturbed haematopoiesis have been linked with exposure to EGME and EGMEA at unknown, probably high, levels. Embryonic deaths in monkeys and impaired spermatogenesis in rabbits have been reported after daily oral doses of 12 and 25 mg per kg body weight, respectively. In several studies, increased frequency of spontaneous abortions, disturbed menstrual cycle, and subfertility have been demonstrated in women working in the semiconductor industry. The contribution of EGME in relation to other exposure factors in the semiconductor industry is unclear.

Keywords: Dermal uptake, ethylene glycol monomethyl ether, ethylene glycol monomethyl ether acetate, haematotoxicity, 2-methoxyethanol, 2-methoxyethyl acetate, occupational exposure, reproductive toxicity, toxicity.

12. Summary in Swedish

Johanson G. Criteria Document for Swedish Occupational Standards. *Ethylene glycol monomethyl ether and ethylene glycol monomethyl ether acetate*. Arbete och Hälsa 1999:13;1-43.

Etylenglykolmonometyleter (EGME) och dess acetatester (EGMEA) är lättantändliga, färglösa, flyktiga vätskor med mycket goda löslighetsegenskaper. De används i färger, lacker, bläck, silkscreenfärger, fotografiska och fotolitografiska processer bland annat inom halvledarindustrin, textil- och läderbearbetning, plastförpackningar avsedda för livsmedel, samt som antifrysmedel i hydraulvätskor och flygplansbränsle.

EGME och EGMEA absorberas effektivt via lungor och hud. Hudabsorption kan bidra till en stor del av det totala upptaget efter hudkontakt med vätske- eller ångformig EGME eller EGMEA. EGMEA ombildas snabbt till EGME i kroppen och de båda ämnena är lika toxiska i djurförsök. Därför bör de två ämnena betraktas som likvärdiga med avseende på hälsorisker.

Påverkan på blodbild, testiklar och spermiebildning har setts hos yrkesmässigt exponerade män vid nivåer av på mellan 0,4 och 10 ppm EGME i luft, och med sannolikt betydande hudexponering. Allvarliga missbildningar och störd blodbildning och har kopplats till yrkesmässig exponering för EGME och EGMEA i okända, troligen höga nivåer. Fosterdöd hos apor och nedsatt spermiebildning hos kanin har setts efter dagliga orala doser på 12 respektive 25 mg per kg kroppsvikt. I flera studier har ökad frekvens spontanaborter, störd menstruation och nedsatt fertilitet påvisats för kvinnor i halvledarindustrin. Betydelsen av EGME i förhållande till andra agens i halvledarindustrin är oklar.

Nyckelord: etylenglykolmetyleter, etylenglykolmetyleteracetat, hematologiska effekter, hudupptag, 2-metoxietanol, 2-metoxietylacetat, reproduktionstörande effekter, toxiska effekter, yrkesmässig exponering

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