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PIMEX. Föredrag vid en konferens om PIMEX-metoden. Solna 23 april 1991.
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Klimatfysiologisk belastning vid arbete i skyddsdräkter för asbestsanering.
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Acute effects from exposure to organic solvents: Experimental approaches and methods. Proceedings from a workshop held at the "Institut für Arbeitsphysiologie an der Universität Dortmund", March 7–9 1990.
36. **M. A. Maclaine Pont:**
DEC and NEG Basis for an Occupational Health Standard. Methyl methacrylate.
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Nordiska Expertgruppen för Gränsvärdesdokumentation. 97. Dimethylsulfoxid.
38. **Sven Byström:**
Physiological response and acceptability of isometric intermittent handgrip contractions.
39. **Gunnar Aronsson och Anneli Strömberg:**
Sociala och psykologiska riskfaktorer i yrkesgrupper med omfattande datoranvändning.
40. **Åsa Kilbom, Marja Mäkäräinen, Lena Sperling, Roland Kadefors, Lennart Liedberg:**
Betydelsen av verktygsutformning och individfaktorer vid arbete med plåtsax.
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Risken för män i fysiskt tunga yrken att förtidspensioneras på grund av sjukdomar i rörelseapparaten.
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Handens känselfunktion hos plåtslagare och montörer utsatta för vibrationer.
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Nordiska Expertgruppen för Gränsvärdesdokumentation. 98. Trikloreten.
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The pattern of activation and relaxation during fatiguing isokinetic contractions in subjects with and without muscle pain.
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DEC and SCG Basis for an Occupational Health Standard. PYRIDINE.
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NEG and NIOSH Basis for an Occupational Health Standard

ETHYL ETHER

Björn Arvidson

ARBETS MILJÖ INSTITUTET
NATIONAL INSTITUTE OF OCCUPATIONAL HEALTH

The National Institute of Occupational Health employs over 300 scientists in research on the work environment. The research is led by 30 professors. The Institute does mostly applied research, but some questions also require focused basic research.

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PREFACE

A memorandum has been signed between the Center for Disease Control, National Institute for Occupational Safety and Health (NIOSH), USA, and the Nordic Expert Group for Documentation of Occupational Exposure Limits (NEG). The purpose of the memorandum is to exchange information and expertise in the area of occupational safety and health. One product of this agreement is the development of documents to provide scientific basis for establishing recommended occupational exposure limits. The exposure limits will be developed separately by each country according to the different national policies.

This document on the health effects of occupational exposure to ethyl ether is the second product of that agreement. The document was written by Björn Arvidson, Dr Med Sc (Department of Occupational Medicine, University Hospital, Uppsala and Swedish National Insitute of Occupational Health,. Solna), and was reviewed by NEG and the Division of Standards Development and Technology tranfer (DSDTT), NIOSH.

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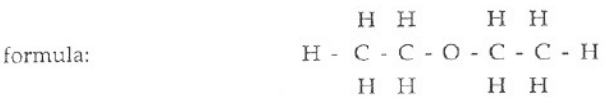
CONTENTS

1. INTRODUCTION

Ethyl ether is a colorless, highly volatile, mobile, liquid with a characteristic pungent odor. Ethyl ether is a serious fire hazard as its vapor readily forms explosive mixtures with air and oxygen. It is miscible with the lower aliphatic alcohols, benzene, chloroform, petroleum ether, other fat solvents and many oils. The primary physiologic effect of ethyl ether is general anesthesia.

2. PHYSICAL AND CHEMICAL PROPERTIES*

Chemical name:	Ethyl ether
CAS number:	60-29-7
Synonyms:	ether, diethyl ether, ethoxyethane, diethyloxide, ethyl oxide, 1,1'-oxybisethane
Molecular formula:	$C_4H_{10}O$
Structural formula:	
Molecular weight:	74.12
Specific gravity at 20 °C :	0.7146
Boiling point (101.3 kPa):	34.6 °C
Melting point:	-116.3 °C
Vapor pressure (20 °C):	58.5 kPa
Saturation concentration (20 °C, 101.3 kPa):	57.75% (1,778,677 mg/m^3)
Flash point:	-45 °C
Distribution coefficient blood/gas	12.1

Distribution coefficient oil/gas	65
Solubility in water at 20 °C :	6.9% by wt.
Viscosity at 20 °C:	0.00233 poise
Conversion factors (20 °C, 101.3 kPa):	1 ppm=3.08 mg/m^3 1 mg/m^3=0.325 ppm

* Data taken from ref nr 2, 3, 7, 8, 28, 44, 72, 151.

Ethyl ether usually starts to oxidize soon after distillation and ether peroxides, acetaldehyde and acetic acid are formed. Ether peroxide is less volatile than ethyl ether and tends to concentrate during evaporation or distillation. Ether peroxides, when concentrated, are a serious detonation hazard. Ethyl ether can be tested for the presence of peroxides by shaking 10 ml of ether for one minute with 1 ml of a freshly prepared 10% aqueous solution of potassium iodide in a 25 ml glass-stoppered cylinder of colorless glass, protected from light. Appearance of a yellow color indicates peroxides (53). Other rapid tests for detecting peroxides in liquids are also available (53). Peroxides can be removed by distillation or by passage through an alumina column. If activated alumina is used, the ether is also dried in the process (53). Ferrous sulfate (30% solution in water) can be used in the proportion of 1 lb (0.4536 kg) to each 30 US gallons (113.5 l) of ethyl ether to extract and to destroy peroxides (7).

Factors which delay decomposition of ethyl ether are absence of light, storage in a cool place, storage in copper tanks or contact with a copper screen. Copper and certain other metals, particularly iron and mercury, prevent the oxidation of ethyl ether since they are oxidized preferentially and consume the oxygen which is combined with ethyl ether (3). Ethyl ether should be stored in the original metal cans rather than in glass bottles. Very dry ethyl ether undergoes oxidation much more readily than ethyl ether containing a few tenths of a percent of water (7).

3. USES AND OCCURRENCE

3.1 Uses

Ethyl ether is produced on a large scale by dehydration of ethanol or by hydration of ethylene, both processes being carried out in the presence of sulfuric acid (3, 28, 80, 151). Ethyl ether has a wide range of uses in the chemical industry. It is a good solvent for fats, oils, dyes, gums, resins, raw rubber, smokeless powder, perfumes, and nitrocellulose. Ethyl ether is also used in the manufacture of

photographic films, in pharmaceutical making, and as a reaction and extraction medium in the chemical industry. In addition, ethyl ether is used as an inhalation anesthetic in surgery, a refrigerant, in diesel fuels, in dry cleaning and as a starting fuel for engines (8, 28, 31, 80, 136). Smith and Zenz (1988) reported an annual production of ethyl ether in excess of 125 million US tons per year in the United States.

Acccording to the Swedish Products Register at the National Chemical Inspectorate, ethyl ether was a constituent in 43 chemical products present on the Swedish market in August 1991. The estimated annual use in Sweden was 40 - 370 metric tonnes.

Ethyl ether is commercially available in different grades. Depending on the consumer and use, specifications vary. In many instances the ether has to meet a specific test which is written in the specification, e.g. it may be important that the ether is free from alcohol and aldehyde, or completetly anhydrous. The technical concentrated ether contains very small amounts of alcohol, water, aldehydes, peroxides and other impurities such as sulfuric acid, sulfur dioxide, mercaptans and ethyl esters (3, 28, 35, 80). Some doubt exists whether or not these impurities as found in ethyl ether are toxic to man. In dogs, concentrations of aldehyde up to 0.5 % and mercaptans up to 1% produced no significant effects. Ether peroxides in a concentration of 0.3% had no effect whereas 0.5% caused a fall in blood pressure and respiratory difficulties. Ethyl sulfide in 1% concentration caused gastroenteritis (23). Ethyl ether containing impurities produced anesthesia in mice more slowly than pure ethyl ether (84).

The more refined grades of ethyl ether, such as anesthetic ether, are obtained from technical ether by redistillation and dehydration followed by alkali or charcoal treatment (80).

3.2 Air concentrations in the working environment

Hirsch and Kappus (70) published the first quantitative data on the concentration of inhalation anesthetic agents in operating room air in 1929. The levels of ethyl ether in several operating rooms during surgical procedures were measured with use of a combustion method. Ethyl ether levels ranged from 10 to 100 ppm (31 to 308 mg/m^3) before any attempt to remove the waste ethyl ether vapor. The concentration of ethyl ether in several operating rooms decreased by 34 to 72% after use of a crude scavenging system, consisting of a vacuum cleaner and a large funnel.

Grigoriew (56), cited by Hayhursth (68), investigated air levels of ethyl ether in two Russian factories manufacturing smokeless powder. The concentrations of ethyl ether in air varied depending on season, temperature of the workroom, apparatus and other factors. In one of the factories, the minimum concentration of ethyl ether in air was reported to be 0.08 vol% (2,464 mg/m^3) and in the other factory 0.007 vol% (215 mg/m^3). The maximum values were 21.18 vol% (652,344 mg/m^3) and 2.7 vol% (83,160 mg/m^3), respectively.

To prevent pollution by anesthetic gases in operating rooms, the Hospital

Engineering Cooperative Groups of Denmark made recommendations in 1974 (146). The recommended highest permissible average concentration in the breathing zones of anesthesia personnel for ethyl ether was 3 ppm (9 mg/m^3).

Air concentrations of ethyl ether were measured in the laboratory of a brewing company in Illinois, USA (154). Ethyl ether was used in an extraction procedure to determine the fat content in corn. Environmental monitoring was conducted using two methods; (1) a direct reading instrument, and (2) personal and area sampling to determine the integrated average exposures over the work shift. All results for the personal and area samples were less than 1 ppm. Measurements with the direct reading instrument showed peak concentrations up to 1,000 ppm (3,080 mg/m^3) around the cork gaskets and pressure release valves on the extraction apparatus. However, the vapors were released inside a plexiglass enclosure where they were properly exhausted.

Personal breathing zone and area samples were taken in an analytical laboratory using solvents in the preparation of soil and water samples (155). The values for ethyl ether were below the limit of quantitation (0.03 mg/sample).

The employee's exposure to xylene, ethyl ether and other vapors was evaluated in the cytology, hormone and histology laboratories in a hospital in Missouri, USA (156). Breathing zone samples were taken on most of the workers with emphasis on those receiving the highest exposures. The concentration of ethyl ether in air varied between 2.6 and 186.6 mg/m^3.

Environmental samples from an army ammunition plant in Virginia, USA, showed that the ethyl ether concentrations ranged from 90 to 712 ppm (277 to 2,193 mg/m^3) (157).

3.3 Analytical methods for ethyl ether in air and body tissues

3.3.1. *Direct field methods*

Analysis of ethyl ether-contaminated air in the work area may be done by means of a commercially available combustible gas indicator. Direct reading detector tubes are also available (8, 92).

3.3.2 *Laboratory methods*

An air sampling technique for diethyl ether has been proposed by NIOSH (109). A known volume of air is drawn through a charcoal tube at a flow rate of 0.01 to 0.2 l/min. The charcoal in the tube is transferred to a small sample container and ethyl ether is desorbed with ethyl acetate. An aliquot of the desorbed sample is then injected into a gas chromatograph and the area of the resulting peak is determined and compared with standards. Advantages with this method is a small, portable sampling device and minimal interferences which can be eliminated by altering chromatographic conditions. A disadvantage is that the the upper limit of the range of the method depends on the adsorptive capacity of the charcoal tube. In addition, the precision of the method is limited by the

reproducibility of the pressure drop across the tubes.

Blood and tissue levels of ethyl ether can be analyzed by infra-red analysis. This method was originally devised by Stewart et al. (144) and was used, with a slight modification, by Chenoweth et al. (33) for measuring blood and tissue levels of ethyl ether and other anesthetics in dogs. This method is also applicable to air analysis (8, 31).

Ethyl ether in blood and urine can be analyzed by gas chromatography. The specimen is injected directly into a gas chromatograph equipped with a flame-ionization detector and a molecular sieve column. Specimens should be stored at 4°C and analyzed as soon as possible. Breath samples may be analyzed by direct injection of 1-2 ml, using as standards suitably prepared dilutions of ethyl ether in air. Calculation is based on a standard curve of peak height versus concentration of the standards (17).

Ethyl ether in air may be analyzed by passing the air through a fritted glass bubbler for reaction of the ethyl ether with acidic potassium dichromate and subsequent iodometric determination (133). A modification of this method has also been used for determination of ethyl ether in blood (6, 117).

3.4. Biological monitoring

Tests for exposure may include expired breath for unmetabolized ethyl ether and blood for ethyl ether content (8). Blood concentrations of ethyl ether have been found to correlate with the degree of ethyl ether exposure and the extent of intoxication. According to Baselt (17), the concentration of ethyl ether in blood should not exceed a level of about 20 mg/l in asymptomatic workers. Gas chromatography can be used for determinations of ethyl ether in blood, urine and breath samples (17). Infrared analysis can be used for detection of ethyl ether in breath and body fluids (8).

4. DISTRIBUTION AND METABOLISM

4.1 Uptake

4.1.1 Uptake by inhalation.

After inhalation, ethyl ether is rapidly transferred from alveoli to blood. The normal alveolar membrane poses no barrier to the transfer of ethyl ether in either direction. The blood/gas distribution coefficient of ethyl ether is high, 12.1. For oil/gas, the distribution coefficient is 65 (44). The more soluble an anesthetic is in blood, the more of it must be dissolved in blood to raise its partial pressure there appreciably. Induction of ethyl ether anesthesia is therefore slow. To achieve deep anesthesia with ethyl ether in medical practice takes 15-25 minutes (35) (the concentration of ethyl ether used for the induction of anesthesia is usually 10 to 15 vol% or 308,000 to 462,000 mg/m^3).

4.1.2. Uptake from the gastrointestinal tract.

No studies on the uptake of ethyl ether after peroral administration were found. According to Hayhursth (68), absorption of ether from the stomach and rectum is very prompt and may be used for anesthesia.

4.1.3. Uptake through the skin.

Smyth et al. (138) investigated the penetration of rabbit skin for different chemical compounds. The fur was removed from the trunk by clipping, and the dose was retained beneath an impervious plastic film. Doses over 20 ml/kg b.w. could not be retained in contact with the skin. For ethyl ether, the single dermal penetration LD_{50} was greater than 20 ml/kg b.w.

No data were found on the extent of uptake of ethyl ether through undamaged skin in humans. A case-report described a 14-year-old boy who applied ethyl ether to his scalp under plastic occlusion to treat a seborrheic dermatitis. The boy was found dead and elevated but non-fatal concentrations of ethyl ether were found in the various postmortem tissues subjected to toxicological analysis. The authors conclusion was that the boy died from intoxication of resorbed ethyl ether. The authors interpreted the sub-lethal ethyl ether concentrations found in various tissues as probably incorrect due to ethyl ether's high volatility (29).

4.2 Distribution

The concentration of ethyl ether in various tissues of rats during ethyl ether narcosis was investigated by Dybing and Dybing (41, 42) and Dybing and Skovlund (43). The animals inhaled ethyl ether at a concentration of 300,000 mg/m^3 (approximately 9 vol%). The concentration of ethyl ether in arterial blood rose rapidly during the first minutes and then more slowly until a diffusion equilibrium with the ethyl ether concentration in alveolar air was attained. The concentration of ethyl ether in the brain rose initially with the same rapidity as in the arterial blood. From about 5 min and onwards, the concentration of ethyl ether in the brain is constantly greater than the arterial concentration, reflecting the greater solubility of ethyl ether in brain tissue. The ethyl ether concentration in muscle was much lower than in the arterial blood or brain in the early stages of anesthesia (41, 42). Ethyl ether was taken up rapidly by omental and perirenal fat, and after a few minutes, the concentration of ethyl ether in fatty tissue was the same as in blood. The maximum concentration of ethyl ether in fat was reached after 1/2 to 1 hour. After continuous administration of ethyl ether for 1 hour, the mean concentration of ethyl ether in blood, omental fat and perirenal fat was 1,270, 2,870 and 2,140 mg/kg , respectively (43).

The distribution of ^{14}C-ethyl ether in the mouse was investigated with use of low-temperature autoradiography (34). Ethyl ether was administered by inhalation for ten minutes. When the animals were killed immediately after the inhalation period, the anesthetic was rather uniformly distributed throughout the body, although higher concentrations were found in the brain, kidney, liver and brown fat. After 2 hours, most of the radioactivity had left the body, but the

liver, kidneys, intestines and nasal mucous membranes were still labelled. A quantitative analysis showed that by 15 minutes, the radioactivity in brown fat had reached its peak relative concentration, whereas the relative concentrations of radioactivity in liver and kidneys continued to increase until the termination of the 2-hour experimental period. At two hours, 3.6% of the administered dose was present in metabolized form in the liver and intestine. By that time, all liver radioactivity was non-volatile.

The distribution of ethyl ether and four other volatile organic solvents in blood was investigated in rats. The animals were exposed to 500 ppm (1540 mg/m^3) of ethyl ether for 2 hours. 49% of ethyl ether in the blood was found in the red blood cells. When a solution of ethyl ether was added to human plasma and red blood cell (RBC) samples, a large fraction of ethyl ether was recovered from ammonium sulphate-precipitated plasma proteins and hemoglobin. A small fraction of ethyl ether was recovered from plasma water and RBC water. The authors conclude that proteins, chiefly hemoglobin, are the major carriers of ethyl ether and other volatile organic solvents in blood (87).

4.3 Biotransformation

It has been estimated that about 8-10% of absorbed ethyl ether is metabolized in the body (55) whereas the remainder is excreted unchanged through the lungs. Ethyl ether is metabolized to ethanol and acetaldehyde by an inducible hepatic microsomal enzyme system, a cytochrome P-450-containing monooxygenase system (32, 145). Ethanol and acetaldehyde are rapidly oxidized to acetate, and the acetate subsequently enters the 2-carbon pool of intermediary metabolism.

Van Dyke et al. (160) showed in rats that approximately 4% of an intraperitoneally-administered dose (0.1 ml) of ^{14}C-ethyl ether was recovered as exhaled $^{14}CO_2$ during a 24-hr period, and 2% of the radioactivity was transformed into non-volatile urinary products. Gréen and Cohen (55) reported that a portion of ^{14}C-diethyl ether administered to mice by inhalation was rapidly transformed into fatty acids (palmitic, stearic and oleic acids) and cholesterol which were recovered from an ether extract of liver. Three other non-volatile radioactive metabolites were tentatively identified as mono-, di- and triglycerides.

Two hours after administation of ethyl ether by inhalation to mice, 3.6% of the administered dose was present in metabolized form in the liver and intestine. Thin-layer radiochromatography of extracts from the liver demonstrated four non-volatile metabolites. The major metabolite was presumed to be a glucuronide of ether (34).

The hepatic microsomal oxidation of ethyl ether is catalyzed primarily by the cytochromes P-450 (32). More recent investigations have implicated specific isoenzymes. Known inhibitors of isoenzyme IIE1 strongly inhibited ether de-ethylation, and a monoclonal antibody to P-450IIE1 had the same effect (24). A mixed-function oxidation known to be catalyzed by cytochrome P-450IIE1, the N-demethylation of dimethylnitrosamine, was inhibited by ethyl ether anesthesia (150). These findings all indicate that ethyl ether is oxidatively metabolized primarily by P-450IIE1 (24).

4.4 Elimination

The majority of inhaled ethyl ether is excreted unchanged through the lungs. In experiments on dogs, Haggard (61) reported that the recovery of ethyl ether in expired air was 79 to 92% (average for 12 dogs 87%). Onchi and Asao (112) attempted to recover inhaled ethyl ether from human patients and volunteers. They used a lower concentration of ethyl ether than Haggard and reported a recovery of 37 to 84% of the administered dose. It is estimated that only about 8-10% of the absorbed dose of ethyl ether is metabolized in the body (55). In rats given 0.1 ml of ^{14}C-ethyl ether by intraperitoneal injection, about 4% of the administered dose was recovered as exhaled $^{14}CO_2$ and 2% was transformed into non-volatile urinary products (160).

The concentration of ethyl ether in brain, blood and muscle was investigated in rats during ether elimination. When the rats had breathed ethyl ether 300,000 mg/m^3 (approximately 9 vol%) for 10 min, there was an abrupt fall of the concentration of ethyl ether in brain and blood immediately after discontinuation of the inhalation. When the inhalation exposures were discontinued after one hour, the fall in the ether concentration of brain and blood was slower (42). The elimination of ethyl ether from fatty tissue occurred slowly, and was practically finished after about 8 hours (43).

According to the experience of anesthesiologists, termination of anesthesia with soluble anesthetics like ethyl ether is slower in obese individuals than in those with a lean body mass. This might partly be due to partioning of the anesthetic agent into certain tissues, e.g. body fat (25).

4.5 Mechanism of ether resistance in Drosophila melanogaster

A few studies have been performed to elucidate the mechanism of ethyl ether resistance in certain strains of *Drosophila melanogaster*. A strain named *Eth-29*, was found to be resistant to ethyl ether and other volatile anesthetic agents like chloroform and halothane. Ethyl ether resistance for lethality was determined using mortality as an endpoint when flies were exposed to very high concentrations of ethyl ether (111). Ethyl ether resistance to anesthesia uses loss of avoidance reflex as an endpoint, and is an incompletely dominant or polygenic character (49). The resistance for ethyl ether anesthesia and for ethyl ether lethality was found to be controlled by different genetic systems.

In 18 strains of *Drosophila melanogaster* with different genetic characteristics, a wide variation in sensitivities to ethyl ether anesthesia, gamma-ray knock-down and gamma-ray lethality was demonstrated. There was no correlation between DNA-repair capacity and ethyl ether sensitivity or gamma-ray knock-down sensitivity, whereas strains deficient in excision repair were found to be sensitive to gamma-ray lethality. These findings indicate that lethality is caused by DNA damage, whereas the targets for ethyl ether anesthesia should be different, possibly being the membrane (50).

5. GENERAL TOXICOLOGY

5.1 Mechanism of action

The mechanism of action by which general anesthetics, including ethyl ether, produce reversible loss of consciousness is still unclear. Anesthesia can be produced by a wide variety of chemical agents, ranging from inert rare gases to steroid molecules (128). This appearent lack of specificity, together with the observation that general anesthesia can be reversed by high pressure, poses a unique pharmacological problem (48). Most theories concern interaction of anesthetics with either membrane lipids or hydrophobic regions of specific membrane-bound proteins (for reviews see 48, 63, 128). One hypothesis is that the anesthetic changes the function of an ion channel protein by modifying the conformation of the protein. Some investigators suggest that the GABA receptor may be the ion channel protein that is affected by inhalation anesthetic agents (25, 101). According to Halsey (63), the most appropriate concept for the mechanism of general anesthesia is a heterogenous site of anesthetic action, including both lipid and protein membrane components linked with the neuronal function.

5.1.1 Effects of ethyl ether on the metabolism of ethanol and certain drugs

Prolonged inhalation of ethyl ether has been shown to cause proliferation of the endoplasmic reticulum in liver cells and induction of drug-metabolizing enzymes (27, 127), whereas acute treatment with ethyl ether has been reported to inhibit drug metabolism. Ethyl ether is oxidatively metabolized in liver microsomes primarily by an ethanol-inducible cytochrome P-450 (P-450IIE1) (24). Ethyl ether can serve as a substrate for P-450EII1 as well as a competitive inhibitor for the metabolism of other substrates (150). This mechanism underlies the inhibitory action of ethyl ether on the metabolism of ethanol (9, 71, 110), since the microsomal oxidation of ethanol is accomplished primarily by cytochrome P-450EII1 (94). The metabolism of other substrates for cytochrome P-450EII1 like N-nitrosodimethylamine (NDMA) and paracetamol is also inhibited by ethyl ether (10, 73, 79, 150, 152).

Rats given pentobarbital i.p. 25 mg/kg and exposed to 3.6 vol% (110,880 mg/m^3) ethyl ether vapor for 40 minutes had higher concentrations of pentobarbital in liver, fat, brain and plasma than did rats given given the same dose of pentobarbital without ethyl ether exposure. Only the increases in liver and plasma pentobarbital concentrations were statistically significant, however. No difference was found in kidney pentobarbital levels (13). The influence of ethyl ether anesthesia on the metabolism of hexobarbital was investigated in rats. The experiments were carried out in a crossover design with a 1-week interval. Five rats received sodium hexobarbital 50 mg/kg i.v. with and without a light ethyl ether anesthesia during the experiments. Ethyl ether was administered continuously by covering the nose of the animals with a flask containing an ethyl ether-soaked cotton plug. The elimination half-life of hexobarbital increased by about 50% in rats exposed to ethyl ether (161).

The metabolism of diphenylhydantoin (DPH) in rats was inhibited by ethyl ether

whereas urethane had no effect. Ethyl ether was administered either continously throughout the 3-hr experiment (three rats) or the rats were anesthetized with ethyl ether for 5 min prior to the drug administration and then discontinued (6 rats). Ethyl ether was administered by covering the nose with a beaker containing a cotton plug soaked with ethyl ether. Continous ethyl ether administration prolonged the DPH half-life 10-fold compared with urethane anesthesia, while brief ethyl ether anesthesia had a delayed inhibitory effect on DPH elimination for about 1 h. The inihibitory action of ethyl ether on DPH metabolism was probably at the hydroxylation step (153).

5.1.2 *Effects of ethyl ether on protein synthesis in animals*

Male Wistar rats were exposed to anesthetic doses of ethyl ether by inhalation for 10 min and were sacrificed 20 or 40 min after initiation of anesthesia. The concentration of ethyl ether in blood at the end of the experiment was 7.1 and 9.0 mM/l (526 mg/l and 667 mg/l), respectively. On the average, the rate of synthesis of liver proteins was reduced with 20% compared to a group receiving no anesthesia. A more pronounced inhibition of synthesis/secretion of plasma proteins was reported, approximately 70-80% compared to animals either receiving no anesthesia or pentobarbital. Protein synthesis was measured by the incorporation of radioactively-labelled valine into liver and plasma proteins. It was suggested that this effect might be due to impaired function of endoplasmic membranes or of membranes belonging to the Golgi-secretory apparatus (19).

Ethyl ether inhibited protein synthesis also in isolated rat hepatocytes. Protein synthesis was measured as the incorporation of radioactively labelled valine into liver proteins. Concentrations of ethyl ether of approximately 10, 20 and 30 mM (741, 1,482 and 2,223 mg/l) caused 27, 50 and 74% inhibition, respectively. In contrast to ethyl ether, pentobarbital reduced the synthesis of cell and medium proteins very little, while the opiate anestheic fentanyl had no inhibitory effect (20).

Light ethyl ether anesthesia for 1-2 min did not afffect the rate of protein synthesis measured in the mammary gland, liver, intestinal mucosa and muscle of lactating rats using a flooding dose of ^{3}H-phenylalanine that was injected intravenously. The fractional rates of protein synthesis were estimated from incorporation of ^{3}H-phenylalanine into tissue proteins (131).

5.2 Acute toxicity

5.2.1. Human experience

5.2.1.1 *Inhalation*

Ethyl ether has been used since 1840 as an anesthetic agent with medical safety. There are few reports of death due to ethyl ether anesthesia in the literature. Campbell (30) did personal autopsies of 195 cases of death associated with anesthesia during a 30-month period from 1957 to the middle of 1959. In 4 cases, ethyl ether was given as a factor causing or contributing to death. Postmortem

blood ethyl ether concentrations of 2,880 and 3,750 mg/l were observed in 2 surgical patients who died within 2.5 hours after cessation of ethyl ether administration.

Almost all of the reported human experience concerning the use of ethyl ether involves its use as an anesthetic agent. Industrial exposure has caused very few deaths or illnesses, and thus very few reports appear in the literature. One case of human death in industry due to acute inhalation of ethyl ether used in perfumery manufacture was reported by Hayhursth (68). The patient developed acute mania and died in uremic convulsions. Symptoms of acute overexposure after inhalation of large quantities of ethyl ether are drowsiness, vomiting, paleness of the face, lowering of the pulse and body temperature, irregular respiration, muscular relaxation and excessive salivation (31, 47). After-effects of acute ethyl ether poisoning are vomiting, irritation in the tracheobronchial tree, headache, salivation and depression or excitation (31). Treatment of overexposure to ethyl ether is symptomatic and no specific antidotes are known. Oxygen therapy may be used in cases of narcosis (7).

5.2.1.2 *Ingestion*

Moeschlin (99) has estimated the lethal dose of ethyl ether after peroral intake to be about 30 ml (21.4 g) or more. A lethal dose of 30-50 g ethyl ether after peroral intake was given by Geldmacher-v. Mallinckrodt (52). A one-year-old child who died of peroral intake of an unknown amount of ethyl ether had a postmortem ethyl ether concentration in blood of 2,360 mg/l (123).

In ethyl ether addiction, tolerance develops and large daily quantities of ethyl ether may be ingested (16, 52). A daily intake of up to 180 g has been reported (52).

5.2.2. Animal studies

5.2.2.1 *Inhalation*

Differences in the induction mixture and the duration of anesthesia may lead to different results for lethal concentrations of inhaled ethyl ether in animals (124). During a continous exposure for 97 min, the lethal concentration of inhaled ether for mice was 133,400 mg/m^3 or 4.4 vol% (86). When rapid induction and short duration of anesthesia was used, the concentration necessary to produce respiratory arrest in mice was 18 vol% (554,000 mg/m^3) (103). The lethal concentrations for the rat, rabbit and dog were 6.4, 10,6 and 7.16 to 19,25 vol% respectively (139). The age of the animal has importance for susceptibility to inhaled ethyl ether. In rats, the median time to death (LT_{50}) for neonates was 5 to 6.5 times greater than for adult rats and the mean concentration of ethyl ether in blood at the respective LT_{50} values was 2.5 to 3 times greater in neonatal rats than in adult rats (132).

5.2.2.2 *Ingestion*

The oral LD_{50} in 2 week-old, young adult (body weight 80 - 160 g) and adult (body weight 300 - 470 g) Sprague-Dawley rats, were reported to be 2.3, 2.4 and 1.7 ml/kg b.w., respectively (83). Smyth et al (138) reported a single peroral LD_{50} for rats of 3.56 ml/kg.

5.3 Chronic toxicity

Long-term exposure to low concentrations of ethyl ether vapor is found especially in the industries which work with nitrocellulose, e.g. in the manufacture of smokeless powder. Reported symptoms are loss of appetite, exhaustion, headache, sleepiness, dizziness, excitation and psychic disturbances (47). Blood samples from some individuals chronically exposed to ethyl ether vapor during the manufacture of smokeless powder showed polycythemia and leukocytosis (65).

Werthmann (168) described effects of chronic exposure to ethyl ether among surgeons and nurses working in an operation theatre. The concentration of ethyl ether in air in an unventilated operation theatre during an operation was estimated to 22,000 mg/m^3 (0.73 vol%). Among the symptoms were tiredness, headache, loss of appetite, irritability and difficulties in concentrating. Blood samples showed an increase in the number of lymphocytes and eosinophils.

Humans generally refrain from drinking ethyl ether due to its irritating effects on mucous membranes. Repeated drinking has, however, taken place, sometimes intentionally to reach a state of euphoria, resulting in the development of the "ether habit". The symptoms are similar to those of chronic alcoholism (28).

6. ORGAN EFFECTS

6.1 Skin, mucous membranes and eyes

Liquid ethyl ether is a mild skin irritant. Ethyl ether does not ususally cause any damage if skin contact is of short duration. Repeated exposure of the skin to ethyl ether, however, causes cracking and drying due to defatting (31).

Topical application of ethyl ether has been used for treatment of herpes simplex labialis (60, 116, 149). The basis for for this treatment is that the infectivity of herpes simplex virus is eliminated after exposure to diethyl ether *in vitro* (76).

Ethyl ether causes conjunctival irritation in either liquid form or high concentrations in the air. Prolonged exposure of the cornea to high concentrations of ethyl ether vapor, as employed in general anesthesia, causes superficial damage to the corneal epithelium. The recovery is usually prompt (54). The eye injury caused by ethyl ether instillation was tested in a standard manner on rabbit eyes. Ethyl ether caused slight reversible injury, graded 2 on a scale of 1 to 10 (138).

6.2 Respiratory system

Ethyl ether vapor is an irritant to the mucous membranes of the nose and tracheobronchial tree (35, 40). Nelson et al. (106) studied the irritating effects of ethyl ether vapor on humans. Complaints of nasal irritation started at 200 ppm (616 mg/m^3), and 300 ppm (924 mg/m^3) was considered objectionable as a working atmosphere. Ethyl ether increases the amount of bronchial secretions but also has a dilating effect on the bronchi and bronchioles, which makes ethyl ether an useful anesthetic agent for patients with asthma and brochiolar spasm (35). Ethyl ether increases the rate of respiration by stimulating the nerve endings in the bronchial tree, and in this way reflexly excites the respiratory centre. Ethyl ether may also sensitize the baroreceptors. With incresasing depth of anesthesia, the paralysant action of ethyl ether causes a steady decline in minute volume until apnoea finally supervenes (35).

Ethyl ether has been used in the treatment of severe attacks of acute asthma (125). The mechanism of action of ethyl ether in asthma is unclear. It has been suggested that ethyl ether anesthesia causes bronchodilation through release of adrenal catecholamines, which leads to relaxation of bronchial smooth muscle through beta-adrenergic stimulation (11). A direct relaxing effect of smooth muscle has also been suggested (22). Ethyl ether given intravenously in baboons had no effect on bronchoconstriction caused by intravenous acetylcholine, histamine or phenylephrine administered either alone or in combination with propranolol (104).

6.3 Liver

Rosenthal and Bourne (126) investigated the effect of anesthetics on hepatic function in dogs. Half an hour of ethyl ether anesthesia caused slight impairment of liver function as measured with the bromsulphalein test. Two hours of ethyl ether anesthesia caused an average dye retention of 14% fifteen minutes after injection (controls 0%). Recovery was usually complete in 24 hrs.

A study of liver function was performed on 100 patients selected at random from those undergoing abdominal surgery. Fifty patients received anesthesia with halothane as the principal agent, and 50 received anesthesia with ethyl ether. After ethyl ether administration, a significant increase occurred in SGOT (serum glutamic-oxaloacetic transaminase) activity. When the two groups were compared, a significantly greater increase in alkaline phosphatase was found after ethyl ether anesthesia, whereas a significantly greater elevation of serum unconjugated bilirubin occurred after use of halothane (37).

Ethyl ether anesthesia has been shown to cause a transient reduction of hepatic uridine diphosphoglucuronic acid (UDPGA) levels in rats (45, 166). UDPGA is necessary for glucuronidation, an important biotransformation pathway in the elimination of endogenous and exogenous compounds. The glucuronidation of bilirubin was decreased in rats by ethyl ether anesthesia (39).

Ethyl ether is metabolized to acetaldehyde by hepatic microsomal enzymes. Long-

term ethyl ether treatment of rats leads to induction of hepatic microsomal enzymes and to proliferation of smooth endoplasmic reticulum (127).

6.4 Kidneys

Albuminuria from tubular irritation has been reported to occur in about one-fourth of patients anesthetized with ethyl ether (68).

Chronic exposure to ethyl ether during the manufacture of smokeless powder has been claimed to cause occasional cases of nephritis (28, 65, 68), but this effect has since been questioned. Hamilton (64) described a man who had worked continously for 7 years and intermittently for 5 years in a smokeless powder factory, and who developed a severe chronic interstitial nephritis verified at autopsy.

Ethyl ether has been used for dissolution of an obstructed Foley catheter baloon. The use of ethyl ether for this purpose has occasionally resulted in a chemical cystitis with permanent damage to the urinary bladder (51, 91, 105).

6.5 Central nervous system

Acute exposure of humans to high concentrations of ethyl ether vapor causes initial excitement followed by narcosis and respiratory depression. The different stages of ethyl ether anesthesia have been described in detail and are given in Table 1. The approximate blood and alveolar levels of ethyl ether in relation to the depth of anesthesia are given in Table 2.

Long-term exposure to low concentrations of ethyl ether vapor in industry, for example during the manufacture of smokeless powder, has been reported to cause various symptoms from the central nervous system such as sleepiness, dizziness, excitation, headache and psychic disturbances (47). Surgeons and nurses exposed for long periods of time to ethyl ether in the operation theatre complained of tiredness, headache, loss of appetite, irritability and difficulties in concentrating (168).

Ethyl ether has been reported to have complex effects on learning and memory in experimental studies in mice. Ethyl ether, like strychnine, appears to be a modulator of learning and memory (96). Some investigators have described retrograde amnesia after exposure to ethyl ether, but due to differences in methodology, the amnestic effects of ethyl ether have not been found consistently (167). Abt et al. (1) studied one-trial conditioning in mice and concluded that ethyl ether could produce amnesia, whereas other investigators have found that ethyl ether enhances learning (170, 171). Alpern and Kimble (4) found that ethyl ether causes retrograde amnesia in mice when ethyl ether was administered at an elevated temperature, but not at room temperature. Van Buskirk and McGaugh (159) reported that ethyl ether (7 ml in a 500 ml jar) administered to mice immediately after training but before electroconvulsive shock (ECS) provided complete protection from the amnestic effects of ECS. The mechanism behind the amnesia-attenuating effect of ethyl ether is obscure.

Ethyl ether causes cerebrovascular dilatation at 2 times the minimum anesthetic concentration (the minimum anesthetic concentration is the concentration at which 50% of the subjects move in response to a surgical stimulus) (172). The cerebral blood flow (CBF), cerebral metabolic rate for oxygen ($CMRO_2$) and cerebrovascular resistance (CVR) were measured in two groups of monkeys inhaling 2 vol% (61,600 mg/m^3) and 5 vol% (154,000 mg/m^3) ethyl ether in air. CVR fell by 30% when ethyl ether concentration was increased from 2 to 5% whereas CBF and $CMRO_2$ were unaltered. The conclusion of this study was that the effect of ethyl ether on CVR probably reflects a complex interaction of a number of factors such as alterations in alfa-adrenergic tone associated with changes in plasma epinephrine levels, alterations in vasoactive metabolites and alterations in beta-adrenergic receptor activity (75).

The effects of ethyl ether on the morphology of the blood-brain barrier within the optic tectum was investigated in hatching chick embryos and young chickens. Ethyl ether was administered on a small compress of surgical gauze covering the chick beak until anesthesia was reached (1-3 min). Horseradish peroxidase was used as a marker of vascular permeability. Ethyl ether anesthesia was reported to produce extravasation of HRP by opening the tight interendothelial junctions. Areas of tracer extravasation were more numerous in the tecta of hatching embryos than in young chickens (108).

Richards and White (122) investigated the effect of volatile anesthetics (ethyl ether, halothane, methoxyflurane and trichloroethylene) on the synaptic transmissions in the dentate gyrus. The experiments were performed *in vitro* using a preparation of the dentate gyrus of the hippocampus in Guinea pigs. Ethyl ether was applied to slices of the dentate gyrus in the gas phase by mixing ethyl ether with the O_2/CO_2 gas mixture that superfused the upper surface of the slice. All four anesthetics depressed synaptic transmission in the dentate gyrus. The mechanism behind this effect was interpreted to be either a reduction of transmitter release, or a decrease in the sensitivity of the postsynaptic membrane to released transmitter, or both effects together.

EEG monitoring in animals during anesthesia with ethyl ether has shown that ethyl ether reduces neuronal excitability (93, 147). The depressive effect of increasing concentrations of ethyl ether on the central nervous system is also evident from Table I.

6.6 Peripheral nervous system

Larrabee and Pasternak (90) studied the concentrations of various anesthetics required to block synaptic excitation of sympathetic ganglion cells and compared that to concentrations necessary to block conduction along sympathetic nerve fibers. The experiments were performed on *in vitro* preparations from cats, rats and rabbits. Ethyl ether depressed synaptic transmission through a sympathetic ganglion in a concentration similar to that assumed to exist in the blood during surgical anesthesia. The conduction along autonomic fibres of different types (A, B and C) was blocked by ethyl ether, but synaptic transmission was depressed more readily than conduction along any type of axon.

Ethyl ether and halothane were found to affect the kinetics of sodium and potassium current *in vitro* in the crayfish giant axon. Both anesthetics caused a reversible, dose-dependent speeding up of sodium current inactivation at all membrane potentials. The activation of potassium currents was faster with ethyl ether present, but there was no change in the voltage dependence of steady-state potassium currents. A theory was proposed that the effects on sodium and potassium channel gating processes was due to either an effect on the state of the lipids surrounding the channels, or a direct effect on the protein part of the channels (18).

A bath concentration of 100-300 mM (7,412 - 22,236 mg/l) ethyl ether blocked the conduction of single action potentials in the bifurcating axon of the lobster deep extensor muscles (58). In frog sciatic nerve, 300 mM (22,236 mg/l) ethyl ether was needed to depresss single axon sodium currents (81). Significant depression of mammalian B and C fibers was produced by 77 mM (5,707 mg/l) ethyl ether (90).

6.7 Muscle

Ethyl ether causes muscle relaxation by its depressing effect on the central nervous system and by affecting neuromuscular transmission and the muscle itself. The mechanism of neuromuscular blocking action of ethyl ether seems to be similar to, but not identical with that of d-tubocurarine (35, 77). When these two drugs are used in the same patient, an additive effect results from their synergism (35). The neuromuscular block produced by ethyl ether was not effectively antagonized by edrophonium or succinylcholine (77) whereas neostigmine has been reported to reverse the effect of ethyl ether on the motor end-plate (57). The reduction of muscle contractility caused by ethyl ether might be due to a pharmacological effect at the level of the sarcoplasmic reticulum (82, 129).

6.8 Gastrointestinal tract

Salivary and gastric secretions are increased during light ethyl ether anesthesia, but are decreased during deep anesthesia. Bowel movement is decreased, due to stimulation of dilator fibres and to depression of plain muscle (162). Nausea and vomiting are common after anesthesia with ethyl ether. Ethyl ether stimulates the vomiting centre in the medulla, and ethyl ether is absorbed in saliva and passes to the stomach where it irritates the mucosa (35). The incidence of postoperative nausea varies with the length of operation and depth of anesthesia (162).

6.9 Circulatory system

Ethyl ether vapor depresses myocardial activity if added to the circulation in a heart-lung preparation (119). Ethyl ether anesthesia causes increased sympathetic nervous activity in the dog and man (98) and the plasma levels of noradrenaline increase with increasing depth of ethyl ether anaesthesia (21). Skovsted and Price

(134) postulated that the increase in sympathetic preganglionic activity caused by ethyl ether anesthesia in cats was due to a central action on the medullary vasomotor center or on spinal vasomotor neurons. The direct myocardial depressant action of ethyl ether seen in the isolated heart preparation is antagonized by the positive inotrope effect of adrenaline and noradrenaline released during ethyl ether anesthesia (26). Ethyl ether seems to block parasympathetic activity in normal man (118). Ethyl ether anesthesia produces remarkably small alterations in blood pressure and pulse rate and rarely leads to cardiac arythmias (35).

In a study in rats, the effects of ethyl ether anesthesia on whole-body hemodynamics and organ blood flow was measured using microspheres. Anesthesia was induced using a bell jar containing a gauze pad moistened with ethyl ether, and the animals were maintained between stage II and stage III of anesthesia. Ethyl ether anesthesia initially decreased arterial pressure and the total peripheral resistance, whereas the cardiac index was increased. Later, the cardiac index returned to normal and there was an increase in total peripheral resistance index. The blood flow to the spleen, stomach, intestine, kidneys and colon decreased during anesthesia whereas the blood flow to the brain and heart increased (141).

6.10. Hematological system

Anesthetic agents may have both direct and hormone-mediated effects on the leukocytes. After ethyl ether anesthesia in man, a postoperative leukocytosis has been reported which is related to the sympatomimetic effects of ethyl ether (164).

Blood samples from workers chronically exposed to ethyl ether fumes in the manufacture of smokeless powder showed in some individuals polycythemia and increased number of leukocytes (65).

The immediate effects of ethyl ether upon some of the blood components was investigated in cats. The animals (12 cats) were placed in a box and ethyl ether was then administered by cone. Blood samples were taken immediately thereafter, usually not more than 10 to 15 minutes after anesthesia had begun. Ethyl ether produced an immediate increase in the hematocrit value, leukocytes, lymphocytes and polymorphonuclear (PMN) cells of the blood of cats drawn from either the heart or ear. There was no change in the relative proportion of lymphocytes and PMN cells (137).

Ethyl ether anesthesia caused a statistically significant increase in prothrombin time and a decrease in bleeding time, coagulation time and platelet count in 25 healthy individuals (age 16-40 years) undergoing elective surgery. Halothane and trichloroethylene anesthesia did not affect coagulation parameters (14).

6.11 Endocrine organs

6.11.1. Man

Anesthesia and noxious surgical stimulation are accompanied by profound changes in endocrine function. Anesthesia is generally considered to have less effect on endocrine responses than surgery, but certain endocrine effects produced by anesthesia alone are recognized (for reviews see 113, 114). Ethyl ether stimulates the adrenal cortex, as shown by the increase in peripheral blood levels of corticosteroids in man (66, 163). Ethyl ether is the strongest stimulant of adrenocortical activity among available anesthetic agents (113, 115). Ethyl ether anesthesia increases plasma cathecholamines in man (21, 120). The increase is mainly due to a rise in plasma noradrenaline (113). The increase in plasma cathecholamines leads to a mobilization of glycogen from both the liver and muscle tissue, and marked rise in blood sugar follows (35).

The levels of thyroid stimulating hormone (TSH) do not change appreciably during ethyl ether anesthesia. The levels of thyroxine increase significantly, whereas the triiodthyronine levels decrease in humans during ethyl ether anesthesia (97).

Plasma aldosterone levels and plasma renin activity increase during ethyl ether anesthesia (15, 115). The plasma antiduretic hormone levels also increase significantly after the induction of anesthesia with ethyl ether (97).

Ethyl ether anesthesia caused a significant decrease in serum calcium levels in 30 patients undergoing various routine surgical operations. Serum calcium returned to near normal levels after 24 h. The mechanism behind this effect is not known (62).

6.11.2 Laboratory animals

Ethyl ether anesthesia administered by placing rats in an ether saturated jar and then maintained with a nose cone for 3 minutes caused a significant increse in plasma ACTH levels. Ethyl ether failed to raise the plasma ACTH levels of rats in which an antero-lateral hypothalamic cut and adrenalectomy had been performed 7 to 8 days previously, and plasma ACTH was also unchanged in rats exposed to ethyl ether 2 h after an antero-lateral cut. The results are interpreted as evidence for that intact neural pathways entering the medial basal hypothalamus from the antero-lateral direction are necessary for the ACTH-releasing action of ethyl ether stress (78).

Plasma corticotropin releasing hormone (CRH), arginine vasopressin (AVP), oxytocin (OXY) and ACTH levels rose to approximately twice the level of control rats 2 min after the onset of a 1-min exposure to ethyl ether. Plasma CRH rose further 5 min after the onset of ethyl ether stress, while plasma AVP and OXY returned to the baseline level at 5 min (67).

Ethyl ether anesthesia did not affect the mean concentrations or dissociation constants for rat uterine estrogen or progesterone receptors (173). No difference in

plasma thyroxine levels were found between control rats and rats exposed to ethyl ether inhalation for 2 minutes (89). Ethyl ether anesthesia in rats increased the concentration of plasma beta-endorphin-like immunoreactivity, probably of pituitary origin. This increase was not associated with significant changes in pituitary or brainstem beta-endorphin content (121).

7. IMMUNE SYSTEM

After treatment of human sera with ethyl ether, there were no significant changes in immunoglobulin levels, whereas the complement activity was lost (142).

The effects on lymphocyte responses were studied in seven patients undergoing surgery under anesthesia with ethyl ether + N_2O + O_2. The variables studied were the leukocyte and differential count, the T- and B-lymphocyte count, and lymphocyte transformation by different substances. There were no significant changes in the total lymphocyte or in the T- and B-lymphocyte counts, whereas the mitogen and purified protein derivate of tuberculin (PPD) responses showed a fall in lymphocyte transformation. The authors concluded that operative trauma rather than anesthesia determined the decrease in lymphocytic responses (130).

The effects of anesthetic agents, surgery and blood loss during operation on the immune system was studied in 18 cancer patients undergoing elective operation for tumor removal. A suppression of the patients peripheral blood lymphocyte blastogenic responses was seen with both ethyl ether and halothane anesthesia, though more significantly with ethyl ether. The B-cell responses were more affected by ethyl ether than the T-cell responses. The volume of blood lost during surgery was also correlated with the degree of immunosuppression. The immunosuppression induced by anesthesia and surgery persisted for at least 7 days (74).

The effects of three different anesthetics (ethyl ether, Avertin and Ketamine) on the activity of splenic natural killer (NK) cells was investigated in mice. Natural killer cells are a subpopulation of large granular lymphocytes displaying spontaneous cytotoxicity against tumor cells, virusinfected cells and some microbial pathogens. All three anesthetics caused a significant inhibition of the induction of NK activity by Poly I:C, but had no effect on baseline NK. Since all anesthetics had the same effect, this effect was probably due to the state of general anesthesia, rather than to the pharmacological properties of the anesthetics (95).

8. MUTAGENICITY, GENOTOXICITY

In an early study, Morgan (102) showed that ethyl ether delievered by inhalation for about 11 days, did not produce mutations in *Drosophila ampelophila*.

Several commonly used volatile anesthetics were screened for mutagenicity in the Salmonella/rat liver microsomal assay system. Ethyl ether was reported to be

not mutagenic (165). When the genotoxic activity and potency of 135 compounds were investigated in the Ames reversion test and in a bacterial DNA-repair test, there was no evidence of genotoxic activity for ethyl ether (38).

9. CARCINOGENICITY

Fluck et al. (46) used differential growth inhibition of two E. coli cultures as a rapid screening technique for chemical carcinogens. Ethyl ether from a freshly opened can yielded negative results, whereas a positive response was obtained with ethyl ether that had been exposed to air. The latter result was considered as false positive, however, due to the formation of peroxide oxidants.

White et al. (169) investigated inhaled anesthetics with the sister chromatid exchange (SCE) technique, a rapid assay of mutagenic-carcinogenic potential. When the cell cultures are exposed to mutagen-carcinogens, the frequency of sister chromatid exchanges increase. Exposure for one hour to 1.97 vol% (19,700 ppm) ethyl ether did not increase SCE values.

10. REPRODUCTIVE TOXICITY

In an epidemiologic study of Russian anesthesiologists, Vaisman (158) reported that 18 of 31 pregnancies among 110 female anesthesiologists, aged 24-38 years, ended in spontaneous abortions. In addition, two premature births were reported and in one case the child had congenital malformations. The anesthesiologists with abnormal pregnancies had exposures of 25 hours/week or more while those with normal pregnancies had less than 15 hours/week exposure. Ninety-eight percent of the anesthesiologists reported use of ethyl ether, 59% nitrous oxide, 28% halothane and 21% other agents. Concentration levels were not presented. Since the anesthesiologists were exposed to several different anesthetics, no conclusion can be drawn about the reproductive toxicity of ethyl ether from this study.

The epididymal spermatozoa of mice were examined for morphologic abnormalities following exposure to or near one tenth of the minimum anesthetic concentration and greater concentrations of several general anesthetics including ethyl ether. The mice were exposed to 1.6 or 0.32 vol% (49,280 or 9,856 mg/m^3) ethyl ether 4 hr/day for five consecutive days. There was no significant increase in the level of morphologically abnormal spermatozoa after exposure to ethyl ether (88).

According to Smith et al. (135), ethyl ether might have teratogenic effects in the chick embryo. Fertile eggs of white leghorn chickens were studied. Exposures were carried out in glass chambers during heating with infrared light. Ethyl ether was vaporized by a Copper Kettle vaporizer, and the carrier gas was compressed air. The concentration of ethyl ether varied from 9 to 30 vol% (277,200 to 924,000 mg/m^3) and the duration of the exposure was 5 to 6 hours. There was an increasing sensitivity to lethal effects of ethyl ether in the first 4 days of incubation. The elevation in rate of abnormal survivors after exposure to ethyl ether was statistically significant in six groups of experiments on days 3 and 4. The death rate was very high, however. For example, exposure to 20 vol% ethyl ether for 6 hrs on day 3 caused 96.1% dead embryos. The type of anomalies produced by ethyl ether exposure was the same as that induced by any generally toxic agent given at the same stage of development.

11. DOSE-EFFECT AND DOSE-RESPONSE RELATIONSHIPS

11.1 Observations in man

11.1.1 Inhalation

Odor detection and odor recognition levels have been investigated for ethyl ether (140). The values between investigations differ greatly due to different methods for making these determinations and because scales used in these evalutions are not standardized (31).

Ethyl ether is used as an anesthetic in clinical medicine. The anesthetic may be given on an open mask or by means of an vaporizer. For induction of anesthesia, concentrations of 10 to 15 vol% (308,000 to 462,000 mg/m^3) in air are needed. Light anesthesia is maintained at approximately 3 to 5 vol% (92,400 to 154,000 mg/m^3), but deep anesthesia may require concentrations up to 10 vol% (308,000 mg/m^3) or more (162). The minimum alveolar anesthetic concentration is defined as that concentration of anesthetic in alveolar or end-expired gas that is present when 50% of the subjects do not respond to a surgical stimulus, usually a skin incision. For ethyl ether, the minimum alveolar anesthetic concentration is 1.92% (expressed as partial pressure of agent in alveolar space divided by standard total atmospheric pressure x 100) (25).

The depth of ethyl ether anesthesia has been divided into four stages by Guedel (59) who did an exhaustive study of open ether anesthetics. As the depth of anesthesia increases, the respiratory pattern changes, more reflexes become suppressed, and characteristic changes in the size of the pupil can be seen. This slow progression of changes has made it possible to correlate the alterations in reflex activity to four stages of ethyl ether anesthesia (Table 1). The stages are: I-stage of analgesia; II-stage of delirium; III-stage of surgical anesthesia; and IV-stage of medullary compression. State III, the level of surgical anesthesia, can be further subdivided into four planes. The approximate blood and alveolar levels of ethyl ether in relation to depth of anesthesia have been determined (Table 2).

Nelson et al. (106) studied the irritating and unpleasant effects on humans of some common solvent vapors. An average of 10 persons of mixed sexes were exposed to a given concentration of solvent vapor for 3-5 minutes in a 1,200 cubic foot gas cabinet. Each individual classified the effect of the vapor on eyes, nose and throat as no reaction, slightly irritating or very irritating. Each person was asked if he believed he could work in the atmosphere for an eight-hour day. The concentration of vapor which the majority rejected as a working atmosphere was termed objectionable. For ethyl ether, complaints of nasal irritation started at 200 ppm (616 mg/m^3), and 300 ppm (924 mg/m^3) was objectionable as a working atmosphere.

According to Cook (36), industrial exposure at 500 to 1,000 ppm (1,540 to 3,080 mg/m^3) did not cause any demonstrable injury to health, but a limit of 500 ppm seemed justifiable to avoid irritation and complaint. Amor (5) also considered a concentration of ethyl ether in the atmosphere greater than 500 ppm (1,540 mg/m^3) as indicative of unsatisfactory conditions. He listed 2,000 ppm (6,160 mg/m^3) as the concentration which may lead to symptoms of illness (not specified) if exposure continues for more than a short time.

Concentrations of ethyl ether of 2,000 to 3,000 ppm (6,160 to 9,240 mg/m^3) may occur in the air during the manufacture of smokeless powder and has been reported to result in an occasional slight intoxication (69). The inhalation of ethyl ether at a concentration of 2,000 ppm (6,160 mg/m^3), if continued to equilibrium, has been calculated to result in the absorption of some 6.25 g of ethyl ether and a blood concentration of 90 mg/l. According to Henderson and Haggard (69), inhalation of ethyl ether at these concentrations would probably induce dizziness in some individuals with an increased risk for industrial accidents.

Concentrations above 3,000 ppm (9,240 mg/m^3) as high as 7,000 ppm (21,560 mg/m^3) have been breathed by some workers for variable periods of time. It has been claimed that these concentrations do not cause any physiological or clinical signs of injury, or any increase in the incidence of industrial accidents (7).

According to Amor (5), inhalation of ethyl ether at a concentration of 8,000 ppm (24,640 mg/m^3) for 1 hour will give rise to severe toxic effects (toxic effects not specified).

A concentration of 35,000 ppm (107,800 mg/m^3) of ethyl ether ususally produces unconsciousness in 30 to 40 minutes (69).

Postmortem blood ethyl ether concentrations of 2,880-3,750 mg/l were reported in 2 surgical patients who died within 2.5 hours after cessation of ethyl ether administration (30).

11.1.2 Ingestion

Ethyl ether is irritating to the mucous membranes and humans therefore usually refrain from drinking it. The "ether habit" by ingestion is well known, however. The symptoms are said to be similar to those of chronic alcoholism but they occur earlier (28).

The lethal dose of ethyl ether after peroral intake has been estimated to about 30 ml (21.4 g) (17, 99). Geldmacher-v. Mallinckrodt (52) reported that the lethal dose of ethyl ether after peroral intake was 30-50 g. A one-year-old child who died of peroral intake of an unknown amount of ethyl ether had a postmortem ethyl ether concentration in blood of 2,360 mg/l (123).

Table 1. The stages of ethyl ether anesthesia. Adapted from (35) and (59).

Stage	respiration		pupils		reflex depression
	rhythm	volume	size	position	
Stage I (analgesia)	irregular	small	small	divergent	nil
Stage II (delirium)	irregular	large	large	divergent	eyelash eyelid
Stage III (surgical anesthesia)					
Plane I	regular	large	small	divergent	vomiting conjuncti-val, pha-ryngeal
Plane II	regular	medium	1/2 dilated	fixed centrally	corneal
Plane III	regular, pause after expiration	small	3/4 dilated	fixed centrally	laryngeal, peritoneal
Plane IV	jerky, irregular	small	fully dila-ted	fixed centrally	anal sphincter, carinal
Stage IV (medullary compression)	apnoea				

11.2 Observations in animals

11.2.1 inhalation

Effects of a 35-day continuous exposure to ethyl ether in concentrations of 0.1 or 1.0 vol% (3,080 to 30,800 mg/m^3) were investigated in young mice, rats and Guinea pigs which were in a phase of rapid body growth. Ethyl ether had a

Table 2. Approximate blood and alveolar levels of ethyl ether in relation to depth of anesthesia. Adapted from (35).

	Blood level in mg/l	Alveolar concentration in mg/m^3	vol%
Stage I	100 - 400	8,747 - 35,112	0.284 - 1.14
Stage II	400 - 800	35,112 - 69,916	1.14 - 2.27
Stage III			
Plane I	800 -1100	69,916 - 96,096	2.27 - 3.12
Plane II	1100 - 1200	96,096 - 105,028	3.12 - 3.41
Plane III	1200 - 1300	105,028 - 113,652	3.41 - 3.69
Plane IV	1300 - 1400	113,652 - 122,584	3.69 - 3.98
Stage IV	1400 - 1800	122,584 - 157,388	3.98 - 5.11

negligible effect on rat or mouse weight gain but produced a statistically significant weight loss in Guinea pigs at the higher concentration. Livers from mice and Guinea pigs treated with 1.0 vol% (30,800 mg/m^3) ethyl ether showed only slight increases in lesions compared to controls, whereas no increase in lesions were seen in rats. No consistent injury to any other organ than the liver was observed. The higher dose of ethyl ether was reported to be lethal to mice and Guinea pigs, but not to rats. A draw-back with this study is that the authors were unable to explain the mechanism behind ethyl ether lethality. The mortality was not related to changes in blood or any tissue examined, including the bone marrow. The animals showed enlargement of the liver, but how this was related to ethyl ether lethality was unclear (143).

The results obtained for the concentration of the ethyl ether-air mixture required for the maintenance of anesthesia, and for the lethal concentration of inhaled ethyl ether varies between different species and also between different investigators for the same species. This variation can partly be explained by differences in induction mixtures and duration of the anesthesia (124). The results of various investigations of inhalation toxicity for ethyl ether in animals is presented in table 3. The lethal concentration for mice during a continuous exposure for 97 min was 133,400 mg/m^3 or 4.4 vol% (86). Molitor (100) obtained a smimilar result for the mouse and calculated the LC_{50} for a continous exposure for 3 hours to be 129,500 mg/m^3 or 4.2 vol%. Swann et al. (148) reported that 3.2 vol% (98,560 mg/m^3) of diethyl ether produced excitation and anesthesia in mice. At 6.4 vol% (197,120 mg/m^3) deep anesthesia was produced and respiratory arrest occured at 12.8 vol% (394,240 mg/m^3). When rapid induction and short duration of anesthesia was used, the concentration required to produce respiratory arrest in mice was found to be 18 vol% (554,400 mg/m^3) (103).

Table 3. Inhalation toxicity of ethyl ether

Species	Conc mg/m^3	Exposure (minutes)	Effect	Ref.
mouse	554,400	10	respiratory arrest	(103)
mouse	394,240	5	irregular respiration respiratory arrest in 1/4	(148)
mouse	197,120	5	deep anesthesia	(148)
mouse (male, strain C57BL/6)	184,800	90	LC_{50}	(85)
mouse	184,800	10	surgical anesthesia	(103)
mouse	133,400	67-120	7/10 died	(86)
mouse	129,500	180	LC_{50}	(100)
mouse	98,560	5	slight excitation and irritation followed by anesthesia	(148)
mouse (male, strain C3H/He)	95,480	90	LC_{50}	(85)
dog	206,360 -246,400	20 - 120	respiratory arrest	(124)

Lethal concentrations of ethyl ether in air for the rat was 6.4 vol% (197,120 mg/m^3) whereas the values for the rabbit and dog were 10.6 vol% (326,480 mg/m^3) and 7.6 -19.25 vol% (234,080 - 592,900 mg/m^3), respectively (133).

Robbins (124) studied the responses in dogs to different concentrations of inhaled ethyl ether. Respiratory failure occurred with air mixtures of 6.7 to 8 vol% (206,360 to 246,400 mg/m^3) and a blood concentration of 1,700 to 1,900 mg/l (average for 20 dogs 1,870 mg/l). The experiments lasted from 20 min to two hours. The knee jerk was abolished at a blood ethyl ether concentration of 1,430 mg/l and the lid reflex at 1,500 mg/l.

The susceptibility to inhaled ethyl ether in rats is influenced by the age of the animal. The median time to death (LT_{50}) for neonates was 5 to 6.5 times greater than for adult rats. At the respective LT_{50} values, the mean concentration of diethyl ether in blood was 2.5 to 3 times greater in neonatal rats than in adult rats (132).

11.2.2 Ingestion

The oral LD_{50} in a 2-week-old, young adult (body weight 80 - 160 g) and adult (body weight 300 - 470 g) rat, were reported to be 2.3, 2.4 and 1.7 ml/kg b.w., respectively (83). Smyth et al. (138) reported a single peroral LD_{50} for rats of 3.56 ml/kg b.w.

12. RESEARCH NEEDS

Most of the investigations on the effects of ethyl ether on humans concern its use as an anesthetic agent. More information is needed about the effects on humans of industrial exposure to low concentrations of ethyl ether vapor, especially effects on the upper respiratory passages and the central nervous system. Additional studies on the effects of long-term inhalation of ethyl ether are needed to evaluate chronic toxicity. There is also a need for more studies on possible teratogenic, carcinogenic and genotoxic effects of ethyl ether exposure. The effects of long-term industrial exposure to ethyl ether in air on the kidneys should be reevaluated. In the older literature, a few case-reports describe the development of nephritis but this effect has later been questioned.

13. DISCUSSION AND EVALUATION

The principal exposure routes to ethyl ether in the occupational situation are inhalation and skin contact. Inhalation of ethyl ether vapor causes irritation to the mucous membranes of the nose and respiratory passages. Liquid ethyl ether is a mild skin irritant due to its defatting properties and repeated exposure may cause dermatitis. Inhalation of ethyl ether has effects on the central nervous system (CNS). Acute exposure to high concentrations of ethyl ether vapor produces initial excitement followed by narcosis and respiratory depression. Long-term exposure to low concentrations of ethyl ether vapor in industry has

been reported to cause various symptoms from the CNS such as sleepiness, dizziness, excitation, headache and psychic disturbances. Ethyl ether causes conjunctival irritation in either liquid form or high concentrations in the air. Ethyl ether anesthesia causes an increase in plasma catecholamines which leads to a mobilization of glycogen from the liver and muscle tissue and a rise in blood sugar.

Investigations of possible mutagenic or carcinogenic effects of ethyl ether have shown negative results. The number of these studies is limited, however.

The irritating effects of ethyl ether vapor on the upper respiratory passages is the critical effect which should be taken into consideration in the establishment of an occupational exposure limit for ethyl ether. Complaints of nasal irritation have been reported to start at 200 ppm (616 mg/m^3) of ethyl ether in air. The effects of low concentrations of ethyl ether vapor on the central nervous system should also be given attention. During the manufacture of smokeless powder, concentrations of 2,000 to 3,000 ppm (6,160 to 9,240 mg/m^3) may occur. These concentrations have been reported to cause dizziness in some individuals with increased likelihood of industrial accidents.

The majority of inhaled ethyl ether (87-90%) is excreted unchanged through the lungs. A fraction of ethyl ether is metabolized to ethanol and acetaldehyde by an inducible hepatic microsomal enyme system. Ethanol and acetaldehyde are oxidized to acetate and the acetate then enters the 2-carbon pool of intermediary metabolism.

14. SUMMARY

Björn Arvidson: Ethyl ether. Nordic Expert Group for Documentation of Occupational Exposure Limits, NIOH and NIOSH Basis for an Occupational Health Standard.

A survey of the literature relevant to the discussion of occupational exposure limits for ethyl ether is presented. Ethyl ether has a wide range of uses in the chemical industry. It is used mainly as a solvent and as an extraction medium. Ethyl ether has been used as an inhalation anesthetic for surgery but to a large extent has now been replaced by more modern anesthetics. The acute and chronic toxicity of ethyl ether is low. The principal exposure routes to ethyl ether in the occupational situation are inhalation and skin contact. The critical effect of ethyl ether is irritation of the upper respiratory passages. Long-term exposure to low concentrations of ethyl ether in air may give symptoms from the central nervous system. Symptom which have been reported are sleepiness, dizziness, irritability, headache and psychic disturbances. Ethyl ether is a mild skin irritant, especially after repeated exposure.

Key words: Ethyl ether, occupational exposure limits, solvents, anesthetics.

15. SAMMANFATTNING

Björn Arvidson: Etyleter. Nordiska Expertgruppen för Gränsvärdesdokumentation, NIOH and NIOSH Basis for an Occupational Health Standard.

En litteraturgenomgång har gjorts för att få fram ett underlag till diskussionen kring ett hygieniskt gränsvärde för etyleter. Inom den kemiska industrin används etyleter främst som ett lösningsmedel och ett extraktionsmedel. Etyleter har tidigare använts som narkosmedel i samband med kirurgiska operationer men har nu i stor utsträckning ersatts av modernare medel. Den akuta och kroniska toxiciteten för etyleter är låg. Vid industriell användning är exponeringsvägarna främst inhalation och hudkontakt. Den kritiska effekten för etyleter är irritation av slemhinnor inom de övre luftvägarna. Längre tids exponering för låga halter av etyleter i luft kan ge symtom från det centrala nervsystemet i form av trötthet, yrsel, irritabilitet, huvudvärk, och psykiska störningar. Etyleter i flytande form ger uttorkning av huden, speciellt efter upprepad kontakt.

Nyckelord: Etyleter, hygieniskt gränsvärde, anestesimedel, lösningsmedel.

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Appendix 1.

Permitted or recommended maximum levels of ethyl ether in air

country	ppm	mg/m^3	comments	year	ref.
Denmark	400			1988	1
Finland	400	1200	8h	1987	2
	500	1500	15min		
Iceland	400	1200		1978	3
Netherlands	400	1200		1989	4
Norway	200	600		1989	5
Sweden	400	1200	8h	1990	6
	500	1500	15min		
USA (ACGIH)	400	1210	TWA	1990-91	7
	500	1520	STEL		
(NIOSH)	400	1200	TWA	1990-91	8
	500	1500	STEL		

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