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CRITERIA DOCUMENTS FROM THE NORDIC EXPERT GROUP 1992

Brita Beije och Per Lundberg (Eds)

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PREFACE

The Nordic Council is an international body for the governments in the five countries, Denmark, Finland, Iceland, Norway and Sweden. One of the committees within the Nordic Council, the Nordic Senior Executive Committee for Occupational Environment Matters, initiated a project with a view to compiling and evaluating scientific information on chemical agents relevant to health and safety at work and the production of criteria documents. The documents are meant to be used by the regulatory authorities in the Nordic countries as a scientific basis for the setting of national occupational exposure limits.

The management of the project is given to a group of scientists: The Nordic Expert Group for Documentation of Occupational Exposure Limits. At present the Expert Group consists of the following members:

Helgi Gudbergsson	Municipal Institute of Public Health, Iceland
Per Lundberg (Chairman)	National Institute of Occupational Health, Sweden
Petter Kristensen	National Institute of Occupational Health, Norway
Vesa Riihimäki	Institute of Occupational Health, Finland
Adolf Schaich Fries	National Institute of Occupational Health, Denmark

The secretariat is located at the National Institute of Occupational Health, S-171 84 Solna, Sweden.

The criteria documents aim at establishing a dose-response/dose-effect relationship and a critical effect, based on published scientific literature. The task is not to give a proposal for a numerical exposure limit value.

The literature is evaluated and a draft is written by a scientist appointed by the Expert Group with the support and guidance of one member of the group. The draft is then sent for a peer review to experts by the secretariat. Ultimately the draft is discussed and revised at the Expert Group Meeting before it is accepted as their document.

Only studies considered to be valid and reliable as well as significant for the discussion have been referred to. Concentrations in air are given in mg/m^3 and in biological media in mol/l or mg/kg. In case they are given otherwise in the original articles they are, if possible, recalculated and the original values are given within brackets.

This volume consists of English translations of the criteria documents which have been published in a Scandinavian language during 1992. The names of the scientists who have written the separate documents are given in the list of contents, where aslo the dates of acceptance by the Expert Group are given.

Solna in December 1992

Brita Beije
Secretary

Per Lundberg
Chairman

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INORGANIC ACID AEROSOLS

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BACKGROUND

Inorganic acids are of prime importance in chemical and metal industries. They are used as raw materials in the manufacture of a wide range of chemicals, as well as in refining, electrolysis, and extraction of chemical processes. Inorganic acids are widely used in pickling processes of electroplating, vehicle production plants, steel producing plants, etc.

This document is restricted to the effects of aerosols, and will not consider the corrosive effects of liquid acids from direct exposure to skin or mucous membranes. The size of liquid aerosols is usually characterized by a central measure, most often the median diameter. Whenever aerosols are described by size in this document, this is a shortcut for either mass median diameter (MMD), mass median aerodynamic diameter (MMAD), or volume median diameter (VMD). The present document does not consider gases as sulphuric dioxide or nitrous gases. There is a vast number of studies on biologic effects from these gases that may be relevant to the assessment of the acids, since these gases partly will exert their effect as acids after dissolution in airway fluids (108). The document will emphasize inorganic acids where the mode of biologic effect is primarely considered to be caused by the hydrogen ion (see chapter 4.1). The most widely used of these acids are sulphuric acid, hydrochloric acid, nitric acid, and phosphoric acid. Sulphuric acid and phosphoric acid will only occur as aerosols under the conditions usually met in work environment, while hydrochloric acid and nitric acid may appear as either vapours or aerosols. Inorganic acids with specific health effects from its anionic part, as hydrogen fluoride and chromic acid, are reviewed in earlier criteria documents issued by the Nordic Expert Group (97,98).

Considering the well documented effects of inorganic acid aerosols and their widespread occurrence, thorough evaluations of their toxicologic significance in the occupational setting are scarce . NIOSH has issued a criteria document for sulphuric acid in 1974 (89). This has been updated in 1981 (90). A criteria document on hydrogen chloride has been issued by the U.S. National Research Council in 1976 (94), and there is a recent document on phosphoric acid from an expert group from the European Communities (117). Contrasting this lack of occupational evaluation is the considerable interest in the health effects of environmental exposure to acid aerosols (45,66,92,93). The present document reviews the toxicologic documentation that is relevant for the setting of occupational standards.

1 PHYSICO-CHEMICAL DATA

Sulphuric acid

CAS number	7664-93-9
Synonyms	battery acid, dipping acid, electrolyte acid, fertilizer acid, hydrogen sulphate, matting acid, Nordhausen acid, oil of vitriol, spirit of sulfur, sulfuric acid
Formula	H_2SO_4
Molecular weight	98.08
Boiling point	327 °C
Melting point	- 2 °C

Specific gravity	1.84
Vapour pressure (20 °C)	< 0.04 kPa (< 0.3 mm Hg)
Vapour density (air=1)	3.4
Solubility (water)	complete
pH (0.05 M solution)	1.0
Odour threshold	> 1 mg m^{-3}
Conversion factor	1 mg m^{-3} = 0.37 ppm, 1 ppm = 2.7 mg m^{-3}
Appearance	colourless (pure) to dark brown, oily liquid; odourless unless heated, then choking; hygroscopic

Hydrochloric acid

CAS number	7647-01-0
Synonyms	chlorohydric acid, hydrogen chloride, hydrochloride, muriatic acid, spirits of salt
Formula	HCl
Molecular weight	36.46
Boiling point	110 °C
Melting point	- 25 °C
Specific gravity	1.19
Vapour pressure (20 °C)	4.5 kPa (30 mm Hg)
Saturation concentration	45,000 ppm
Vapour density (air=1)	1.3
Solubility (water)	complete
pH (0.1 M solution)	1.0
Odour threshold	Range 1-50 mg m^{-3} (1-35 ppm)
Conversion factor	1 mg m^{-3} = 0.7 ppm, 1 ppm = 1.4 mg m^{-3}
Appearance	colourless to slightly yellow, fuming liquid with pungent, irritating odour

Nitric acid

CAS number	7697-37-2
Synonyms	aqua fortis, azotic acid, hydrogen nitrate
Formula	HNO_3
Molecular weight	63.02
Boiling point	121 °C
Melting point	- 42 °C
Specific gravity	1.41
Vapour pressure (20 °C)	1.2 kPa (9 mm Hg)
Saturation concentration	12,000 ppm
Vapour density (air=1)	1.4
Solubility (water)	complete
pH (0.1 M solution)	1.0
Odour threshold	not found
Conversion factor	1 mg m^{-3} = 0.4 ppm, 1 ppm = 2.5 mg m^{-3}
Appearance	clear, colourless liquid; suffocating odour

Phosphoric acid

CAS number	7664-38-2
Synonyms	orthophosphoric acid
Formula	H_3PO_4
Molecular weight	98.00
Boiling point	158 °C
Melting point	21 °C
Specific gravity	1.71
Vapour pressure (20 °C)	0.3 kPa (2.2 mm Hg)
Saturation concentration	3,000 ppm
Vapour density (air=1)	3.4
Solubility (water)	complete
pH (0.1 M solution)	1.5
Odour threshold	not found
Conversion factor	1 mg m^{-3} = 0.25 ppm, 1 ppm = 4.08 mg m^{-3}
Appearance	clear, colourless, syrupy liquid; odourless

The equilibrium in air between liquid and vapour phase of the different acids is indicated by their vapour pressures. At ambient conditions sulphuric acid and phosphoric acid are in particulate (liquid) phase while nitric acid and hydrochloric acid predominantly are in vapour phase. Since these strong acids are hygroscopic, the liquid-gas equilibrium is strongly dependent on temperature and relative humidity (49). Fenton and Ranade (49) have investigated conditions for aerosol formation and droplet growth for hydrochloric acid which is the most volatile of the four. At 25 °C a relative humidity of 81 percent or more promotes aerosol formation and droplet growth, when the HCl concentration is in the 10-40 mg m^{-3} range.

2 OCCURRENCE AND USES

2.1 Usage

Sulphuric acid is a raw material in the manufacture of several acids, synthetic fertilizers, nitrate explosives, artifical fibers, and dyes. It is used in dehydration and drying of ethers and esters, as well as gases, and in refining of mineral and vegetable oils. Sulphuric acid is the electrolyte of lead-acid storage batteries. It is further employed for qualitative and quantitative analyses in laboratories, and in the pharmaceutical industry (64, pp 2124-6).

Hydrochloric acid is used in the manufacture of fertilizers, dyes, paint pigments, and artifical silk. It is used in the refining of edible oils, fats, and soaps, in petroleum extraction, as well as in the photographic, textile, and rubber industry. Anhydrous hydrochloric acid is used in polymerization reactions, as in the production of vinyl chloride (64, pp 1084-5).

Nitric acid is applied in the manufacture of acids, metallic nitrates, dyes, pharmaceuticals and explosives (64, pp 1443-5), while **phosphoric acid** is used in the making of fertilizers, and as a cleaning agent in the printing industry (64, p 1683).

Inorganic acids (all mentioned above) are also used extensively in pickling, for the purpose of removing metal oxides and scales from metal surfaces before metal coating

processes. Sulphuric acid and hydrochloric acid are the acids most commonly used in pickling processes (64, pp 1702-4).

2.2 Occupational exposure

Some of the reported epidemiologic studies give data on acid aerosols, mainly sulphuric acid, in the storage battery industry (12,44,85), and in pickling processes (12).

Anfield and Warner (12) have given a comprehensive and systematic report of airborne sulphuric acid levels. Samples were taken approximately 1.5 m above floor level for periods ranging from ½ hour up to several hours. Considerable variation in acid levels were attributed to differing processes in various departments, variation in production rates, and the effect of forced and natural ventilation. Levels were highest in acid cleaning (pickling) of small steel automobile components. Samples (N=85) from an unventilated, open tank showed a mean sulphuric acid concentration of nearly 3 mg m^{-3}. Mean concentration was considerably lower (0.333 mg m^{-3}, 48 measurements) in a continuous sheet pickling operation, with enclosure and ventilation. Measurements in two separate lead-acid battery plants, during plate forming operations, showed mean concentrations of 1.38 and 0.97 mg m^{-3}, respectively (50 observations). The operations were partly enclosed or a seal was provided by detergents. The aerosol size was up to 14 µm.

The exposure levels in the epidemiologic studies agree well with area and personal sample levels in several work-place surveys, performed by NIOSH in the late 1970s. Exposure levels of sulphuric acid in metal cleaning and pickling operations varied widely, while levels in lead-acid battery plants were well below 1 mg m^{-3} (90). Jones and Gamble (65) found an average sulphuric acid mist level of 0.18 mg m^{-3} (5 µm) in lead acid battery production, while Steenland *et al* (128) report average levels in pickling of approximately 0.2 mg m^{-3} in the 1970s.

In a laboratory experiment Anfield and Warner (12) further demonstrated that sulphuric acid aerosol levels were dependent on the temperature and mechanical agitation of the fluid, but foremost on the degree of gas (hydrogen) evolution during the process. A few inches above the beaker the sulphuric acid concentration was 45 µg m^{-3} at 90 °C, and 4.1 mg m^{-3} with agitation at the same temperature. With hydrogen bubble evolution concentrations were nearly 300 mg m^{-3} at 60 °C, and the filter collapsed at 90 °C. Use of floating plastic balls on the liquid surface to blanket the reaction reduced sulphuric acid aerosol levels by 50 %.

PVC may contain about 50 percent by weight of chlorine. During combustion, at relatively low temperatures, most of the chlorine is lost as hydrogen chloride may combine with water to hydrochloric acid. Some 70 percent of potential hydrogen chloride production may take place in 10 minutes at air temperatures of 272 °C. In an experimental setting the burning of wood inside a compartment of 22.5 m^3 where the walls were lined with a total of 100 kg rigid PVC yielded HCl concentrations of approximately 40,000 mg m^{-3} (3 %) within 5-10 minutes (22).

HCl formation from PVC in electrical components in building fires is a potential occupational problem for firemen. Based on measurements hydrochloric acid seems to be

found infrequently during fires (24). Exposure levels during fire fighting have been measured up to 200 ppm, but is most frequently below 50 ppm (132).

The levels from environmental pollution of inorganic acids are considerably lower than occupational exposures. In the U.S.A., sulphuric acid levels may reach levels in the 5-25 µg m^{-3} range (11).

2.3 Determination of inorganic acid aerosols in air

Samples can be collected in a solid sorbent tube (silica gel), using a personal sampling pump (flow rate 0.2-0.5 L min^{-1}). The anions in the sample is analyzed with ion chromatography. The main interference is from the particulate salts of the acid. The method is described by NIOSH (91).

Hydrochloric acid and nitric acid may occur both in vapour and particulate phase in workplace conditions, there may be a need for analyses of both vapour and aerosol phases. The use of ionic chromatography is a possibility for separation and determination of ions in inorganic acids (129).

It is considered outside the scope of the document to describe the many different techniques of determination of particle size.

3 DEPOSITION IN AIRWAYS

Deposition of acid aerosol particles on the surfaces of skin and mucous membranes is the only relevant toxicokinetic aspect, and the literature is restricted to deposition in airways. The fate of the dissociated hydrogen ion is outlined in chapter 4.1. The anion probably enters the body electrolyte pool, and does not play a specific toxicologic role (117).

The site of deposition in the airways, as well as the concentration at the deposition site, are dependent on physicochemical properties, such as volatility and hygroscopicity. In general, large particles or acid vapours will deposit in the proximal airways, whereas low caliber aerosols deposit in small airways or in the alveoli (84). A number of other factors count, such as temperature, humidity, and breathing pattern. An overview is given by Larson (74).

The model for airway deposition level in man as a function of particle size (aerodynamic diameter) is given by e.g. Rudolf *et al* (103). The larger the particle, the more complete is the deposition. In the submicron range approximately 20-40 % deposits, while particles over 2 µm will deposit nearly complete. During nasal breathing of 1 µm particles a fraction of 0.2 will deposit in the nasal mucosa, while nearly 100 percent deposits in the nose when particle size is 10 µm. Particles in the 1-10 µm range will also deposit in the larynx, the trachea, and bronchi, approximately 5-10 percent of the total for particles sized 8-9 µm. Alveolar deposition occurs in the 0.2-5 µm range, with a maximal deposition fraction of 0.4-0.5 for 1 µm particles.

Inorganic acids are hygroscopic and will deposit proximally in the airways (extrathoracic)

in the vapour phase (74). Particles will apply to the outlined model, but particle size and acid concentration will be strongly influenced by the hygroscopicity (see Chapter 1). A sulphuric acid particle with a dry diameter of 1 µm, will at equilibrium at 90 percent relative humidity reach 2.5 µm. At 99.4 percent relative humidity particle size will be 4.5 µm and the acid diluted one hundredfold. At a light fog with relative humidity of 100.015 percent the particle will be 30 µm and be $3x10^4$ times diluted (74). Apart from temperature and humidity the gas-liquid equilibrium will also be dependent on droplet pH. Nitric acid will preferentially be in aerosol phase in droplets of pH above 2 (often large, dilute droplets), and in vapour phase in the presence of small (subsaturated) acid haze particles (74). Carabine and Maddock (32) have investigated growth rate of sulphuric acid particles in the submicron range. At this size, growth rate is independent on droplet size, and the rate limiting factor is the vapour diffusion. Dilution to an equilibrium will be reached within fractions of a second (32).

NH_3 in the airways will neutralize the acid, and lower the deposition of an acid aerosol (73,74). The amount of NH_3 is larger in the mouth, and thus counts more during mouth breathing. The neutralizing effect of NH_3 will in particular decrease the alveolar deposition of small (< 0.3 µm) particles (74).

The pattern of respiration influences the deposition of the inhaled aerosol. During mouth breathing a larger fraction of medium-sized particles (0.5-1 µm) will deposit in the larynx and the tracheobronchial tree compared to nose breathing (74). With increasing respiratory flow rate, the deposition of 0.3-0.7 µm particles will shift in proximal direction, with a higher fraction deposited in the larynx (74). Data from Bowes *et al* (23), where the deposition of a radioactive 10 µm sulphuric acid aerosol was followed, indicate that the deposition pattern may be different in persons with or without bronchial obstruction.

Differences in deposition between species have been studied by Dahl and Griffith (41). Deposition and species differences were highly dependent on particle size (0.4 or 1.2 µm). Compared to the guinea pig, the rat had a much larger fraction of the 1.2 µm particles deposited in the upper respiratory tract.

4 GENERAL TOXICOLOGY

4.1 Toxicologic mechanisms

The toxicologic action of acid aerosols in the airways is determined by the site of deposition, cf. Chapter 3. The physical state and size of an aerosol will therefore to a large extent determine the toxicologic properties (81). The hygroscopic acid vapours or large particles will mainly deposit in the upper airways, and to some extent in the larynx and the proximal parts of the tracheobronchial tree, with a potential of unspecific irritative effects or changes in bronchial structures. Small particles will, to a large extent, deposit in periferial portions of the conducting airways as well as alveoli, with a potential risk of changes in alveolar clearance or the alveolar lining. The evaluation of the toxic potential of different particle sizes is complicated by the fact that the physical phase, as well as size, changes quickly within the airways.

Most researchers studying particle size have used subjective symptoms (80,121), signs of obstruction or increased resistance (5,80,121), or histologic changes (4,130) as effect criterion. Most of these studies indicate that the larger aerosols are more toxic in the 0.5-10 µm range. This may not be so straightforward, though, since aerosols of different size may have different steepness of the concentration-effect curve, with comparative toxicity changing over different concentrations (5).

Concerning toxic effects in the peripheral portions of the lung, there are few indications as to an optimal particle size. Last *et al* (76) found that a 0.5 µm sulphuric acid aerosol (near the size of optimum alveolar deposition) was more effective than a 0.02 µm aerosol in causing alveolar effects in coexposure with ozone. Changes in gas transfer (37) or alveolar macrophage function (114) have been found in studies where very small particle sizes (0.05-0.3 µm) were applied. The studies of Amdur and Chen (8) and Chen *et al* (37) indicate also that ultrafine (<0.1 µm) acid coated solid particles may be more toxic than liquid acid aerosols.

The inorganic acids are hygroscopic and take up water in exothermic reaction. They desiccate tissues more or less and may therefore exert a toxic effect indirectly.

There seems to be consensus that the hydrogen ion is the active component in the inorganic acids for various endpoints, including pulmonary mechanics, mucociliary clearance, alveolar clearance, and macrophage function (11,17,75,76,81,114,135). The anions of the four acids considered here are essential, with low toxicity. The body pools of these anions are fairly large, and it is therefore unlikely that occupational aerosol exposures significantly contribute to the normal body load (117).

Fine *et al* (50) have examined specific airway resistance responses among volunteer asthmatics exposed to aerosols of HCl and H_2SO_4, both with and without glycine as a buffer. They demonstrate that responses were stronger at a given pH when the buffer was added to the acid. This may be explained by the larger pool of available H^+ ions in the buffered aerosol, that can be expected to cause a more persistent decrease in airway surface pH.

Holma (60) reviews the effects of the hydrogen ion on airway mucus. The mucus protects underlying tissues in the airways by absorbing H^+. High molecular glycoproteins (> 100,000 dalton) are the main buffers. Mucus that is acidified will have an increased viscosity compared to the mucus with high remaining buffer capacity. This may play an important role in the pathogenesis of airways disease. Besides influencing mucociliary clearance an increased mucus viscosity has been demonstrated to correlate with increased airway resistance and reduced pulmonary gas exchange. Normally the mucus protein content is sufficient to avoid adverse acidification, but asthmatics and smokers may be risk groups with mucus with low buffer capacity.

Eicosanoids are potent mediators of the inflammatory response, and modulation of their production may be one important mechanism in the pathogenesis of environmentally related lung disease. Acid aerosols may be such modulators, but results of studies performed so far have been inconsistent. Chen *et al* (36) exposed guinea pigs for ultrafine (median diameter < 0.1 µm) ZnO particles coated with H_2SO_4 (0.025-0.084 mg m^{-3}) for 3

hours in 4 days, and a found concentration-dependent increase in prostaglandin $F_{2\alpha}$ and a decrease in leukotriene B_4 in the lungs. Schlesinger *et al* (115) found that exposure to 0.25-1.0 mg m^{-3} H_2SO_4 (0.3 µm aerosol) one hour daily for five days induce changes in eicosanoid metabolism of the airways in a dose-dependent manner in rabbits. The sulphuric acid, probably due to a direct action of the H^+ ion, depresses the production of the prostaglandins E_2 and $F_{2\alpha}$, and tromboxane B_2, but not leukotriene B_4 (115).

The comparative role of exposure concentration and exposure duration in determining acid aerosol responses is much debated (11). There are limited data from animal and volunteer experiments indicating that several effects may be a function of both concentration and time (11). This documentation seems most developed for exposure induced changes in lung defense mechanisms (78,107,125).

The pathogenesis of adverse reactions caused by acid aerosols may be intricate, especially concerning respiratory disease. This is more fully described in Chapters 5.2 and 10.

The remarkable species differences in tolerance towards acid aerosols are of interest. Some of the explanation of the rat's high tolerance may be the anatomic structure of its nasal passages. Exposure where rats have been forced to breathe by mouth demonstrate a higher sensitivity compared to the natural nose-breathing exposure (127). The oral exposure route has also proved to be more toxic than nasal breathing exposure in the rabbit (111).

Data on interactive effects from coexposures of acid aerosols and other irritants, in particular gases, such as O_3, SO_2, and NO_2, are somewhat conflicting (11). While some animal experiments demonstrate that O_3-induced parenchymal lesions are potentiated by sulphuric acid (75,76), others do not indicate that modification of action occurs (33,34). Schlesinger *et al* (113) demonstrate that the combination of H_2SO_4 and NO_2 exposure have a different effect on mucociliary clearance than any of the exposures alone. Also animal studies with lung function test or gas transfer as end points (37), gas trapping (119), or airway responsiveness (120) indicate interaction of effects. Volunteer studies on combined exposures of pneumotoxic gases (O_3, SO_2, and NO_x) and nitric acid (13) or sulphuric acid (62,69,126) indicate independency of effects. The airway contents of NH_3 seem to neutralize inhaled acids and influence the effect of sulphuric acid on lung function (139). The degree of neutralization depends both on NH_3 concentration, breathing pattern, and particle size (73).

4.2 Acute toxicity

Acute toxicity assays have been performed on a variety of animal species, although the guinea pig is most commonly used. Some median lethal concentrations of sulphuric acid aerosol are shown in Table 10.2 (Chapter 10).

A considerable interspecies variation in sensitivity to acid aerosols is reported among laboratory animals. Cavender *et al* (33) exposed groups of 20 Fischer rats and guinea pigs to sulphuric acid mist (MMD 0.5-1.7 µm) in concentrations up to 100 mg m^{-3}. Rats exposed up to one week showed no pathological changes at the maximal concentration, while 30 mg m^{-3} caused fatal pulmonary oedema in the guinea pig.

Treon *et al* (133) exposed small numbers of guinea pigs, mice, rabbits, and rats to sulphuric acid mist (< 2 µm) 6-7 hours daily. Concentrations were ranging from 87 to 1,600 mg m^{-3}. They found that the guinea pig showed proportionally more signs of irritation and pathological findings in the lung, and died at concentrations less than 1/6 of the lethal concentrations for the other species. Rabbits were most resistant, followed by rats and mice.

The acute toxicity of sulphuric acid is highly influenced by particle size, also within the submicron range. In the 0.4-2.7 µm size range larger particles are more toxic than smaller. Wolff *et al* (144) found an LC_{50} of 100 mg m^{-3} for particles sized 0.4 µm, while 30 mg m^{-3} killed 50 percent of the guinea pigs when particles were 0.8 µm. Pattle *et al* (100) found LC_{50} for 0.8 µm particles to be 40 mg m^{-3} for guinea pigs, while 2.7 µm particles gave a LC_{50} value of 18 mg m^{-3}.

Amdur *et al* (9) and Pattle *et al* (100) report similar pathological findings in the lungs of guinea pigs exposed to fatal sulphuric acid levels. Animals that died of high short-term concentrations had distended lungs with few other serious lesions, probably from acute asphyxia from laryngeal spasm. Animals that survived the initial phase showed signs of parenchymal lung damage. The sensitivity of the guinea pig may be caused by its tendency for bronchoconstriction and laryngeal spasm compared to other small laboratory animals (7).

Other factors may influence acute toxicity as well. Amdur *et al* (9) found that young guinea pigs (1-2 months of age) had much lower LC_{50} values (18 mg m^{-3}) compared to animals 1.5 years old (LC_{50} 50 mg m^{-3}). Pattle *et al* (100) found lower LC_{50} values for guinea pigs treated at 0 ^{0}C compared to room temperature.

The acute toxicity data of other acids are more sparse. Darmer *et al* (42) have investigated the acute toxicity of hydrogen chloride vapour and aerosol (64 % of particles < 1 µm). Sprague Dawley rats (N = 10) had a 30 minutes LC_{50} value of 8,300 mg m^{-3} for aerosol and 6,580 mg m^{-3} (4,701 ppm) for vapour. ICR mice (N = 15) had 30 minutes LC_{50} values of 3,200 mg m^{-3} for particles and 3,700 mg m^{-3} (2,644 ppm) for vapour phase exposure. The animals had shallow respiration, and the lungs showed microscopic signs of epithelial damage, atelectasis, oedema, and haemorrhage.

4.3 Subchronic and chronic toxicity

Guinea pigs have been long-term exposed to sulphuric acid in three different studies, at different exposure levels (4,34,130). Cavender *et al* (34) exposed 140 animals to 10 mg m^{-3} (aerosol size 0.83 µm) 6 hours per day, 5 days a week for 6 months (half the animals were coexposed to 0.5 ppm O_3). Thomas *et al* (130) used 152 guinea pigs in a complex protocol where animals were continuously exposed to aerosols of different sizes and levels for 18-140 days (sizes 0.5, 0.9, 4 µm; levels up to 4 mg m^{-3} for the coarse and medium aerosols, up to 26.5 mg m^{-3} for the fine aerosol). Alarie *et al* (4) exposed 200 animals continuously to 0.1 mg m^{-3} H_2SO_4 at two different aerosol sizes for one year. Minimal changes, only slight alveolar macrophage infiltration and loss of ciliated epithelium in trachea, were found on macroscopic and microscopic examination of animals

exposed intermittently to the 0.83 µm aerosol (34). In contrast, animals exposed continuously to a lower concentration (4 mg m^{-3}) of an aerosol of the same size (0.9 µm) showed more extensive microscopic lung changes (130). These animals had hyperemia, oedema, haemorrhage, leukocyte infiltration, and epithelial damage to the small airways and lung tissues (130). Changes were less marked in animals exposed to the fine and coarse aerosol compared to the 0.9 µm aerosol (130). Animals exposed to 0.1 mg m^{-3} H_2SO_4 showed no treatment effects (4).

Cynomolgus monkeys, in groups of 9 animals, were continuously exposed for 78 weeks to sulphuric acid in five groups (4). There were two exposure levels, each with two aerosol sizes. Animals exposed to 2.43 and 4.79 mg m^{-3} with particles of 3.60 µm and 0.73 µm, respectively, had bronchial epithelial hyperplasia and hypertrophy, focal thickening of the bronchial walls, and increased thickness of the alveolar septa. Five of the nine animals exposed to the low dose large aerosol (0.38 mg m^{-3}, 2.15 µm) had slight hyperplasia of the bronchial epithelium. The low concentration small aerosol exposure group (0.48 mg m^{-3}, 0.54 µm) had no clear treatment effects. There were no apparent effects in other organ systems, no teeth changes were reported.

Fischer rats (N = 140) showed no macroscopic or microscopic treatment effects after exposure to 10 mg m^{-3} sulphuric acid (6 h/d, 5 d/w, 6 months). Half the animals were coexposed to 0.5 ppm O_3 (34).

5 ORGAN EFFECTS

5.1 Effects on skin, mucous membranes and eyes

Bushtueva (30,31) reports that 0.7 mg m^{-3} sulphuric acid aerosol increase the light sensitivity of the dark adapted eye in volunteers after a few minutes. The interpretation of this result is unclear (7).

In experiments where animals have been exposed to high levels of acids, superficial erosion of the cornea (94) or corneal opacities (29) has been observed. Rats and mice exposed to acute doses in excess of 3,200 mg m^{-3} HCl as vapour or aerosol groom and preen excessively, and may develop scrotal ulcers (42).

5.2 Respiratory effects

5.2.1 Respiratory effects in humans

5.2.1.1 Experimental studies

All the reported volunteer studies use short-term exposures (maximum four hours). Usually healthy young subjects are exposed, but relatively symptomless asthmatics have been volunteers in many studies. Study subjects are usually their own controls, being exposed to size-specific acid aerosols or control (NaCl) aerosols with a time interval of a few days. Many studies have examined effects during combined exercise and exposure. Most results are outlined in Table 10.1 (Chapter 10).

Acute bronchoconstriction

The majority of human experiments have been performed to give evidence of the potential for acid aerosols (foremost sulphuric acid) in provoking symptoms or signs of acute airway obstruction and bronchoconstriction. The purpose of several studies have been to clarify whether asthmatics belong to a subgroup with increased sensitivity to acid aerosols. Results among healthy and asthmatic volunteers should be assessed separately.

The only study that clearly give evidence for bronchial obstruction from acid aerosols in healthy subjects is that of Sim and Pattle (121). Very high exposures (39 mg m^{-3} dry mist and 21 mg m^{-3} wet mist) to 1 µm aerosols for ½-1 hour produced severe symptoms of irritation of the upper airways, and clinical signs of bronchial obstruction at auscultation. Two volunteers had symptoms and signs of bronchial obstruction for several days post exposure (121). All other studies with healthy volunteers have applied more sensitive measures of bronchoconstriction, but have failed to demonstrate clear exposure effects (0.1-2 mg m^{-3} H_2SO_4 range) from submicron particles (15,57,61,62,68,69,80,96,137). Some report marginal decrements in lung functions (61,96). Kleinmann *et al* (69) report a small decrement in FEV_1 among exercising subjects exposed for 2 hours to 0.5 µm, 0.1 mg m^{-3} H_2SO_4, together with 0.37 ppm O_3 and 0.37 ppm SO_2. Utell *et al* (136) found an enhanced bronchoconstrictor response after carbachol challenge among healthy volunteers exposed to 0.45 mg m^{-3} H_2SO_4 (0.8 µm) for 4 hours, but only after a 24 hours latency time.

In some of these studies, subjective irritation is reported when exercising healthy subjects were exposed to 1 mg m^{-3} sulphuric acid or more (57,61,80), but there are also studies with exposures in the 1-1.6 mg m^{-3} range where symptoms have not been reported (15). It seems like exposure to large mist particles (10 µm or more) produces stronger subjective irritation and less objective signs than submicron particles (80). Exposure to submicron H_2SO_4 levels in the 0.1-0.5 mg m^{-3} range fails to produce symptoms, even during exercise (68,69,126).

Results concerning bronchoconstriction among asthmatic subjects are evidently more conflicting. Experimental protocols seem to be quite similar for most studies. Subjects are usually young adults with few or no baseline symptoms and limited medication. Most studies exercise the volunteers during exposure (whole or part time). Exposure durations vary, some studies apply exposures for a few minutes, others an hour or more. Most studies use sulphuric acid aerosols, usually close to 1 µm median mass aerodynamic diameter, while Aris *et al* (14) and Linn *et al* (80) compare small and larger (6 µm or more) particles. Changes in dynamic lung function, or signs of increased resistance, or exposure-induced specific reactivity to cholinergic substances are the usual end-points in the reported studies.

Linn *et al* (80) found sulphuric acid induced bronchoconstriction and symptoms of irritation among asthmatics exposed during exercise to 1 µm or 10-20 µm particles at 2 mg m^{-3} for one hour. Avol *et al* (15) report bronchoconstriction and symptoms after exposure to 1.06 mg m^{-3}, but not 0.38 mg m^{-3}, for one hour. Hackney *et al* (57) found also symptoms and signs among asthmatics exposed for one hour to 0.9 µm and 10 µm particles of 1 mg m^{-3} (nonsignificant for the larger particles). Spektor *et al* (124) report bronchoconstriction at 1 mg m^{-3}, but not 0.3 mg m^{-3}, for one hour at rest (0.5 µm

MMAD). Utell *et al* have found signs of bronchoconstriction after exposure to 0.45 mg m^{-3} H_2SO_4, but not 0.1 mg m^{-3}, at rest for 16 minutes (135,137) or in an exercise protocol for four hours (136,138). Koenig *et al* (72) exposed nine adolescent asthmatics to 0.068 mg m^{-3} H_2SO_4 for 40 minutes including 10 minutes exercise, and found marginal effects in dynamic lung function parameters. In an earlier study, applying the same subjects and study protocol, 0.1 mg m^{-3} H_2SO_4 induced a mean decrement of FEV_1 of 5 percent, and a 40 percent increase in total respiratory resistance (70). The lowest exposure concentration of sulphuric acid that has produced small decrements in dynamic lung function is 0.051 mg m^{-3}, in a study where 22 adolescent asthmatics (including some of the subjects in the study of Koenig *et al* (70)) were exposed for 40-45 minutes with exercise part of the time (58). Moderate reduction in FEV_1 and forced vital capacity was found 2-3 minutes after exposure to 0.051-0.176 mg m^{-3}, there were still nonsignificant decrements in the group 20 minutes post exposure (58). The authors noted a marked intersubject variation in responses, with larger exposure responses among subjects with a high degree of bronchial hyperresponsiveness to exercise (58).

By contrast, exposures to 2.8 mg m^{-3} (6.1 µm particles) or 2.9 mg m^{-3} (0.4 µm) H_2SO_4 at rest for 16 minutes, or exposure for one hour, with exercise, at 1.4 mg m^{-3} (6.6 µm), have failed to cause bronchoconstriction among asthmatics (14). Linn *et al* (79) investigated dynamic lung function and bronchial reactivity in a group of asthmatic subjects and found no exposure effect of 0.41 mg m^{-3} sulphuric acid (0.6 µm particles, 1 hour duration, exercise during exposure). In an older study, Sackner *et al* (104) were unable to demonstrate bronchoconstriction with 1 mg m^{-3}, 0.1 µm (10 minutes duration, resting condition). The results of Koenig *et al* (70) have been tried to be replicated in a study by Avol *et al* (16). They did not produce significant bronchoconstriction among adolescent asthmatics exposed for one hour to 0.127 mg m^{-3} sulphuric acid during exercise. Their results may however indicate some heterogeneity among the study subjects in reactivity towards exposure at this low level.

Studies on acute bronchial obstructive effects from acids other than sulphuric acid are scarce. Nitric acid effects have been investigated in two studies. Koenig *et al* (71,72) have exposed adolescent asthmatics to HNO_3 (probably in vapour phase) with a similar design as in their H_2SO_4 studies described above. Nine subjects exposed for 40 minutes either to 0.13 mg m^{-3} (0.05 ppm) or 0.25 mg m^{-3} HNO_3, or 0.13 mg m^{-3} HNO_3 combined with 0.068 mg m^{-3} H_2SO_4 during exercise, demonstrated decrements in FEV_1. Aris *et al* (13) exposed a group of 39 healthy subjects to HNO_3 alone or followed by ozone exposure later on the same day. The subjects were selected on basis of their sensitivity to O_3 after provocation, and had also as a group increased responsiveness to metacholine. Exposures to 0.43 mg m^{-3} HNO_3 fog (size 6 µm) for two hours during exercise did not induce decrements in the battery of lung function tests. The O_3-induced decrements in FEV_1 and FVC were attenuated rather than potentiated by prior exposure to the HNO_3 (or H_2O) fog (13).

Mucociliary clearance

A few volunteer studies have investigated effects from acid aerosols on mucociliary clearance. The studies are performed in steps, first by exposure to an acid aerosol, followed by deposition of radioactively tagged particles in the airways and measurement

of clearance rates of the latter. The interpretation of these studies may be difficult, since the results depend both on size of the acid aerosol (i.e. site of action), and size of the particles that are measured (i.e. site of deposition). Leikauf *et al* (77,78) have demonstrated that exposure to 1 mg m^{-3} H_2SO_4 (0.5 µm, one hour) decreases mucociliary clearance among healthy nonsmoking volunteers. 0.1 mg m^{-3} sulphuric acid increased the clearance rate of 7.6 µm MMAD ferric oxide particles (77), while this low exposure decreased clearence rate of 4.2 µm MMAD ferric oxide particles (78). The interpretation by the authors is that the small particles to a larger extent deposited in small caliber airways where the acid aerosol deposited and had its action (78). These experiments have been extended to measure the influence of exposure duration (125). When the clearance of 5.2 µm ferric oxide particles was measured, the rate reduction was much more marked after exposures (0.1 mg m^{-3} H_2SO_4, 0.5 µm) of two hours' duration compared to exposure for one hour (125). The same group of investigators (124) have also investigated mucociliary clearance rates in asthmatic volunteers, and found a clear slowing of clearance after exposure to 1 mg m^{-3} sulphuric acid, but only small, nonsignificant departures from controls at exposures to 0.1 or 0.3 mg m^{-3}. In contrast to these results, Newhouse *et al* (96) found accelerated clearance of 3 µm particles after exposure to a 0.5 µm aerosol of 1 mg m^{-3} H_2SO_4 (2.5 hours). The experimental protocol was different though, since all the healthy volunteers were exercised during part of the exposure.

Gas transfer

One investigation reports alveolar gas transfer capacity in humans. Sackner *et al* (104) found no difference in diffusing capacity among healthy and asthmatic adults (N = 12) that were exposed to a 0.1 µm 1 mg m^{-3} H_2SO_4 aerosol for 10 minutes, compared to the sodium chloride exposed controls.

5.2.1.2 Observational studies

No analytic epidemiologic studies considering the noncancer respiratory effects of occupational exposures to acid aerosols have been found.

The environmental exposure to irritant pollutants, including inorganic acid aerosols, have since long been recognized as causative factors of different respiratory disorders. The increased morbidity from noncancer respiratory disorders, along with increased hospitalization and mortality, has been observed in several incidents where exposure levels have peaked, eg, in Meuse Valley, Belgium 1930, in Donora, Pennsylvania 1948, and in London 1952. Although it is obvious that the effects from these episodes are results from a complex mixture of irritants including sulphur dioxide, smoke particles and acid aerosols, there seems to be concensus that the latter play a partial role (11). The description of these episodes, as well as several epidemiologic studies on the effects of environmental acid pollution, is beyond the scope of this document. These studies are nontheless of interest concerning the occupational scene, in particular since the hydrogen ion and sulphuric acid seem to play an important role in the pathogenesis of these disorders. More recent commentaries or reviews on this subject have been published (11,43,84,105). An example of studies on the effects of environmental exposures to airborne acid aerosols is the study of Ostro *et al* (99). In a prospective study were daily concentrations of hydrogen ion, acidic particulates and vapours followed for a group of 207 asthmatics in Denver, Colorado. Symptoms and need for medication were related to

airborne hydrogen ion, as well as particulate and sulphate levels (99).

Due to work-related respiratory complaints among a group of 21 workers in an Australian mineral analysis laboratory, a survey among 20 of the workers (including workers on sick-leave) was performed. The work-force were exposed to several inorganic acids (levels not given). The survey revealed cough and breathlessness among some workers. Workers with bronchial hyperreactivity at examination (N = 5) had more chest tighness. Two workers had FEV_1 fall in serial measurements over the workshift. The bronchial reactivity of two workers returned to normal after several months away from work (88).

In an electric accumulator factory, Williams (142) compared respiratory morbidity of men in the forming department, who were exposed to H_2SO_4 mist, with unexposed workers in other departments. Exposures had earlier been measured by Anfield and Warner (12), with a mean H_2SO_4 concentration of 1.4 mg m^{-3} (range up to 6.1 mg m^{-3}) of particles up to 14 µm. Exposed men had sickness absence from spells of respiratory disease more often than nonexposed men. Changes in lung function parameters over a work-shift were measured during a week. Changes between exposed and non-exposed workers were not significant. Only men on duty had lung function tests measured, and smoking habits were not recorded.

In a survey among 80 spinning mill workers who were exposed to high levels of ammonia and sulphuric acid, more than half the examined workforce had slight or moderate impairments in lung function tests (59). In a case group description among patients with reactive airways dysfunction syndrome, Brooks *et al* (26) include one male that acquired long-term hyperreactivity after an episode of acute exposure to heated acid (obivously high levels). Goldman and Hill (56) describe chronic bronchopulmonary disease, including atelectasis, after an accident where sulphuric acid aerosol and liquid was released in the worker's face when a valve blew up.

Renke *et al* (102) investigated prevalences of chronic lung disorders among 116 employees in a Polish phosphate fertilizer plant. No exposure levels are given, but phosphoric acid, sulphuric acid, and fluorides, were among the reported exposures. Chronic bronchitis was more prevalent among production workers than among employees in supervising and management, but occurred only among smokers and workers with more than 10 years employment. In the phosphoric acid production 7/23 workers had chronic bronchitis, while 3/10 workers in sulphuric acid production had chronic bronchitis (102). In an Italian survey in phosphoric acid production (46), nearly half the 35 workers had chronic bronchitis. Emphysema and reduced diffusing capacity were also reported, as well as two cases of pneumoconiosis. The effects were related to the levels of fluoride exposures, and phosphoric acid exposure levels are not given (46). In a Czech study of 46 phosphoric acid production workers (exposure levels 1-2 mg m^{-3}), no adverse health effects were reported after clinical examination and biochemical blood analyses (141).

Toyama *et al* (131) investigated 22 workers exposed either to hydrogen chloride aerosol (electric appliances manufacture) or sulphuric acid (copper smelter). The aerosol median diameter were 6 µm and 3 µm for HCl and H_2SO_4, respectively. The authors report small decrements in peak flow rates during exposures to 8.7 mg m^{-3} HCl and 1.9 mg m^{-3} H_2SO_4, compared to 15 unexposed controls. As an extention of this surveys the authors exposed

the 15 control subjects to the same levels of acid aerosols in a trial, and found a more marked reduction in peak flow rates among controls compared to the 22 workers exposed at the work-place.

The literature assessing chemical occupational risks among firemen involve a complex mixture of compounds (24,132), and is not very informative concerning effects from hydrochloric acid.

5.2.2 Respiratory effects in animals

Several species have been investigated for respiratory effects, but most studies deal with rabbits or guinea pigs. Almost all studies consider effects from sulphuric acid. The most important studies deal with effects that may be related to chronic obstructive lung disease, i.e., mucociliary or alveolar clearance, or histologic changes in small airways and alveoli. Most of the reported studies are outlined in Table 10.2 (Chapter 10).

Mucociliary clearance

Several investigations on acid aerosol effect on the deposition pattern and mucociliary clearance of radiolabelled particles have been performed. Schlesinger *et al* studied deposition and clearance effects from acute (109) and chronic (110) H_2SO_4 exposure in the donkey. The radiollabelled particle was 5 µm MMAD ferric oxide. In all the experiments on donkeys the sulphuric acid exposure had no influence on the deposition pattern (fraction, site) of the ferric oxide particles. The mucociliary clearance was influenced by both short-term and long-term exposure. Mucociliary clearance rates slowed down in 3 out of 4 animals during exposure for one hour to 0.4-1.1 mg m^{-3} sulphuric acid aerosol (0.3-0.6 µm MMAD). The picture of considerable inter-animal difference was strenghtened by a difference in development of the clearance rates during the days of the different acute experiments (109). In the chronic exposure experiment (0.1 mg m^{-3} sulphuric acid, 0.5 µm aerosol, 1 hour/day, 5 days/week for one year) 2 out of the 4 donkeys demonstrated slowing of mucociliary clearance rates (110). The slow clearance got considerably worse after 8 months, and was not reversed to normal within three months after the termination of exposure (110).

The same group has also investigated clearance rates in the rabbit. The animals have been exposed to a 0.3 µm sulphuric acid aerosol, and the clearance has been investigated in 4.5 µm ferric oxide particles. A biphasic relation between exposure concentration and clearance rates during exposure for one hour has been demonstrated (35,107,112). In the exposure range 0.26-2.2 mg m^{-3} H_2SO_4 did exposures $\leq$ 0.4 mg m^{-3} accelerate clearance while exposure concentrations $\geq$ 1.0 mg m^{-3} progressively retarded the clearance rates. Clearance rates in the rabbit have also been followed after longer exposure. When exposure duration was 14 days (2 hours daily), 0.5 mg m^{-3} induced slowing of mucociliary clearance in the exposed group as a whole, with a marked increase in variability of clearance rates compared to sham exposed animals (113). When rabbits were exposed 1 hour daily, 5 days a week for one year to 0.25 mg m^{-3} H_2SO_4, clearance rates slowed down and got progressively slower after approximately 8 months. Clearance rates had not normalized after an exposure-free period of 3 months (54,55).

Other research groups have investigated deposition pattern and mucociliary clearance with

slightly different designs. Sackner *et al* (104) found that sheep exposed to a 0.1 µm H_2SO_4 aerosol, 14 mg m^{-3} for 20 minutes or 4 mg m^{-3} for 4 hours had no slowing in the clearance of radioopaque Teflon discs of 1 µm diameter. Clearance was not measured during exposure in this experiment (104). Fairchild *et al* (47) found that a labelled 2.6 µm streptococcus aerosol was deposited more complete, and with a proximal shift, in guinea pigs that had been exposed to 0.03-3.0 mg m^{-3} 0.6 µm sulphuric acid aerosol. The clearance of the same aerosol was slowed down after exposure to 15 mg m^{-3}, but not 1.5 mg m^{-3} sulphuric acid in mice (48).

Alveolar defense mechanisms

Schlesinger and associates have also investigated alveolar macrophage and clearance function in rabbits in several experiments. In these experiments animals are exposed to a 0.3 µm sulphuric acid aerosol. Naumann and Schlesinger (95) exposed animals to 1 mg m^{-3} for one hour, and observed that alveolar macrophage phagocytosis was not significantly altered. In bronchopulmonary lavage fluid no change in viability or number of macrophages were found, but the macrophage adherence was reduced after acid exposure compared to sham exposure (95). When rabbits were exposed to 0.5 mg m^{-3} sulphuric acid 2 hours per day for several days, a biphasic pattern was demonstrated in the number of macrophages in the lavage fluid (106). The number of phagocytically active macrophages and the level of such activity were increased on day 3, but became depressed by day 14 (106). When rabbits were exposed one hour daily for five days to different exposure concentrations, only concentrations ≥ 0.5 mg m^{-3} induced a significant depression in the phagocytosis of inert latex particles (114).

Gas transfer

Gas transfer changes after exposure of guinea pigs to ultrafine (median diameter < 0.1 µm) ZnO particles coated with sulphuric acid has been investigated by Amdur and Chen (8) and Chen *et al* (37). Results indicate that repeated daily 3-hour exposures to concentrations as low as 0.02-0.03 mg m^{-3} H_2SO_4 reduce diffusing capacity after a few days. The same exposure regimen also increase the protein content in pulmonary lavage fluid and increase the lung weight to body weight ratio after 2-3 days (8). A 3-hour exposure to a liquid aerosol of H_2SO_4 at a concentration of 0.31 mg m^{-3} induces the same reduction in diffusing capacity (approximately 25 %) as an exposure to 0.03 mg m^{-3} H_2SO_4 coated on the ZnO-particles (8). Guinea pigs exposed to 0.01 mg m^{-3} H_2SO_4 for 52 weeks or monkeys exposed to 4.8 mg m^{-3} H_2SO_4 for 78 weeks (both exposures continuous) had no treatment effects on diffusing capacity (4).

Histologic changes

Histologic alterations in lung tissue, small airways and alveoli in particular, are end points in several animal studies.

Acute exposures to high concentrations in LC_{50} studies show that sulphuric acid aerosols induce haemorrhagia, atelectasis, oedema, and thickening of alveolar septa in the guinea pig (9). The rat is far less sensitive (33). Cockrell *et al* (39) demonstrate that exposure of guinea pigs to 25 mg m^{-3} H_2SO_4 for 6 hours daily in two days induce the picture of an alveolitis, with increased numbers of macrophages in alveolar septa and the alveolar lumen, as well as injury to the distal airways and vascular endothelium. Buckley *et al* (28) exposed Swiss-Webster mice to 433 mg m^{-3} (309 ppm) HCl (probably in vapour phase), 6

hours daily for two days, and found lesions of the epithelium and subepithelial inflammation only in the nasal region.

Histologic examination after long-term exposure to submicron aerosols of sulphuric acid indicate that low doses induces moderate alterations in small airways and alveoli. In the guinea pig, Cavender *et al* (34) found only minimal proliferation of alveolar macrophages after 6 months' exposure (6 hours/day, 5 days/week) to 10 mg m^{-3}, and Alarie *et al* (4) found no changes from 0.1 mg m^{-3} for one year. In the rabbit did one-hour daily exposures (5 days a week) to 0.25 mg m^{-3} cause different changes in small airways (54,55,111). After this exposure regimen for 4 weeks, increased epithelial thickness and number of secretory cells was demonstrated (111). When the rabbits were exposed for one year, the airway diameter distribution was altered, with an increased frequency of smaller airways. This shift in airway caliber was normalized after a 3 months recovery period. In addition did the density of secretory cells in small airways increase, and there was a shift from neutral to acidic glycoproteins in the secretory cells. The changes in secretory cells did not return to normal after the 3-month exposure-free period (55). Histologic examinations of the cynomolgus monkey has also been performed after 78 weeks' continuous exposure (4). Results indicate that exposure to 0.38 mg m^{-3} H_2SO_4 in a 2.15 µm aerosol induced slight changes, while a similar concentration of a submicron aerosol did not. At exposure concentrations of 2.4-4.8 mg m^{-3} both submicron and a 3.6 µm aerosol induced changes. At examination a focal hyperplasia of the bronchiolar epithelium, and increased thickness of the bronchiolar wall, was demonstrated (4).

Lung function parameters

Several investigators report effects on dynamic lung function and lung mechanics in animal experiments as well. The guinea pig is the species most often used, and sulphuric acid is most thoroughly investigated. Amdur (5) found increased pulmonary flow resistance at exposure levels of 2 mg m^{-3} sulphuric acid for one hour, with a concentration-effect dependent relation for aerosols of different sizes. An exposure concentration of 15 mg m^{-3} increased resistance for 1-2 hours post exposure, while 40 mg m^{-3} increased resistance more than 2 hours post exposure, much more marked for the 2.5 µm compared to the 0.8 µm aerosol. In addition to an increased resistance, a reduction of pulmonary compliance was demonstrated, both suggesting bronchial constriction as the mechanism involved (5). Trapped gas volumes of excised lungs, and observable dyspnoea, both probably less sensitive signs of obstruction, was not demonstrated in guinea pigs exposed to 12 mg m^{-3} sulphuric acid for one hour (119). Some of the guinea pigs exposed to 19-40 mg m^{-3} sulphuric acid aerosols (1 µm MMAD) for one hour demonstrated increased histamine sensitivity, measured by the response in pulmonary compliance and resistance (120). The increase in resistance and decrease in compliance were still present 2 hours after exposure, but baseline levels were reached after 19 hours (120). Amdur and Chen (8) report that the amount of acetylcholine that is necessary to double the airway resistance in guinea pigs is only half that of baseline levels 2 hours after an one-hour exposure to 0.02 mg m^{-3} H_2SO_4-coated ZnO particle or 0.2 mg m^{-3} H_2SO_4 liquid aerosol. Gearhart and Schlesinger (53) report that airway hyperresponsiveness is induced in rabbits during and after long-term exposure (1 hr/day) to 0.25 mg m^{-3} sulphuric acid. The pulmonal resistance response to acetylcholine was progressively increased after 4, 8, and 12 months of exposure (53). Wong and Alarie (145) used an altered response in tidal volume and respiratory frequency during CO_2 inhalation as an end point indicative of

airway obstruction. Guinea pigs exposed to 23.5 mg m^{-3} sulphuric acid for one hour demonstrated such an altered response after CO_2 challenge (145).

Hydrochloric acid response has been examined with the same CO_2 challenge method, where the lowest dose applied (450 mg m^{-3}, probably vapour phase) induced changes in the respiratory pattern after 20 minutes (29). The HCl concentration (probably vapour phase) that elicits a respiratory rate decrease of 50 percent (RD_{50}) has been estimated to 433 mg m^{-3} (309 ppm) in Swiss-Webster mice (28). Kaplan *et al* (67) examined the respiratory pattern and lung function of 12 baboons after a 15 minutes exposure to 700-2,100 mg m^{-3} HCl. They found concentration-dependent changes in the respiratory pattern, whereas lung volumes or diffusing capacity was unaltered 3 days and 3 months post exposure (67).

There is one report on the response to four hours' exposure to 4 mg m^{-3} (1.6 ppm) nitric acid among sheep. Seven normal sheep and seven sheep that were allergic to a common environmental antigen was challenged with carbachol after exposure, and lung resistance was measured. The group of allergic sheep had a significant increase in specific lung resistance both when challenged and measured directly after HNO_3 exposure and 24 hours post exposure (1).

5.3 Gastrointestinal effects

In early surveys several authors have reported high prevalences of dental erosion among workers exposed to sulphuric acid aerosols in pickling and storage battery production (12,27,44,85). In a memorandum, the British Dental Association bring old references on erosions due to hydrochloric or nitric acid as well (25). In a cross-sectional study of more than 500 workers in the pickling and battery industry, a prevalence of erosions of 32 percent was found (27). In a follow-up 20 percent had a progression of the erosions, workers in the battery industry in particular (27). Concentrations of sulphuric acid mists were measured to be higher than 1 mg m^{-3} in both industries by Anfield and Warner (12), but even higher concentrations have been measured (85). The changes may start after a few weeks' exposure with a superficial etching of the enamel, and progress to erosions after a few months' exposure (27). Picklers exposed to iron salts had discolouration of the teeth as well (27).

5.4 Hepatic effects

No data that arise suspicion of an exposure effect on the liver are reported.

5.5 Renal effects

Apart from effects of dehydration at high exposures to sulphuric acid (116), no reported data indicate renal effects from inorganic acid aerosols.

5.6 Haematologic effects

Routine haematological measurements were performed at death of mice exposed to 80-175 mg m^{-3} sulphuric acid aerosol. Results on animals dead after 2-3 days of exposure indicate

dehydration and haemoconcentration (116).

5.7 Cardiovascular effects

Asthmatic and healthy adults (N = 12) exposed to a maximum of 1 mg m^{-3} H_2SO_4 for 10 minutes had no exposure effects on haemodynamics, based on measurements of heart rate, capillary blood flow, diffusing capacity, O_2 consumption, pulmonary capillary plus tissue volume, or functional residual capacity (104).

In a large U.S. cohort mortality study of steel workers, small subcohorts of pickling workers have been identified (86,101). Part of these workers were exposed to acid vapours and aerosols (sulphuric, hydrochloric, and phosphoric acid). Besides acid aerosols workers in these subcohorts might be exposed to gases (coke, oil refinery, natural gas) and furnace exhaust products (86). Twelve out of 45 workers engaged in batch pickling and sheet dryers died of arteriosclerotic heart disease when followed up 1953-1966 (expected 5.4 deaths)(86). The risk was still increased in this group when follow-up was extended through 1975 (101).

Five anaesthesized dogs that were exposed to sulphuric acid with maximum concentrations of 8 mg m^{-3} (7.5 minutes) or 4 mg m^{-3} (4 hours) showed no change in cardiac functions compared to dogs exposed to sodium chloride aerosols. Pulmonary and systemic arterial blood pressures, cardiac output, heart rate, stroke volume and arterial gas tensions were measured (104)

5.8 Nervous system effects

No data are found.

5.9 Endocrinologic effects

No data are found.

6 IMMUNOTOXICITY AND ALLERGY

Swiss-Webster mice were exposed to 141 mg m^{-3} H_2SO_4 (mass median aerodynamic diameter 0.45 µm) continuously for 3-14 days. After incubation of tracheal organ cultures from mice culture fluids were processed for interferon titers. Interferon titers in mice exposed 3, 7, or 14 days were lower than among controls. The result may indicate that sulphuric acid exposure cause a diminishment in alveolar macrophage ability to synthethize interferon (116).

7 MUTAGENICITY AND GENOTOXIC EFFECTS

In the Ames test, phosphoric acid is not mutagenic (with or without S9) to four examined strains of *Salmonella typhimurium* (3,38).

Genotoxic insults may be associated with low tissue pH (146). After incubation in a

medium containing phosphoric acid, increased rates of developmental and genetic abnormalities has been demonstrated in sperm and embryos of the sea urchin *Sphaerechinus granularis* (38).

8 CARCINOGENICITY

8.1 Carcinogenicity in humans

Soskolne *et al* (123) refer that several reports since 1936 have given evidence in support of an increased risk of respiratory tract cancer from acid aerosols.

There are several reports on laryngeal cancer among workers exposed to acid aerosols. During 1958-1979, Ahlborg *et al* (2) found 3 cases (expected 0.06) among 110 men (1,458 person-years) with employment in a factory unit for pickling. Sulphuric and nitric acid were used in the pickling baths during the 1950s. Soskolne *et al* (122) performed a case-control study based an industrial population who had ever worked for at least one year at a large U.S. refinery and chemical plant. The population comprised 50 upper respiratory cancer cases. A fourfold cancer risk was found among workers who were classified as exposed to high levels of sulphuric acids (that was the *a priori* agent under suspicion). For the laryngeal cancer cases (N=34) the odds were even higher (Odds ratio estimate 13.4, 95 % confidence interval 2.1-86), and with a dose response relation. Results were adjusted for potential confounders (alcohol, tobacco, other work-place chemical agents)(122). An increased laryngeal cancer risk was also found in a historic cohort of U.S. steelworkers exposed to acid mists (mainly sulphuric) during pickling operations (128). The workers had held exposed jobs for a minimum of 6 months before 1965, the sulphuric acid exposure levels averaged 0.2 mg m^{-3} in the 1970s. Nine cancer cases were observed, compared to 3.92 expected based on U.S. rates. Data on smoking and alcohol consumption were recorded and judged to be an unlikely explanation of the increased incidence rates (128). An increased risk of laryngeal cancer among white males exposed to sulphuric acid is also reported in an abstract published 1985, from the results of a case-control study (40). An interaction between smoking and sulphuric acid exposure is suggested by the authors (40). In an Italian historic cohort of men with a minimum employment of one year in soap production (N = 361, follow-up 1972-1983), 5 incident laryngeal cancers were found, approximately one case expected (based on the choice of reference) (52). Exposure levels were monitored from 1974, the workers were mainly exposed to sulphuric acid mist (0.64-1.12 mg m^{-3}), nickel dusts (up to 0.07 mg m^{-3}) and mineral oils (52). In a study addressing lung cancer mortality among 20,000 Dow chemical workers with a high prevalence of HCl vapour exposure, a deficit in laryngeal cancer deaths was found (5 observed, 11.3 expected) (21).

Increased risk of lung cancer has also been suspected among workers exposed to inorganic acids. In the Italian soap industry study (52) five men had died of lung cancer 1969-1983 (2.9 expected). Another mortality study among 1,165 workers exposed to sulphuric and other (hydrochloric) acids in steel pickling also indicates an increased risk of dying from lung cancer with the U.S. death rates as standard (SMR 1.64, 95 % confidence interval 1.1-2.3, based on 35 observed deaths)(18). The highest risk among workers exposed to sulphuric acid was found when analysis was restricted person-years that were at least 20

years after the first exposure. An excess lung cancer mortality was also found among workers classified as exposed to other acids. The lung cancer mortality was also increased when other steel workers served as comparison, in particular for workers exposed to "other acids" (18). In contrast, the lung cancer risk was as expected (with a local reference) in a study among nearly 20,000 Dow chemical workers (20). From this cohort, a nested case-control study was performed (308 cases, 616 controls) (21). The main hypothesis of an association between HCl exposure (based on classification by an industrial hygienist) and lung cancer was not confirmed (odds ratio estimate 1.0, 95 % confidence interval 0.8-1.3) (21).

In a large U.S. cohort mortality study of steel workers, small subcohorts of pickling workers have been identified (86,101). Part of these workers were exposed to acid vapours and aerosols (sulphuric, hydrochloric, and phosphoric acid). Among 384 workers who had at some point worked in the stainless annealing or pickling processing, SMR for digestive and peritoneal cancer was doubled (significant at 5 % level) when followed up 1953-1975 (101).

8.2 Carcinogenicity in animals

Sprague-Dawley rats were lifetime exposed to 14 mg m^{-3} HCl vapour (N= 99), 14 ppm formaldehyde (N = 100), or both compounds combined (N = 200). Exposures were 6 hours/day, 5 days/week. Formaldehyde exposed groups showed increased incidence of nasal carcinoma or epithelial metaplasia in the anterior portion of the nasal cavity. Hydrogen chloride alone did not induce such tumours, nor influence the carcinogenic potency of formaldehyde. HCl exposed animals (with or without formaldehyde coexposure) had increased lifetime risk of hyperplasia in the larynx and trachea, changes that are interpreted as moderately irritative but not precancrous (118).

9 REPRODUCTION AND TERATOGENICITY

Groups of 35 bred mice and 20 bred rabbits were exposed to 5 or 20 mg m^{-3} H_2SO_4, 7 hours daily during days of organogenesis (days 6 through 15 in the mice, days 6 through 18 in the rabbits). The high dose showed slight toxicity in both species. No evidence of foetotoxicity or teratogenicity was seen in either species (87).

10 RELATION BETWEEN EXPOSURE, EFFECT AND RESPONSE

10.1 General remarks

The main basis for the assessment of relations between exposure concentrations or doses, and the effect or response, is outlined in Table 10.1 and Table 10.2. In addition are the observational data given in Chapters 5 and 8 of importance concerning dose-response relations. There is an abundant literature concerning sulphuric acid and scarce documentation on the other acids. The toxicologic evaluation can nevertheless, to a large extent, be done, since most investigators seem to agree that the hydrogen ion is the active pathogenetic component.

When making the assessments on threshold concentrations, one should keep in mind the importance of the physical state of the compound as well as the size of the aerosol, and the fact that particle size is influenced by the microclimate of the airways (84). This is the most plausible explanation behind the very scarce effects in the peripheral airways by HCl, that usually is in vapour phase (66). The modifying effect of particle size can simply be viewed as a consequence of different deposition sites (see Chapter 3), but is probably more complex (8). This fact led NIOSH (90) to suggest that future occupational exposure limits ideally should be size-specific.

Effect and response should possibly be related to hydrogen ion concentrations rather than concentrations of the acid. This measure of exposure has not been used except for the most recent reports, however (e.g., Hanley *et al* (58)).

Population heterogeneity and individual susceptibility influence exposure-response relations for acid aerosols. The considerable variation in thresholds of different airway responses was early demonstrated for humans (121) and animals (109,110). Amdur (6) gives more examples of this in her review. This has been most thoroughly addressed for asthmatics. Although individual susceptibility has been demonstrated in asthmatics (58,84), the documentation as to the mechanism and degree of susceptibility is not clear, however (13).

Finally, the possibility of effect modification from other factors should be kept in mind. There is documentation of an increased susceptibility among young subjects (16,58,72), when exposure and exercise are combined (84,134).

The three responses of foremost interest are bronchial asthma, chronic obstructive lung disease/chronic bronchitis, and laryngeal cancer. Other responses will also be commented.

10.2 Bronchial asthma.

The mechanism behind, and threshold levels for, acute airway obstruction in healthy and asthmatic volunteers are of concern. Although human experiments are most relevant, the guinea pig may represent a good animal model for acute bronchoconstriction (11). While short term exposures to submicron H_2SO_4 in concentrations around 1 mg m^{-3} to healthy volunteers has not produced signs of acute bronchoconstriction in most studies (10,57,62), several studies have concluded that asthmatic subjects get symptoms and signs of acute bronchoconstriction at lower levels (58,70,124,135,137,138). Sensitivity increases when subjects are exercised under exposure, and the lowest level of effect (0.051 mg m^{-3} sulphuric acid) has been reported among adolescent asthmatics (58). Several studies have produced evidences in conflict with this, indicating absence or only marginal bronchoconstriction at exposure levels even higher than 1 mg m^{-3} (14-16,80,104). The varying results can only partly be ascribed to different selection criteria of asthmatics and different exposure protocols (51), and studies that in fact have tried to replicate earlier results have come up differently (eg, Avol *et al* (16) vs Koenig *et al* (70)). This discrepancy is unexplained, and is reviewed from different angles by several authors (14,84,134). It could be due to other reactions than constriction, eg, laryngeal irritation, or increased or altered mucus secretion during exposure (14). Hanley *et al* (58) emphasize the considerable intersubject variation in acid aerosol responses among young asthmatics, with

a more marked effect among those who had highest bronchial responsiveness to exercise.

10.3 Chronic bronchitis/chronic obstructive lung disease.

Another matter concerns the potential role of acid aerosols in the pathogenesis of chronic obstructive lung disease (chronic bronchitis). A general review on pulmonary defense mechanisms and the possible role of acid aerosols is given by Schlesinger (108). Human experiments give valuable information on short-time exposures and transitory effects on mucociliary clearance. Animal studies are needed when long-term exposures and endpoints as histologic changes in small airways are of concern.

The literature reporting changes in mucociliary clearance is abundant (35,54,77,82,83,96, 124,143). It seems that single exposures of low sulphuric acid doses (<0.5 mg m^{-3}) induce a reactive increase of mucociliary clearance both in humans (77) and rabbits (35). Repeated exposures at the same levels cause slowing down of the clearance rate in rabbits (54,113) or donkeys (110). Concentrations at 1 mg m^{-3} or above cause a slowing of the clearance rates in humans or animals even during single exposures (77,107).

The persistent histologic changes in small airways, including increased epithelial thickness, changes in secretory cells, and narrowing of small airway diameter, that are found after long term exposure to 0.25 mg m^{-3} H_2SO_4 (0.3 µm) give further evidence that long-term exposure to low doses of acid aerosols may play a role in the causation of chronic bronchitis (54,111).

10.4 Laryngeal cancer

Several epidemiologic studies conclude that a highly increased risk of laryngeal cancer have been found among groups of workers in different trades that are exposed to sulphuric acid aerosols (see Soskolne *et al* (123) for review). The exposure assessment has been done in retrospect, and is in some studies based on earlier measurements. Steenland *et al* (128) report average exposure levels of 0.2 mg m^{-3} in the 1970s. The most relevant exposures may be those of an earlier date. The levels indicated in this report may therefore be an underestimate of exposures with true risk increase.

There are no animal assays that give relevant additional documentation, the only carcinogenicity study reported concerns HCl vapour, and was designed to investigate combined effects with formaldehyde (118).

The potential mechanisms for carcinogenic effects from acid aerosols are discussed by Soskolne *et al* (123). From the chronic irritative effects of the airways, an epigenetic mechanism would be most plausible. It is therefore relevant to discuss a lower threshold level for carcinogenic effects, eg, doses that induce chronic reactive changes in airway epithelium.

10.5 Other responses

Amdur and Chen (8) report that 0.02 mg m^{-3} sulphuric acid coated on ultrafine metal

Table 10.1. Relation between sulphuric acid exposure and responses in volunteer studies

N	Concentration ($mg\ m^{-3}$)	MD† (μm)	Duration	Response/Remarks	Reference
12	39 (dry mist)	1	60 min	Symptoms. Airways resistance increase	121
12	21 (wet mist)	1	30 min	Severe symptoms, increased airways resistance	121
15	5	1	15 min	Coughing	10
11	2.9	0.4	16 min	Asthmatics. No increase in symptoms or specific airway resistance	14
11	2.8	6.1	16 min	Asthmatics. No increase in symptoms or specific airway resistance	14
10	2.4-6	NG‡	< 120 min	Pronounced irritation and cough	30
20	2§	10	1 hr	Symptoms, lung function tests normal	57
41	2§	10 or 20	1 hr	Lower and upper respiratory irritant symptoms. Asthmatics: lung function decrements	80
41	2§	1	1 hr	Irritation and lung function decrements in asthmatics only	80
9	1.6§	0.05	20 minx3	Normal lung function tests	62
10	1.40§	6.6	1 hr	Asthmatics. No increase in symptoms or specific airway resistance	14
9	1.2§	0.05	20 minx3	Coexposure: 0.25 ppm O_3. Normal lung function tests.	62
10	1.1-2.4	NG‡	60-120 min	Irritation, cough	30
42	1.06§	0.9	1 hr	Cough. Asthmatics: Symptoms, decrease in lung function, no change in airways reactivity	15
15	1-3	1	15 min	Perceived irritation	10
10	1§	0.5	2.5 hr	Reduced mucociliary clearance	96
20	1§	0.9	1 hr	Symptoms. Decrease in FEV_1 among asthmatics	57
20	1§	10	1 hr	Symptoms, normal lung function tests in healthy and asthmatics	57
10	1	0.5	1 hr	Asthmatics. Reduction in lung function tests and mucociliary clearance	124
10	1	0.5	1 hr	Reduced mucociliary clearance	77
17	1	0.8	16 min	Reduced airway conductance and FEV_1	135,137
12	1	0.1	10 min	Asthmatics. No change in cardiopulmonal function tests	104
11	0.94§	0.9	2 hr	Subjective irritation, nonsignificant decrease in FEV_1	61
3	0.7	NG‡	4.5 min	Increased light adaption of eyes	31

Table 10.1 continued

N	Concentration ($mg\ m^{-3}$)	MD† (μm)	Duration	Response/Remarks	Reference
10	0.6-0.85	NG‡	60-120 min	Sensation threshold	30
10	0.55-0.7	NG‡	60-120 min	Maximal concentration that is not sensed	30
20	0.5§	10	1 hr	Moderate irritation in healthy and asthmatics, normal lung function tests	57
20	0.5§	0.9	1 hr	Moderate irritation symptoms among asthmatics, normal lung function tests	57
12	0.45§	0.8	4 hr	Asthmatics. FEV_1 decrease	138
17	0.45	0.8	16 min	Lowered airway conductance (asthmatics only)	135,137
14	0.45§	0.8	4 hr	Increased carbachol response	136
11	0.42§	0.9	2 hr	No symptoms, normal lung function	61
27	0.41§	0.6	1 hr	Asthmatics. no exposure effect on lung function or reactivity	79
42	0.38§	0.9	1 hr	No symptoms, normal lung function among asthmatics and healthy	15
15	0.35-0.5	1	15 min	Altered respiratory pattern	10
15	0.35§	0.8	30 min	Asthmatics. Lung function decrements	139
10	0.3	0.5	1 hr	No significant symptoms or function changes in asthmatics	124
32	0.127§	0.5	1 hr	Adolescent asthmatics. No significant bronchoconstriction or symptoms	16
28	0.1§	0.1-0.3	4 hr	No symptoms or lung function changes	68
45	0.1	0.55	4 hr	No symptoms or lung function changes	126
12	0.1§	0.8	4 hr	No symptoms or lung function changes in healthy or asthmatics	136,138
19	0.1§	0.5	2 hr	Coexposed to O_3 and SO_2. Small FEV_1 reduction	69
18	0.1	0.5	1 hr	Changes in mucociliary clearance rates	125
10	0.1	0.5	1 hr	Increased mucociliary clearance rates	77
17	0.1	0.8	16 min	No symptoms or lung function changes	135,137
9	0.068§	0.6	40 min	Adolescent asthmatics. Marginal effects on FEV_1/respiratory resistance	72
22	0.051-0.176§	0.72	40-45 min	Adolescent asthmatics. Marginal decrease in FEV_1/FVC	58

† MD = median diameter, either MMD, MMAD, VMD.
‡ NG = not given
§ Exercise during exposure period or part of exposure period

Table 10.2. Relation between sulphuric acid exposure and responses in animal studies

Species/ N	Concentration (mg m^{-3})	MD* (μm)	Duration	Response/Remarks	Reference
Monkey					
9	4.79	0.73	78 wk	Bronchiolar histological changes, functional lung changes	3
9	2.43	3.60	78 wk	Bronchiolar histological changes, functional lung changes	3
18	0.38-0.48	0.54-2.15	78 wk	Increased respiratory rate	3
Donkey					
4	0.194-1.364	0.3-0.6	1 hr	Decrease in mucociliary clearance No change in respiratory mechanics	109
4	0.1	0.5	1 hr/d 6 mo	Sustained decrease in mucociliary clearance in 2/4 animals	110
Sheep					
10	14	0.1	20 min	Slow mucociliary clearance	104
6	4	0.1	4 hr	Slow mucociliary clearance	104
Dog					
5	8	0.1	7.5 min	No cardiopulmonary function changes	104
5	4	0.1	4 hr	No cardiopulmonary function changes	104
Rabbit					
5	1	0.3	2 hr	Decrease in mucociliary clerance	107
5	1	0.3	1 hr	Pulmonary macrophage function change	95
8	0.828	0.3	1 hr	Decrease in mucociliary clearance	35
3	0.5	0.3	1hr/d 5 days	Decreased phagocytic capacity of pulmonary macrophages	114
5	0.5	0.3	2hr/d 14 days	Decrease in mucociliary clearance	113
15	0.5	0.3	2hr/d 14 days	Change in pulmonary macrophage activity	106
8	0.260	0.3	1 hr	Increased mucociliary clearance	35
20	0.25	0.3	1hr/d, 5 d/w, 1y	Histological changes, airway hyperresponsiveness, reduced compliance and mucociliary clearance	53-55
15	0.25	0.3	1hr/d 5d/w 4w	Epithelial thickening of small conducting airways	111
5	0.25	0.3	1hr/d 5d	Changes in pulmonary arachidonic acid metabolism	115
3	0.25	0.3	1hr/d 5d	No change in pulmonary macrophage activity	114

Table 10.2, continued

Species/ N	Concentration (mg m^{-3})	MD* (μ)	Duration	Response/Remarks	Reference
Guinea pig					
16	109	0.41	21 days	LC_{50}	144
50	100	0.3-0.4	< 7 days	LC_{50}	116
NG†	50	1	8 hr	LC_{50} (95 % confidence limit 34-71) Animals 1.5 years old	9
58	40	0.8	8 hr	LC_{50} at room temparature	100
36	32	0.8	8 hr	LC_{50} at 0 °C	100
16	32	0.84	21 days	LC_{50}	144
20	30	0.5-1.7	5-28 d	Fatal pulmonary oedema	33
20	25	1	6 hr/d 2 days	Profound histological changes in alveoli and distal airways	39
5	23.5	0.92-1.06	1 hr	Reduced response to CO_2 on tidal volume and respiratory frequency	145
23	19	1.01	1 hr	Increased bronchial responsiveness	120
NG†	18	1	8 hr	LC_{50} (95 % confidence limits 16-21) for animals aged 1-2 months	9
32	18	2.7	8 hr	LC_{50}	100
40	12	0.63	1 hr	Bronchoconstriction	119
70	10	0.83	6h/d 5d/w 6 mo	Moderate alveolar macrophage proliferation, epithelial changes	34
20	10	0.53-1.66	5-28 d	Histological alveolitis	33
10	3.02	1.8	1 hr	Proximal shift of deposition of inhaled monodisperse particles	47
6	1.9	0.8	1 hr	Bronchial constriction (reduced compliance, increased resistance)	5
8	0.4	0.08	1 hr	Reduced alveolar gas transfer	37
14	0.32	0.6	1 hr	No change in deposition of inhaled monodisperse particles	47
100	0.10	2.78	1 year	No histologic or function changes	3
8	0.084	0.05	1 hr	H_2SO_4-coated ZnO-particles. Co-exposure to 0.15 ppm O_3 induce reduced alveolar gas transfer	37
100	0.08	0.84	1 year	No changes	3
59	0.08	0.24	1h/d 1-7 days	H_2SO_4-coated ZnO-particles. Reductions in lung function and diffusing capacity when co-exposed with 0.15 ppm O_3	37

Table 10.2, continued

Species/ Number	Concentration (mg m^{-3})	MD* (µm)	Duration	Response/Remarks	Reference
8	0.02	0.1	3hr/d 5d	H_2SO_4-coated ZnO-particles. Changes in lung function and bronchial lavage. Increased airways resistance. Increased lung weight	8
Rat					
20	100	0.7-0.9	7 days	No histologic changes	33
70	10.34	0.83	6hr/d 5d/w 6mo	No histologic changes	34
Mouse					
369	125-154	0.3-0.6	10-14 d	No histologic changes	116
15?	15	3.2	90 min	Decreased mucociliary clearance	48
9	1.5	0.6	4 hr	No change in mucociliary clearance	48

* MD = median diameter, either MMD, MMAD, VMD
† NG = not given

particles, exposed 3 hours daily for 5 days, cause a reduction of alveolar diffusing capacity. Changes in alveolar clearance and macrophage function have also been reported in animals exposed to low doses of 0.3 µm sulphuric acid particles (55,106,114,115). A single exposure to 1 mg m^{-3} for one hour does not change phagocytosis activity (95), but concentrations of ≥ 0.5 mg m^{-3} for 3-4 days decrease the phagocytic activity of the alveolar macrophages (114). There are indications other than the effects on alveolar macrophage function for an effect of acid aerosol exposure on defense mechanisms against respiratory infection. Schwartz *et al* (116) demonstrate a sulphuric acid effect on interferon levels in airway tissues. Birnbaum *et al* (19) show a synergistic action when H_2SO_4 and particulate antigen are inhaled, with an increased permeability of the alveolocapillary membrane and immune complex formation between circulating antibodies and the particulate antigen. These responses may play a role in the lung's defense mechanisms against chemical or biologic agents, but there are limited documentation that gives an understanding of dose-effect or dose-response relations.

Amdur *et al* (10) found already in 1952 that H_2SO_4 in concentrations as low as 0.35 mg m^{-3} alters the pattern of respiration in human volunteers, by increasing respiration rate and altering the tidal volume. The biologic significance of this endpoint is not clear, and NIOSH did not consider this an adverse effect in its assessment (140).

Etching and erosion of teeth among exposed workers have been described in surveys 20-30 years ago. Measurements performed and descriptions of the work environment indicate that these effects appear at H_2SO_4 exposure levels around 1 mg m^{-3} and above.

11 NEEDS FOR FURTHER RESEARCH

Studies of effects from acid aerosols other than sulphuric acid are needed, these may clarify whether there are common acid aerosol effects, and the role of the hydrogen ion in the pathogenesis. The exposures met in different occupations are not well characterized, studies concerning exposure characterization and particle sizes (and particle growth in the airways) are warranted. Although there is sound documentation demonstrating that cumulative dose more than concentration is of concern regarding chronic airway reactions, studies are needed to clarify the role of cumulative dose in the low dose area. Further studies on effects in subgroups that are potentially susceptible to acid aerosol exposures are of great concern. Studies on subjects with chronic obstructive lung disease, and among smokers, is highly relevant for occupational populations. Further studies may clarify and explain the discrepancy concerning acute effects among asthmatics. Further carcinogenicity studies should be performed, both animal assays and observational studies addressing respiratory cancer other than laryngeal cancer, and exposures other than sulphuric acid. Human studies involving histological examinations from upper airways of workers exposed long term to acid aerosols are warranted.

12 DISCUSSION AND EVALUATION

The critical effects of acid aerosols are acute and chronic irritation of the airways. Due to lack of documentation the risk of laryngeal cancer is not possible to relate to exposure levels with certainty. Etching and erosion of teeth occur at exposure levels well above levels that induce airway effects.

The relative importance of study method is different for different end points of acid aerosol effects. Human volunteer experiments are of most concern in the evaluation of acute airway responses (bronchial asthma). Concerning the role of acid aerosols in the development of chronic bronchitis, the most important findings are in animal experiments, while observational studies so far are of most value in the evaluation of cancer as endpoint. Evaluations of the different endpoints are characterized by the strengths and limitations of the different methods. The main problem of the volunteer studies is linked to the necessity for exposures of low concentrations and short duration, as well as the limited number of participants. The main problem of the animal experiments is their relevance for the human situation, while the observational studies have inherent validity problems.

The evaluation is complicated by several factors discussed elsewhere in this document. There seems to be agreement that the hydrogen ion play a crucial role in the pathogenesis of irritant reaction from the airways, but it is still with some uncertainty that acid aerosols as such can be evaluated together. There is also agreement that response is dependent on deposition site, and particle size and the other factors that deposition site is dependent on. There is still uncertainty, however, as the liquid particles are not of fixed size. There are also indications that the quality of the particle may play a role, with more potent responses from metal particles coated with acids. Another uncertainty is that we know little of the role of co-exposure of several irritants, or protective compounds as ammonia gas. We know little about the role of other factors as exercise, subject age, or the physiologic state

of exposed subjects. We know that asthmatic subjects are susceptible to acute airway responses caused by acid aerosols, but the degree and nature of this susceptibility is disputed. We know practically nothing about susceptibility for other important subgroups, such as subjects with chronic bronchitis, and smokers. Our knowledge on the relative role of exposure concentration and duration is limited, although cumulative exposure seems to be the most relevant measure as far as chronic effects are concerned.

There is increasing evidence that long-term low-concentration exposure of acid aerosols, as low as approximately 0.1 mg m^{-3}, play a role in the development of chronic bronchitis. There is little evidence that weighs against this. Most important is the effect on mucociliary clearance, an effect that is not readily normalized even when exposure concentrations are as low as 0.1 mg m^{-3}. The biologic relevance of this effect may be questioned, but it should be noted that cigarette smoke induces nearly identical changes as acid aerosols both in humans and donkeys. Other factors of importance are the histologic findings in animals exposed long-term to concentrations below 0.5 mg m^{-3}. Bronchiolar wall thickening has been found in monkeys and narrowing of small caliber airways in rabbits. Changes in mucus secretory cells and increase in the number of secretory cells during, and for months after, long-term exposures are also findings indicative of a chronic inflammatory response.

The role of acid aerosols for acute airway responses is less clear. The triggering of marked bronchoconstriction has not been convincingly demonstrated in human volunteers, healthy or asthmatic, unless exposure concentrations have been very high. Exposures to very high concentrations can undoubtedly induce bronchial hyperreactivity, but at low concentrations (0.25 mg m^{-3}) this has only been demonstrated in rabbits. It is not easy to interpret the more limited effects in increased airway resistance and increased responsiveness to cholinergic challenge that has been found in some, but not all, studies in exercising asthmatics during low exposures (0.05-0.5 mg m^{-3}). The discrepancies over studies may, at least in part, be due to considerable intersubject variation. The effects documented by the lowest exposure levels are not strong, and may be of limited biological importance.

There is due cause to suspect that low cumulative doses of acid aerosols increase the risk of laryngeal cancer. Separately, the studies may have weaknesses in design that may bias results. This is a less plausible explanation for all studies, though. Insufficient control of confounders as an explanation for the highly increased risks is unlikely. The question on harmful doses is not clear, however, due to the uncertainty of historic exposure levels. There is a lack of animal carcinogenicity assays on acid aerosols, making the assessment of these compounds still more uncertain. IARC[1] (63) has not evaluated acid aerosols concerning carcinogenic evidence.

As for other endpoints indicating changes in the alveolar lining and clearance functions in the respiratory part of the lung, changes has been demonstrated in animals exposed for several days to concentrations of 0.5 mg m^{-3} or below. The role of these findings concerning development of human lung disease is as yet unclear.

[1] After the deadline of this document, IARC has evaluated inorganic acids (63b). Strong-inorganic-acid mists containing sulphuric acid is evaluated to be in Group 1 (carcinogenic to humans), the evidence is considered to be sufficient. Accordingly, hydrochloric acid is not classifiable as to its carcinogenicity in humans (Group 3), the evidence is considered inadequate.

13 SUMMARY

P. Kristensen: Inorganic acid aerosols. Nordic Expert Group for Documentation of Occupational Exposure Limits. Arbete och Hälsa 1993:1, pp 7-54.

Relevant data are summarized in this document for the purpose of giving the knowledge basis necessary to establish permissible levels of occupational exposure to inorganic acid aerosols. Among the health effects described, the corrosive and inflammatory effects on mucous membranes should be taken into consideration in the setting of occupational exposure limits. The acid aerosols' potential role in the development of laryngeal cancer should be taken into account as well.

The critical effect of acid aerosols is airway irritation. Some human volunteer studies indicate that sulphuric acid aerosols in the one-micron size range may induce moderate increase of airway resistance in asthmatics at concentrations around 0.1 mg m^{-3} and even lower. These results have not been replicated by others, possibly due to considerable intersubject variation in responsiveness and that the effects are moderate at these low concentrations. In well established animal models, submicron long-term exposures to sulphuric acid aerosols at concentrations in the 0.1-0.5 mg m^{-3} range induce changes in small caliber conductive airways as well as the respiratory parts of the lungs. From this evidence it may be assumed that similar exposures to man can be a causative factor for chronic obstructive lung disease. Human evidence in favour or against this assumption is scarce, however.

Several epidemiologic studies have demonstrated a markedly increased laryngeal cancer risk among workers that are long-term exposed to acid aerosols. Chance or confounding are less likely explanations to the results, and the studies have differences in design and conduction that weighs against a common source of bias. Long-term acid aerosol exposures in doses found in several industries should therefore be suspected as a causative factor for laryngeal cancer. Carcinogenicity animal assays to support this suspicion have not been reported.

In English, 146 references.

A Norwegian version is available in Arbete och Hälsa 1992:33.

Key words: Sulphuric acid, hydrochloric acid, nitric acid, phosphoric acid, aerosol, occupational exposure limits, acute airway response, chronic airway response, laryngeal cancer.

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Appendix 1.

List of permitted or recommended maximum concentrations of sulphuric acid in air

Country	mg/m^3	ppm	Comments	Year	Ref.
Denmark	1	-		1988	1
Finland	1	-	8 hr	1988	2
	3	-	15 min		
Iceland	1	-		1978	3
The Netherlands	1	-		1989	4
Norway	1	-		1989	5
Sweden	1	-	TLV	1990	6
	3	-	STEL		
USA (ACGIH)	1	-		1990-1991	7
(NIOSH)	1	-		1989	8

STEL = short term exposure limit
TLV = threshold limit value

List of permitted or recommended maximum concentrations of hydrochlorid acid in air

Country	mg/m^3	ppm	Comments	Year	Ref.
Denmark	7	5		1988	1
Finland	7	5	15 min	1988	2
Iceland	7	5		1978	3
The Netherlands	7	5	CL	1989	4
Norway	7	5		1989	5
Sweden	8	5	CL	1990	6
USA (ACGIH)	7.5	5	CL	1990-1991	7
(NIOSH)	7	5	CL	1989	8

CL = ceiling limit

List of permitted or recommended maximum concentrations of nitric acid in air

Country	mg/m^3	ppm	Comments	Year	Ref.
Danmark	5	2		1988	1
Finland	-	-		1988	2
Iceland	5	2		1978	3
The Netherlands	5	2		1989	4
Norway	5	2		1989	5
Sweden	5	2	TLV	1990	6
	13	5	STEL		
USA (ACGIH)	5.2	2		1990-1991	7
(NIOSH)	5	2		1989	8
	10	4	STEL		

STEL = short term exposure limit
TLV = threshold limit value

List of permitted or recommended maximum concentrations of phosphoric acid in air

Country	mg/m^3	ppm	Comments	Year	Ref.
Denmark	1	-		1988	1
Finland	1	-	8 hr	1988	2
	3	-	15 min		
Iceland	1	-		1978	3
The Netherlands	1	-		1989	4
Norway	1	-		1989	5
Sweden	1	-	TLV	1990	6
	3	-	STEL		
USA (ACGIH)	1	-		1990-1991	7
(NIOSH)	1	-		1989	8

STEL = short term exposure limit
TLV = threshold limit value

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Aluminium

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Contents

1. Background, physical and chemical data

Aluminium is a metal present in abundance, covering about 8% of the earth's crust. Aluminium has long been considered as virtually non-toxic and non-absorbable from the gastrointestinal tract. Studies during the last decade have revealed that significant absorption of inhaled and ingested aluminium compounds exist. Elimination from the body takes place mainly via the urine. Humans with severely impaired kidney function (uremia patients) may accumulate the metal in the body and this accumulation is associated with severe health effects on the skeleton and the central nervous system.

Industrial exposure to different forms of aluminium may cause asthma, pulmonary fibrosis, and possibly effects on the nervous system.

Physical and chemical data:	
CAS registry number:	7429-90-5 (metallic aluminium)
Atomic number:	13
Atomic weight:	26.98
Melting point:	660.4° C
Boiling point:	2467° C
Density:	2.7 g/cm^3

Pure aluminium is a light, ductile metal, which is a good conductor of both heat and electricity. When aluminium is exposed to air, a thin film of oxide forms on the surface, creating a protective coating resistant to corrosion. Aluminium is used in alloys together with, e.g. copper, zinc, manganese, and magnesium.

2. Occurrence

The element aluminium was first identified in 1827. In 1855, Napoleon III's most exclusive plates were made of aluminium. Charles Dickens reported about a newly available metal named aluminium in 1856 (25).

Aluminium occurs in nature as inorganic compounds. Aluminium oxide (Al_2O_3) is the raw material used in industrial production of the metal. This oxide has two isomeric forms alpha-Al_2O_3 and gamma-Al_2O_3.

2.1. Production

Initially aluminium was very expensive to manufacture, but towards the end of the 19th century production on commercial scale became feasible. The production of aluminium increased rapidly in the 20th century, especially after the Second World War period. In the 1970s and early 1980s, approximately 15 million tons were produced per annum. Aluminium is produced from bauxite, a mineral containing aluminium oxide, ferrous oxide and silica. Bauxite is abundant in the earth's crust in large areas of the world. By a chemical process bauxite is refined to aluminium oxide. Pure aluminium is then produced by using an electrothermal process, where electrolysis takes place in a carbon-lined steel container with molten cryolite

(Na_3AlF_6). Carbon anodes are dipped into the liquid molten cryolite. A direct current generates molten aluminium in the bottom of the cell.

2.2. Uses

Aluminium is an extremely versatile metal with a wide variety of uses, e.g. in packing materials, several types of containers, kitchen utensils, auto-bodies and components, airplanes, and building panels. Certain aluminium compounds are used in paint pigments, pyro-technical products, insulating materials, abrasives, cosmetics, and even food additives (89, 131). Aluminium sulphate is used in the treatment of drinking water and sewage. Some aluminium compounds are employed therapeutically, e.g. aluminium hydroxide is one common component of antacids. Relatively large doses of aluminium hydroxide were previously prescribed for patients who, as a result of renal failure, had high blood phosphate levels. Aluminium forms an insoluble salt with phosphate in the gut and thereby prevents phosphate absorption. Aluminium acetotartrate in solution is used in the treatment of sores and for other dermatological purposes. Aluminium chloride hexahydrate is very commonly used in antiperspirants (94).

Aluminium phosphide is used as a fumigant against insects and rodents in stored grain. This compound may release toxic phosphine by the following reaction: $AlP + 3H_2O \rightarrow Al(OH)_3 + PH_3$ (99, 154). Ingestion of aluminium phosphide as well as inhalation of the released phosphine have caused several deaths (99, 154). Several hundred fatal cases have ben reported from India (8, 74). Most deaths are suicidal, but fatal accidents and even homicides are known. The number of people killed by liberated phosphine every year in India may well be greater than the methyl isocyanate deaths at Bhopal in 1984 (74).

3. Toxicokinetics

3.1. Absorption

3.1.1. Absorption by inhalation

Occupational exposure to different aluminium-containing particles has resulted in increased levels of aluminium in blood and urine, table 1. Thus inhaled aluminium is absorbed but the degree of absorption is not known. The highest concentrations in blood and urine have been observed among welders and workers manufacturing aluminium flake powders. Aluminium-containing welding fume consists of particles smaller than 1 µm (141) and the size of flake powders varies from 5 to 200 µm in diameter and from 0.05 to 1 µm in thickness (90).

The absorption of inhaled aluminium has been confirmed in animal experiments. Eight rabbits were exposed to Al_2O_3 in a dusting chamber to a mean of 0.56 mg Al/m^3 eight hours a day, five days a week for five months. The size of the particles was not given. The concentrations of aluminium increased from 4.1 to 10.1 µg/g dry tissue in brain and from 18.2 to 22.2 µg/g dry tissue in bone (114).

An influx of aluminium into the brain via the olfactory nerve has been observed in rabbits after exposure to aluminium chloride and lactate in solution (108). The quantitative importance of this route of absorption is today unknown.

3.1.2. Absorption by the gastrointestinal tract

For a long time, it was thought that absorption of aluminium from the gastrointestinal tract was more or less non-existent. In balance studies of metabolism using human subjects who had taken large doses of antacids containing aluminium, it has been shown that the major portion of the dose was eliminated with the feces. The net balance was, however, positive, i.e. the given dose was higher than the total fecal excretion, and this implies that certain amounts of aluminium were probably absorbed (20, 54). It has been demonstrated that urinary excretion of aluminium increases several-fold after exposure to large doses in the form of aluminium-containing antacids (75, 110). The urinary concentration of aluminium increased about 3 times when the total amount of aluminium in food rose from 5 mg/day to 125 mg/day (56). The absorption from the gastrointestinal tract is probably influenced by several factors. Dietary citrate enhances the absorption (130). In rabbits administered orally aluminium hydroxide together with citrate or maltolate the urinary aluminium output increased 5-fold by citrate and 90-fold by maltolate (22).

3.2. Distribution

The total aluminium body burden of aluminium has been estimated to be around 30 mg in subjects without excessive exposure to aluminium and with a normal renal function (144). These subjects have the highest level of aluminium in the lungs (5-35 µg Al/g wet tissue), followed by the skeleton (1-12 µg/g) and the skeletal muscles (1-4 µg/g). The gray matter of the brain contains 2.2 µg aluminium per g dry weight among persons not excessively exposed (4) and this is lower than the bone (3.3 µg/g) and the lung (56 µg/g). The concentration of aluminium in the lungs increase with age in non-occupationally exposed subjects (4). This is probably a result of deposition in the lung of aluminium-containing dust during many years.

The normal serum level of aluminium has been found to be less than 0.4 µmol/l (10 µg/l) and transferrin is an important carrier. It has been demonstrated that there is an approximate equal distribution of aluminium between plasma and erythrocytes (145).

Intravenous injections of aluminium chloride to dogs (1 mg Al/kg/day) 5 days a week for 3 to 5 weeks increased the plasma levels of aluminium from 0.4 to 40 µmol/l and the concentrations in bone from 1 to 100 µg/g fat free dry weight (60).

In dialysis patients the bone contains between 1.5 and 113 µg aluminium per g dry weight (36, 39). Two aluminium exposed welders had bone concentrations of 18 and 29 µg Al/g dry weight, thus clearly above the reference range 0.6-5 µg Al/g (36).

Nine mothers, who had taken aluminium-containing antacids during their pregnancy, had a median serum level of aluminium of 0.19 and their newborns had a level of 0.26 µmol/l (148). The consumption of antacids was rather low as the serum level did not exceed the level of non-consuming mothers.

3.3. Elimination

The urine appears to be the major excretion route for aluminium but the metal is also excreted via the bile (153). The importance of reabsorption from the gut is not yet known.

Dogs recieving one single dose of aluminium chloride intravenously excreted 10-30% in the urine during the following two hours (60, 81) and the plasma half-time was 4-5 hours (60).

The half-time of aluminium was estimated in rabbits after one single intravenous infusion of aluminium lactate (156). Estimated half-times were 113 days in spleen, 74 days in liver, 44 days in lung, 42 days in serum, 4.2 days in kidney cortex, and 2.3 days in kidney medulla. In a later phase the levels of aluminium in the kidneys decreased with a slower rate corresponding to a half-time greatly exceeding 100 days.

Volunteers exposed to aluminium-containing welding fume for one day displayed a half-time of aluminium concentrations of about eight hours (127). Among welders exposed for less than one year the half-time was about nine days whereas among welders exposed for more than ten years the urine half-time was calculated to six months or longer (125).

Similar observations have been made in workers exposed to aluminium flake powders (90). Active workers, followed during four to five weeks without exposure, showed a urinary half-time of five to six weeks, whereas retired workers had half-times from one to eight years.

3.4. Biological monitoring

Measurements of aluminium in human biological media such as blood and urine is difficult particularly due to the severe risk of contamination. Many of the early measurements of aluminium in biological media are therefore erroneous (44, 146). Even today the "normal" concentratrion of aluminium in blood and urine is not precisely known. It may however be concluded that it is less than 0.4 µmol/l, table 1.

Increased blood and urine concentrations of aluminium have been found among several groups of occupationally exposed workers, table 1. The highest levels have been seen among welders and flake powder producers. Among foundry workers exposed between 1 and 17 years to current levels of 0.03-0.58 mg Al/m^3 a mean serum aluminium value of 0.6 µmol/l and a mean urine value of 0.7 µmol/l have been reported (113) and this is in approximate agreement with previous results.

A linear relationship has been found between blood and urine concentration of aluminium in industrially exposed workers. Urinary concentration of aluminium (µmol/l) = 5.2 x (blood concentration µmol/l) - 0.1 (128) when urine levels are below 13 µmol/l. This relation probably changes at higher levels.

Patients suffering from dialysis encephalopathy due to the accumulation of aluminium in the brain exhibit markedly increased levels of aluminium in serum compared with healthy individuals. Elevated levels of aluminium in serum are likely reflecting an increased body burden but the association may not be linear (17). In order to prevent aluminium encephalopathy among dialysis patients, it has been recommended that the serum level of aluminium should be kept below 7.4 µmol/l

Table 1. Postshift blood/plasma/serum and urine concentrations of aluminium in different industrial exposures and among occupationally non-exposed (µmol/l).

Exposure (Reference)	Blood/plasma/serum		Urine	
	Median	Range (n)	Median	Range (n)
Al-powder-production (128)	0.5	<0.2-6.3 (20)	1.4	<0.1-156 (19)
Al-sulphate-production (128)	0.3	<0.2-0.8 (23)	0.2	<0.1-1.7 (22)
Corundum (Al_2O_3) production (142)	0.5	0.2-6.1 (110)	1.4	0.4-8.2 (110)
Cryolite-production (55)	0.8	0.4-1.7 (8)	3.8	0.7-5.4 (8)
Elektrolytisk produktion (128)	<0.2	<0.2-0.6 (31)	0.3	<0.1-0.7 (31)
Electrolytic production (118)	1.3	1.1-1.7 (6)	-	-
Grinding (58)	0.4	0.1-1.0 (51)	0.4	0.1-1.4 (48)
Grinding (38)	-	-	0.2	0.1-0.7 (14)
Melting and foundring (38)	<0.1	<0.1 (16)	0.4	0.1-1.6 (16)
Welding (128)	0.3	<0.2-2.5 (18)	3.0	0.5-75 (18)
Occupationally non-exposed	<0.4		<0.4	

(200 µg/l) (117). This limit may however not be safe. In a recent study it has been reported that long-term hemodialysis patients, with a mean serum concentration of 2.2 µmol/l, had abnormalities in several computerised tests of psychomotor function indicative of a subclinical aluminium intoxication (6).

A seasonal variation of serum aluminium levels in non-occupationally exposed persons have been observed in the Oslo-region. Peaks of aluminium were found in September possibly caused by a waterborne factor with chelating properties which increased the gastrointestinal absorption of the metal (104).

The concentrations of aluminium in hair were not related to the daily aluminium intake, nor to the cumulative aluminium intake, nor to bone and plasma aluminium levels in a study of dialysis patients and healthy volunteers (152).

4. General toxicology

Aluminium exposure is associated with restrictive as well as obstructive pulmonary disorders. The mechanisms behind these disorders are not clearly elucidated. The restrictive disorders include fibrosis, alveolitis and alveolar proteinosis and these lesions have been associated with exposure to different compounds of aluminium.

Aluminium induces a sequence of pathological events in the primate brain where nerve cell death is the final stage. The metabolic failures that may underlie nerve cell death have not been investigated in detail. Out of several toxic effects of aluminium on the neuronal metabolism the following have been implicated: damage to the cytoskeleton, calcium imbalance, accumulation of cytotoxic metabolites (14, 49).

5. Effects on organs

5.1. Skin

Skin telangiectasias have occurred among workers in a Canadian aluminium-producing plant and have tentatively been related to fluoride or organofluorine exposure (137, 138).

5.2. Respiratory organs

The pulmonary diseases are here classified as restrictive, obstructive and emphysema.

5.2.1. Restrictive pulmonary disease

In the handling of *minerals which contain aluminium*, e.g. bauxite and corundum, exposure to aluminium is accompanied by exposure to silica. This combined exposure may lead to the development of fibrosis of the lung, Shavers disease (59, 120). Musk and coworker (101) examined workers exposed to *artificial aluminium silicate* in Australia. Out of 17 workers, three were suspected of having pulmonary fibrosis. On follow-up only one of these three subjects had deteriorated appreciably and the authors conclude that this type of aluminium silicate does not pose a significant toxic effect on the lungs (102).

Stamped aluminium powder is produced by crushing and grinding hard unmelted aluminium. This aluminium powder is chiefly used in the manufacture of pyrotechnical products, and to a certain degree in the production of some aluminium dyes. Stamped aluminium powder consists of fine particles with 95% of the particles less than 5 µm in size. Despite the relatively small particle size, stamped aluminium powder has rather large surface area because of the flakelike form of the particles. Cases of severe fibrosis of the lung due to exposure to stamped aluminium powder were reported from Germany during the 1930s and 1940s (30, 78, 95) and from Sweden (3, 136) and England (72, 93, 100) during the 1960s. Data on dose and response from the German, Swedish, and British studies are presented in table 2. In contrast to the European experience, cases of fibrosis of the lung have rarely been reported from North America (57). In North America, artificial exposure to *McIntyre powder*, consisting of finely ground aluminium and aluminium oxides, has been used as a prophylactic (29, 52), and in the treatment of silicosis (24). Kennedy in 1956 presented a controlled clinical trial and concluded that the treatment had no effect on the patients with silicosis (76). The British Medical Council (BMC) later concurred with this evaluation and did not recommend the use of aluminium powder in the treatment or prevention of silicosis. Despite the recommendation from BMC aluminium powder was used as a prophylactic agent until 1979 in the mines i northern Ontario, Canada. This prophylaxis may, according to Rifat et al (111), have affected the miners cognitive function.

Table 2. Dose-response relationship for fibrosis of the lung (aluminosis) caused by inhalation of aluminium dust (37).

Type of exposure	Concentration of respirable aluminium dust	Prevalence of fibrosis (number of cases/ number of exposed)	Reference
Grinding dust	0.1-2.7 mg/m^3	0/92	67
Abrasive dust	0.2-45 mg/m^3	9/1000	71
Stamped aluminium powder	0.2-10 mg/m^3	1-(3)*/53	93
Stamped aluminium powder	4-50 mg/m^3	5-8/35	136
Stamped aluminium powder	50-100 mg/m^3	6/27	100

* Chest X-ray examination revealed another two cases with slight roentgenological changes among the 14 most heavily exposed workers. These two workers, however, did not have any symptoms.

Several years later *aluminium lactate* was used as a prophylaxis against silicosis in animal experiments and inhalation of this compound altered the response to quartz in sheep (33).

One case of sarcoidlike lung granulomatosis and helper T-lymphocyte alveolitis has been reported after 8 years inhalation of *aluminium powders* (28).

Grinding and polishing aluminium might be associated with an extremely dusty work environment. One case of pulmonary alveolar proteinosis (98) and one case of pulmonary fibrosis (27) have occurred after long-term performance of such operations. These manifestations are probably rare but the incidence is not known.

Nine workers producing *Al_2O_3 abrasives* presented abnormal chest X-rays. Their mean exposure time was 25 years. In each of three lung biopsies, interstitial fibrosis with honeycombing was seen on routine section with absence of asbestos bodies and silicotic nodulus. The authors conclude that aluminium oxide dust is the most likely cause although mixed dust exposure may explain the findings (71).

Three case reports suggest that pulmonary fibrosis (143), chronic interstitial pneumonia (61), and pulmonary granulomas (19) may occur after long-term exposure to *aluminium-containing welding fumes*. On the other hand no signs of pulmonary fibrosis were found in a cross-sectional study of 64 aluminium-exposed welders in Sweden (129).

A report from Italy (115) indicates that *aluminium production* workers may also suffer from pneumoconiosis. Chest X-ray examination of 119 potroom workers from two plants in northern Italy, and a similarly sized referent group revealed that the exposed workers included more cases with small opacities or accentuations of the bronchopulmonary markings (30%) compared with the referents (15%). Signs of pneumoconiosis were more common among long-term exposed workers compared with short-term exposed. The average exposures to airborne dust in the two plants were 3.4 and 6.5 mg/m^3 respectively.

Slight but obvious signs of pulmonary fibrosis were observed in a man who had worked for 24 years as an operator and 13 years as a foreman in electrolytic aluminium production. His lungs contained 1 mg aluminium per g wet weight which is about 50 times the reference value (48).

A heavy lung burden of fibrous and nonfibrous particles was found in a smelter worker, who had worked for 19 years in the aluminium smelting industry, including 14 years in potrooms. He died 55 years old due to diffuse interstitial fibrosis. This report raises the question whether fibers play a role in aluminium-induced fibrosis (51). Swedish potroom workers have been found to have high concentrations of albumin and fibronectin in their bronchoalveolar lavage reflecting an increased alveolar capillary permeability and an activation of alveolar macrophages. On the other hand the level of hyaluronan, a fibroblast marker, was normal (35). However, the exposure of total particles among these potroom workers was comparatively low 1.8 mg/m^3 (range 0.5-4.5 mg/m^3).

5.2.2. Obstructive pulmonary disease

In a large production plant 1142 male employees were exposed to dust produced in the *mining and refining of bauxite and the production of aluminium-containing chemicals*. In a cross-sectional study a decrease of FEV_1 was observed related to

increasing duration of exposure and cumulative total dust exposure among smokers as well as as nonsmokers (140).

Canadian *potroom workers* comprising 495 individuals spending more than 50% of their working time in the potroom had a greater prevalence of cough and wheeze and also a lower FEV_1 compared with 713 referents from the office and casting departments (18).

In a study comprising seven Norwegian aluminium reduction plants including 1760 *potroom workers*, work-related asthmatic symptoms occurred in 8% of the workers employed for less than five years and 15% of the workers employed for more than 10 years (79). Ten out of 35 *potroom workers* with asthma reported persistant asthma, dyspnea at night and on exertion one year after cessation of exposure (150). It seems as a rule that bronchial hyperreactivity does not disappear when exposure is discontinued (116).

An increased prevalence of bronchial reactivity has been observed among potroom workers exposed to a mean concentration of 1.2 mg gaseous and particulate fluorides per m^3 (26). However, bronchial reactivity could not be observed among nonatopic potroom workers exposed to a mean concentration of gaseous and particulate fluorides of 0.3 mg/m^3 (86).

Abramson and coworkers have in detail reviewed the literature on potroom workers and lung diseases in 1989 (1).

Production of *aluminium fluoride and aluminium sulphate* has been associated with reversible bronchial obstruction or asthma (123). In an aluminium plant producing aluminium fluoride in Sweden 6 cases of asthma occurred in 1975, and 7 in 1976. The number of exposed workers was 35-40. The levels of aluminium fluoride were assessed during these two years and the mean concentration was 3-6 mg/m^3. In 1977, improvements were made thereby reducing the mean levels of aluminium fluoride to 0.4-1.0 mg/m^3. During the years 1978-1982, only two cases of asthma occurred (123).

An average of 37 workers produced aluminium sulphate during 1971-1980. Four subjects had obtained short-lasting asthma, mainly in connection with heavy dust exposure during rinsing or repair work. The average aluminium sulphate dust concentrations varied between 0.2 and 4 mg/m^3 (123).

Potassium aluminiumtetrafluoride, which sometimes is used as a flux for soldering aluminium, may precipitate asthma and bronchial hyperreactivity (64).

5.2.3. Emphysema

An increased number of deaths due to pulmonary emphysema has been observed in two studies of *potroom workers* (97, 112). However none of them had any information on smoking which is a very important causal factor to this disease.

5.3. Gastrointestinal tract

Crohn's disease is an inflammatory disease of the small and large intestine and the etiology of this disease is still unknown. After reviewing the metabolism and toxicity of aluminium, Ganrot (50) has speculated regarding aluminium as one possible etiologic agent to this disease.

5.4. Liver

The liver is one of the organs in which aluminium accumulates during repeated exposure. Rats given high doses of aluminium intravenously developed cholestasis and disturbances of the hepatic microsomal functions, including drug metabolism (32).

5.5. Kidney

Rats were given aluminium chloride, 0.05 and 0.5 mg/kg body weight, intraperitoneally five times weekly for 12 weeks. Loss of concentrating ability as well as increased renal excretion of p-aminohippurate indicative of tubular dysfunction were reported (13). Increased levels of serum creatinine, indicative of a decreased glomerular filtration rate, have been observed in dogs recieving repeated injections of aluminium chloride (60).

5.6. Blood and blood-forming organs

A possible relation between aluminium and microcytic anemia among dialysis patients has been discussed. Treatment with deferoxamine, a chelating agent, sometimes leads to an improvement of the anemia. It has been suggested that aluminium inhibits the synthesis and ferrochelation of hemoglobin, similar to that observed in lead poisoning (32).

5.7. Cardiovascular system

An increased prevalence of ischemic heart disease has been reported in Canadian potroom workers but the search for associations with nine specific contaminants proved inconclusive (139). One aluminium compound, aluminium acetylacetonate, has shown cardiotoxic effects on rabbits (157). Today there is, however, no indication that workers are exposed to this compound.

5.8. Bone

Osteomalacia is the most common aluminium-associated skeletal disorder occurring among dialysis patients but other forms such as the aplastic lesion of renal osteodystrophy have also been observed. Deposits of aluminium are prominent at the junction between surface osteoid seams and adjacent mineralized bone (53). A survey of 1293 patients from eighteen dialysis centres in the UK showed a correlation between the incidence of fracturing dialysis osteodystrophy and the level of aluminium in the dialysate (107).

Also persons without renal failure taking several grams of aluminium per day as antacids over a long period of time may sometimes suffer from osteomalacia. This is attributable to the phosphate imbalance secondary to aluminium intake (68). A marked decrease in the gastrointestinal absorption of phosphorus can be detected after ingestion of a comparably small dose of antacids (132).

5.9. Muscles and joints

An association of joint pain and proximal muscle weakness with the clinical syndromes of dialysis osteomalacia and encephalopathy has long been noted. The arthralgias are predominantly localized in large joints. Proximal myopathy of the upper and lower extremities is generally mild but may be incapacitating in some patients. Joint and muscle pain as well as proximal myopathy often improve after the interruption of aluminium overload or after treatment with deferoxamine (32). Thus aluminium may have a role in these common disabilities among dialysis patients.

5.10. Central nervous system

5.10.1. In patients with renal failure

In 1972 Alfrey and his colleagues report the first outbreak of encephalopathy in a dialysis unit (5, 25). These patients on hemodialysis began to develop a fluctuating to permanent dysfunction of the brain. The main symptoms were speech and language disorders, tremor, myoclonus and epilepsy with paroxysmal EEG activity. Clouding of the sensorium, personality changes, and intellectual deterioration were also observed. Recovery was exceptional. Death often occurred within one year after the first symptoms (14). The condition was related to the presence of aluminium in the dialysis fluids (43) and the concomitant intake of aluminium-containing drugs in order to lower the plasma levels of phosphate. Typical levels of aluminium found in blood or serum usually range from 7 to 30 µmol/l in patients with aluminium induced encephalopathy. One case of dialysis encephalopathy with only a moderately raised plasma aluminium of 3.3 µmol/l improved on deferoxamine treatment (11). In patients with aluminium induced encephalopathy the gray matter of the brain contained approximately 25 µg aluminium per g dry weight which is 20 times higher than the normal level (4).

Nowadays nephrologists are aware of the risks from aluminium accumulation in patients with severe renal failure and try to limit the exposure from drugs and dialysis fluids as much as possible. Dialysis fluid water is thouroghly monitored at most dialysis centers and the aluminium level is kept below 0.4 µmol/l (10 µg/l). Aluminium free phosphate binders such as calcium carbonate are preferably used. Aluminium is nevertheless still of clinical concern as recent data indicate that more subtle signs of aluminium toxicity may develop at lower levels of exposure. 27 long-term hemodialysis patients, with a mean serum concentration of 2.2 µmol/l, were compared with referents matched for age and estimated premorbid IQs of the patients concerning cerebral function. These hemodialysis patients had longer response time in a symbol digit coding test. They also displayed abnormalities in five other computerised tests of psychomotor function indicative of a subclinical aluminium intoxication (6).

5.10.2. In workers occupationally exposed

In 1921 Spofforth (133) described a man with loss of memory, tremor, jerking movements and impaired coordination, which the author related to occupational aluminium exposure. The man had been dipping red-hot metal articles, contained in an aluminium holder, into concentrated nitric acid. According to our experience,

this exposure regarding aluminium must be low. Urinary aluminium excretion data are given in the report, but they are most probably erroneously high. Thus, one cannot rely on this old case report.

One case report suggests a causal relationship between occupational aluminium exposure and encephalopathy. A heavy aluminium exposed worker in a ball-mill room of an *aluminium powder* factory developed a rapidly progressive encephalopathy and pulmonary fibrosis (93). The lungs and the brain of this man was reported to contain about 20 times the amount of aluminium found in occupationally non-exposed persons. It is noteworthy that this case of encephalopathy was reported before the recognition of aluminium-induced encephalopathy in dialysis patients.

Longstreth and coworkers 1985 (91), reported three men, who had worked in the same *potroom* for 12 years and developed incoordination and intention tremor. Two of the men also had cognitive deficits. The aluminium exposure was considered to be relatively low, as bone assays contained normal levels of aluminium.

Welders exposed to *aluminium-containing welding fume* for more than 13 years had an increased prevalence of symptoms from the nervous system when compared with welders exposed to iron-containing fume (126).

Between 1944 and 1979 *McIntyre powder*, consisting of finely ground aluminium and aluminium oxides, was used as a prophylactic agent against silicotic disease in mines in northern Ontario. The miners inhaled the particles for 10 minutes before each underground shift. 261 aluminium-exposed miners were compared with 346 unexposed miners. Three cognitive state tests were performed. Impaired cognitive function, was observed in 4% of the unexposed,10% of the miners with 0.5-9.9 years of exposure, 15% of the miners with 10-19.9 years of exposure and 20% of miners with longer exposure than 20 years (111). The study thus revealed a clear dose-response relationship and the estimated annual alveolar burden of aluminium was approximately 375 mg. No relationship was observed concerning reported diagnoses of neurological disorder (111).

Foundry workers exposed to aluminium for more than 6 years were compared with a referent group of non-exposed workers comparable regarding age, job seniority and social status. Slower psychomotor reaction and dissociation of oculomotor coordination were found in the exposed workers (66). However, the presented levels of aluminium in blood among the referents do not agree with previous results.

5.10.3. Alzheimer's disease

Alzheimer's disease or senile dementia of Alzheimer type consists of deterioration of mental functions involving memory, judgement, abstract thinking as well as changes in personality and behaviour. Morphologically, Alzheimer's disease is a neurodegenerative disease characterised by neurofibrillary degeneration, senile plaques, and deposition of amyloid substance. Aluminium has been detected in association with senile plaques and amyloid (23).

Progressive dementia occurred in a male patient who had worked as an *aluminium refiner* for 30 years. He died due to bronchopneumonia and neuropathological examination revealed characteristic features of Alzheimer's disease with marked atrophy of the occipito-temporal lobes and senile plaques of

the cerebellum. Wavelength-dispersive X-ray microanalysis disclosed focal aluminium accumulation within the nucleus and cytoplasm of the tangle-bearing neurons (77).

An association between aluminium in drinking water and Alzheimer's disease has been reported from Norway, UK, France and Canada. The French and Canadian studies are still only available in abstracts.

Flaten (41, 42) studied the incidence of dementia and content of aluminium in drinking water in Norway. The registration of senile and presenile dementia was based on death certificates. There was a correlation between the content of aluminium in drinking water and the incidence of dementia among males as well as females.

Likewise the incidence of Alzheimer's disease was investigated from the records of computerized tomographic scanning units that served 88 county districts in England. The risk of Alzheimer's disease was 1.5 times higher in districts where the mean aluminium concentration in drinking water exceeded 4.1 µmol/l than in districts where concentrations were less than 0.4 µmol/l (92).

In south-west of France 40 probable cases of Alzheimer dementia were found in a sample of 2792 subjects above 65 years of age. The relative risk of having the disease was 4.5 when the drinking water contained 3.7 µmol aluminium per liter or above (96).

In the Province of Ontario 2344 patients with Alzheimer's disease or presenile dementia aged 55 or over were obtained as cases and 2232 patients with non-psychatric diagnoses were referents. The risk of having Alzheimer's disease was 1.5 times higher when the drinking water contained more than 7.4 µmol aluminium per l compared with a water content of 0.4 µmol/l (103).

There are many uncertainties in these epidemiological studies; the diagnosis of Alzheimer's disease is nonspecific and the diagnostic criteria are likely to differ between geographical areas. Exposure to aluminium takes place via the oral route and the content in drinking water is a very crude estimate of peroral exposure as it contains only a small fraction of ingested aluminium. An intake of one liter drinking water a day containing 3.7 µmol aluminium per l corresponds to 1.5 mmol (40 mg) per year and 60 mmol (1.6 g) in a 40 year period. This dose spread over 40 years is approximately the same as one recommended daily dose of an antacid. Thus it seems quite impossible that this intake of aluminium-containing water per se could explain an increased risk of developing Alzheimer's disease. However, it might be possible that the drinking water contains specific today unknown complexes of aluminium which are easily absorbed from the gut.

In case-referent studies of Alzheimer's disease no relation was found between the disease and intake of antacids (7, 12) or aluminium-containing antacids (10, 63). One study reports a relationship between Alzheimer's disease and the use of aluminium-containing antiperspirants (10). The study do not differ between different forms of application, by aerosol or by a direct dermal solution. It should perhaps be emphazised that surrogate responders are used as a rule as the cases suffer from a severe memory impairment.

Epidemiological studies published sofar are far from convincing concerning the possible relationship between aluminium exposure and the development of Alzheimer's disease.

5.10.4. Amyotrophic lateral sclerosis and myelopathy

The term amyotrophic lateral sclerosis (ALS) is generally used to indicate a syndrome characterized by a degeneration of both the upper motor neurons in the cerebral cortex and of the lower in the medulla and spinal cord. The symptoms of ALS are progressive muscle weakness and paralysis. Several metals have been suspected as causes behind the development of ALS. However, the reasons for connecting aluminium exposure to ALS are today vague (49).

A myelopathy can be induced in rabbits by the intracisternal inoculation of aluminium chloride (100 μg) at monthly intervals for up to eight months (135).

5.11. Peripheral nervous system

Sixtyfour patients on hemodialysis were investigated concerning nerve conduction velocity. Their mean conduction velocity was 42 m/s, being lower than average but not in the pathological range. In four patients denervation potential was found, whereas suspected denervation was present in 22 patients. However, there was no correlation between serum aluminium levels and any of these parameters (85).

In an experiment rabbits received aluminium chloride intramedullary into three intervertebral spaces in the lumbar region. This treatment results in a characteristic neurological syndrome where the affected rabbits show extensive neurofilamentous lesions of both large and small neurons in the lumbar spinal cord. The choline acetyltransferase activity was measured in the sciatic nerve and was found to be decreased by 39% among the treated animals (80).

6. Immunotoxicity and allergy

Contact allergy to aluminium is rare (15). Sensitization occurs sometimes after repeated application of aluminium chloride hexahydrate in antiperspirants (40), medical application of aluminium acetotartrate (94), or from aluminium adjuvants in vaccines and pollen extracts (21). The two types of reactions observed are persistant granuloma at the injection site (45) and recurrent eczema (15).

Accumulated aluminium in dialysis patients has been suggested having an immunosuppressive effect as a smaller proportion of patients with a high level of aluminium in their bones rejects kidney allografts compared with a higher proportion among patients with lower levels (105).

7. Mutagenicity and genotoxicity

7.1. Mutagenicity

Filter extracts of airborne particles from a Söderberg potroom and an anode paste plant were mutagenic mainly after metabolic activation by the Salmonella reversion assay (83). Sputa from workers employed in an electrolytic aluminium production plant of Söderberg-type were mutagenic contrasting sputa from smoking and nonsmoking referents (84). These mutagenic activities are most probably explained by concomitant exposure to polyaromatic hydrocarbons.

Aluminium compounds have been evaluated as non-mutagenic by most standard methods of mutagenic assay using bacteria and mammalian cells in vitro (82, 88).

7.2. Genotoxicity

Workers employed in an electrolytic aluminium production plant and consequently exposed to polyaromatic hydrocarbons had a similar rate of overall chromosome aberrations when compared with non-exposed referents (62). However, these workers were hardly exposed to aluminium as they manufactured pre-baked carbon anode blocks.

8. Carcinogenicity

SPF Wistar rats were inoculated intrapleurally with several materials including asbestos (147). One case of mesothelioma was observed among 35 animals treated with non-fibrous aluminium oxide particles having less than 10 μm projected area diameter. O'Gara and Brown (106) induced sarcomas in 8 of 18 NIH Black rats by subcutaneously implanting aluminium foil, about 0.05 mm thick, wheras alumina fibers with a median diameter of 3.5 μm administered intrapleurally or intraperitoneally to rats had no effects (109, 134). This supports the hypothesis that the dimension of the implants rather than their chemical composition is related to carcinogenicity (9, 82). As reviewed by Léonard (87), most animal studies have failed to demonstrate carcinogenicity attributable to Al metal powder, $Al(OH)_3$, Al_2O_3, or $AlPO_4$ administered by various routes to rats, rabbits, mice, and guinea pigs (46, 47, 121). On the other hand there are even some results indicating aluminium nitrate to inhibit growth of transplanted carcinoma in rats (2).

In 1984 the International Agency for Research on Cancer (IARC) reviewed surveys of exposure and toxicological and epidemiological studies regarding electrolytic production of aluminium (69) and in 1987 IARC concluded that there is sufficient evidence that certain exposures occurring during aluminium production cause cancer, e.g. cancer of the lung and bladder. Pitch volatiles have fairly consistently been suggested in epidemiological studies as being possible causative agents (70).

Synthetic abrasive materials containing aluminium oxide, silicon carbide, and different additives have been used for more than 50 years (149). Exposure to aluminium may occur during production of these materials and when they are used for metal grinding or polishing. An increased risk for stomach cancer has been observed in two studies (73, 149) and an increased risk for lungcancer has been observed in one (122). This inconsistent pattern of cancer (34, 73, 122, 149) might be explained by varying degrees of exposure or confounding exposures e.g. hard metal dusts. Accordingly further studies are needed to explore the relationship between aluminium oxide and cancer.

In summary there is evidence that workers engaged in primary aluminium production run an increased risk of developing cancer. This effect is probably the result of exposure to a variety of polyaromatic hydrocarbons released during the electrolytic process and not to aluminium itself.

9. Reproduction and teratogenicity

Intravenous administration of 5 µmol (135 µg) aluminium as $AlCl_3 \cdot 6H_2O$ to dams caused an increased frequency of fetal internal hemorrhage in mice (151). In another experiment pregnant mice were given aluminium lactate (25, 500 or 1000 µg Al/g diet) during gestation and lactation. The exposure did not produce maternal toxicity but the offsprings were affected in forelimb and hindlimb strengths and thermal sensitivity, tested by dipping the tail in warm water (31).

Pregnant rabbits received 20 subcutaneous aluminium lactate injections (0, 25, 100, or 400 µmol Al/kg/injection) between days 2 and 27 of gestation.The highest dose resulted in a perinatal mortality of 58% compared with 7% among referents. Learning a classical conditioned reflex in the offspring was facilitated by lower and impaired by higher aluminium exposure. Offspring receiving higher exposure also showed impaired memory of the learned reflex (155).

10. Relation between exposure, effect and response

Dose-response relationships have been established for some settings of exposure, table 3 a, b, and c. The dialysis encephalopathy described in table 3 a is a very serious disease, 90% of the patients die within 12 months from the onset of nervous symptoms if treatment is not given. It should be recognized that the dialysis patients received aluminium parenterally, via the dialysate, and that they had a severly impaired elimination due to their renal disease. The discrepancies observed when comparing the study of miners and welders might be explained by too rough dose estimates, differencies concerning pulmonary absorption, distribution, and target-dose and different outcome estimates.

Exposure to stamped aluminium powder has led to aluminosis after long-term exposure. The exposure leading to this pneumoconiosis has been above 5 mg/m^3, table 2.

Potroom asthma is a well-known disease among workers in the aluminium electrolytic production industry. Exposure to several salts of aluminium is associated with asthma. Exposure to aluminium fluoride within the range 0.4-1.0 mg/m^3 and exposure to aluminium sulphate within the range 0.2-4.0 mg/m^3 has generated some cases of asthma (123). Exposure to potassium aluminiumtetrafluoride, another aluminium-based salt, around 1 mg/m^3 has provoked asthma or bronchial hyperreactivity in five out of seven exposed workers (65).

Table 3a. Cumulative aluminium exposure from dialysate and attack rate (cumulative incidence) of dialysis encephalopathy (119).

Dose (g)	Cumulative incidence (%)
0	0.7
0.01-4.0	0.5
4.01-8.0	10.3
8.01-12.0	17.5
>12.0	18.6

Table 3b. Aluminium-containing welding fume exposure and prevalence of symptoms from the nervous system (126), assuming a pulmonary ventilation of 20 l/min, a median aluminium exposure of 4 mg/m^3 (127, 129) and an alveolar deposition of 30% (16). The mean prevalence of symptoms among the non-exposed was 2.6.

Alveolar dose (g)	Odds ratio (95% confidence limits)
0.3-11.3	1.0 (0.4-2.7)
11.3-29.5	2.4 (1.0-5.7)
>29.5	2.8 (1.1-7.2)

Table 3c. Aluminium exposure and cognitive function among miners exposed to aluminium powder and a calculated annual alveolar burden of 375 mg (111). The air exposure was 30 mg/m^3 during 10 minutes per day (Muir personal communication) corresponding to an 8-hour TWA of 0.6 mg/m^3.

Alveolar dose (g)	Prevalence with impaired cognitive function (%)
0	4
0.2-3.7	10
3.8-7.5	15
>7.5	20

11. Research needs

More knowledge is needed about the dose-response relationships, particularly as regards early effects on the central nervous system in populations exposed to levels relevant for the occupational environment. The effects of exposure to different forms of aluminium particles should also be clarified. The possible relationship between aluminium exposure and Alzheimer's disease remains to be elucidated.

Future studies should clarify the absorption, distribution and excretion of aluminium and its complexes.

There is also a lack of knowledge of the effects of aluminium on the human fetus.

12. Discussion and evaluation

The critical organ regarding aluminium exposure in general is the central nervous system. However, some aluminium compounds e.g. aluminium fluoride, aluminium sulphate and potassium aluminiumtetrafluoride can provoke asthma and this effect might occur at lower levels of aluminium exposure.

The relationship between aluminium exposure and dialysis encephalopathy is well established (25). A significant systemic exposure to this metal has been observed among aluminium exposed welders and flake powder producers (90, 125). Symptoms from the nervous system have been reported from welders (126) and impaired cognitive function from miners exposed to finely ground aluminium powder (111).

Abnormalities of psychomotor function have been observed among hemodialysis patients with mean serum concentrations of 2.2 µmol aluminium per l (6). This serum level (2.2 µmol/l) corresponds to a urine level of approximately 12.4 µmol/l in persons not having kidney failure. This postshift urine level corresponds to an air level of 1.7 mg/m^3 in a welder who had been exposed for 40 years when using the formula: U-Al (µmol/l) = 1.5 x air-Al (mg/m^3) + 0.25 x exposed years - 0.17 (124, 125), table 4.

Table 4. Calculations of air levels of exposure to aluminium-containing welding fume in relation to duration of exposure (10, 20, 30, and 40 years) based on two studies of effects of the nervous system.

	Air levels of exposure (mg/m^3) at different duration of exposure (years)			
	10	20	30	40 years
Increased number of nervous symptoms among welders (126)	4.5	2.9	1.3	-
Disturbed psychomotor function in dialysis patients (6)	6.5	4.9	3.3	1.7

An increased number of symptoms from the nervous system has been observed after approximately 13 years of aluminium welding fume exposure (126). Based on the presented equation and an air concentration of 4 mg aluminium per m^3, the median exposure for MIG-welders in 1975 (127, 129), the urine concentration was calculated to be 9.2 µmol/l in these welders.

The extrapolations made from these two studies are conservative in relation to the dose-response relationship reported from the Canadian miners (111). An 8-hour TWA exposure to aluminium particles of 0.6 mg/m^3 for 10 years resulted in a doubling of the prevalence of impaired cognitive function. Thus, these proposed tentative dose-response relationships between aluminium exposure and effects on the central nervous system are somewhat divergent. Therfore these relationships have to be confirmed by further studies.

To prevent aluminosis after long-term exposure to stamped aluminium powder air levels should be below 5 mg/m^3.

Asthma and bronchial hyperreactivity may occur already at exposure to aluminium salts in air at concentrations below 1 mg/m^3.

13. Summary

Bengt Sjögren and Carl-Gustaf Elinder. Aluminium 105. The Nordic Expert Group for Documentation of Occupational Exposure Limits. Arbete och Hälsa 1993:1, pp 55-84.

The document constitutes a survey of the literature on aluminium and its compounds to be used as a background for discussion on occupational exposure limit values. The central nervous system is the critical organ after long-term exposure to aluminium. Higher exposure can cause a pneumoconiosis, aluminosis. Exposure to aluminium fluoride, aluminium sulphate, and potassium aluminiumtetrafluoride is associated with asthma.

In English, 157 references.

Key words: Aluminosis, aluminium, aluminium compounds, asthma, nervous system, occupational exposure limit.

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Appendix 1

List of permitted or recommended maximum concentrations of aluminium metal and aluminium oxide in air

Country	mg/m3	ppm	Comments	Year	Ref.
Denmark		-		1988	1
powder & dust	10	-			
fume	5	-			
Finland				1987	2
inorganic dust	10	-			
Iceland				1989	3
total dust	10	-			
respirable dust	5	-			
The Netherlands	10	-	MAC-TGG	1989	4
Norway				1989	5
Al-oxide	10	-			
powder	5	-			
welding fumes	5	-			
Sweden		-			6
total dust	10	-	NGV		
respirable dust	4	-	NGV		
USA (ACGIH)				1991-92	7
dust	10	-			
welding fumes	5	-			
pyro powder	5	-			
USA (NIOSH)				1989	8
total dust	10	-			
respirable dust	5	-			
pyro powder	5	-			
welding fumes	5	-			

MAC-TGG = maximum concentration values in workplace - time weighted average
NGV = threshold limit value

List of permitted or recommended maximum concentrations of soluble Al-compound

Country	mg/m3	ppm	Comments	Year	Ref.
Denmark	2	-	incl alkyles	1988	1
Finland	2	-		1987	2
Iceland	2	-		1989	3
	5	-	"pot room dust"		
The Netherlands	2	-	MAC-TGG	1989	4
Norway	2	-	incl alkyles	1989	5
Sweden	2	-	NGV	1990	6
USA (ACGIH)	2	-	incl alkyles	1991-92	7
USA (NIOSH)	2	-	incl alkyles	1989	8

MAC-TGG = maximum concentration values in workplace - time weighted average
NGV = threshold limit value

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Cadmium

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Contents

Introduction

This document is based on the scientific literature published before January, 1991. Of particular importance for the assessments in this document are earlier versions of Swedish/Nordic criteria documents (34, 95) and the surveys and assessments in the comprehensive toxicological and epidemiological summaries made by Friberg et al in 1985/86, by IPCS in 1992, and by Nordberg et al in 1992. Only a few important original references are given in this document: the reader is referred to the above-mentioned surveys for a fuller list of works published before 1989.

A draft of this document was sent for review and comment to a number of Swedish medical experts in cadmium research: C. G. Elinder, L. Friberg, T. Kjellström, M. Nordberg and M. Piscator. Their suggestions for improving the text were incorporated as much as possible in the present version, in accordance with discussions in a working meeting of the Nordic Expert Group.

1. Physical and chemical data

Cadmium (Cd)	
Atomic weight:	112.4
Atomic number:	48
Density:	8.6
Melting point:	320.9 °C
Boiling point:	765 °C
Valence:	+ 2

Cadmium acetate, cadmium chloride and cadmium sulfate are soluble in water, while cadmium oxide and cadmium sulfide are virtually insoluble.

Salts of organic acids, such as cadmium stearate, have relatively low solubility. Organometallic cadmium compounds have been synthesized, but they break down rapidly and have not been found either in the environment or in organisms.

Conversion factors

1 µg/l = 0.89 µmol/l = 890 nmol/l

1 µmol/l = 112 µg/l

1 µg/g creatinine = 1 nmol/mmol creatinine

1 mmol/kg = 112 mg/kg

2. Occurrence, use

2.1. Uses

The use of cadmium in Swedish industry has declined considerably in the past decade due to the "cadmium ban" (Section 45 in the ordinance on hazardous substances, SFS 1979:771, which entered into force on July 1, 1982 in accordance with SFS 1980:84, with certain exceptions as set forth in SNFS 1981: Section 5, Chapter 13), which specifies that cadmium may not be used as a pigment, in surface coatings, or as a stabilizer. One of the major remaining areas of cadmium use in Sweden is in the manufacture of alkaline accumulators, where large groups of workers may be exposed. Cadmium exposure can also occur in some jobs that do not primarily involve the handling of cadmium. It can occur for example in the use and processing of zinc, since zinc may contain small amounts of cadmium as an impurity. Cadmium exposure can also occur during the handling or smelting of metals from ores. It can also occur during welding of metals containing cadmium, or when alloys containing cadmium are being produced, and during soldering with cadmium-containing solders such as silver solder, but the use of this substance has also declined considerably in Sweden over the past years.

One exposure that is relatively difficult to quantify, and that may have increased, is exposure to cadmium during the handling and recycling of scrap metals containing cadmium.

2.2. Air concentrations in the work environment

Soldering or welding of materials containing cadmium can result in extremely high exposures, sometimes high enough to cause fatal poisoning. Exposure levels in the cadmium industry were extremely high during the 1940s and 1950s, with air concentrations ranging from 1000 to 10,000 µg/m^3. During the 1950s the levels declined to about 200 µg/m^3, and then further to about 50 µg/m^3 during the 1960s.

In the cadmium industry in Sweden, air concentrations in the breathing zone were generally in the range of 5 to 10 µg/m^3 during the latter half of the 1970s and throughout the 1980s (2), though there were a few instances of higher concentrations.

2.3. Methods for analysis of air concentrations

Air concentrations of cadmium can be determined with either stationary monitoring equipment or personal monitors. As with other air monitoring in the work environment, the personal monitors provide a better idea of individual exposures, while the stationary monitors provide information on emission sources (71).

In determining cadmium in workplace air it is important to be able to discriminate between different particle sizes, since occupational exposure limits are different for respirable dust and total dust. A pre-filter is therefore generally used to collect the coarser dust; the cadmium particles collected on the filter thus provide a measure of respirable dust when the filter is analyzed. With a flow of 2 liters per minute, enough dust for analysis by atomic absorption spectrophotometry can usually be collected within 4 hours. Atomic absorption spectrometry is performed after the filter is dissolved (2, 71).

3. Kinetics

3.1. Uptake

Skin uptake of cadmium from dry dust and similar sources is negligible unless the skin has been damaged. Application of a cadmium salt solution to the skin of experimental animals results in uptake of only a couple of percent after several hours.

Occupational exposure to cadmium is primarily via inhalation. Uptake from aerosols of cadmium-containing particles is dependent on the particle size and on the solubility of the particles in vivo. Available literature on this and other aspects of cadmium uptake via different exposure routes is summarized in References 84 and 85. With low breathing volume and mouth closed, uptake via respiratory passages ranges from 0.1 to 35% of the inhaled amount. Total uptake, including also particles that are swallowed, ranges from 5.1 to 37%. The higher figures apply to smaller particles (about 2 µm), while the lower figures apply to larger particles (10 µm). Uptake also varies to some extent with the solubility of the

cadmium compound. Less soluble compounds, such as cadmium sulfide, are absorbed to a lesser extent than more soluble ones (89).

Uptake of cadmium via the digestive tract is usually about 5%, but can be up to 20% or so in persons with iron deficiencies. Under normal conditions, uptake via skin is negligible. There is some cadmium in tobacco, about 1 to 2 µg per cigarette. About 10% of this cadmium is inhaled during smoking, and a portion of it is taken up in the body. Smokers therefore have considerably higher cadmium uptake than non-smokers, even when cigarettes or pipe tobacco are not contaminated by cadmium from the work environment. For non-smokers who are not industrially exposed, most cadmium uptake is via food (in Sweden, usually about 5% of about 13 µg per day). In a work environment where cadmium occurs, it is important for smokers to see that cigarettes and pipe tobacco are stored so that they are not contaminated by cadmium. If the tobacco is contaminated, by dirty fingers for example, cadmium exposure can increase considerably (96).

3.2. Distribution

The toxic effects of long-term industrial exposure to cadmium appear in several organs. The transport of cadmium from the lungs and other absorption sites to these target organs is therefore of decisive importance.

After uptake, cadmium is initially bound to albumin and other high molecular weight proteins in plasma. This form of cadmium is rapidly taken up by the liver, where the cadmium is liberated from the albumin and induces synthesis of metallothionein, a low molecular weight protein that binds cadmium quite effectively. Only a few days after a single exposure, or during prolonged exposure, most of the cadmium in the liver is bound to metallothionein. A small portion of the metallothionein-bound cadmium in the liver re-enters the blood. Cadmium metallothionein in blood plasma is very effectively filtered through the glomeruli in the kidneys, largely due to its low molecular weight. It is thereafter efficiently taken up in the proximal portion of the kidney tubuli, where it gradually accumulates. In the kidneys there is an intracellular breakdown of cadmium metallothionein in the renal lysosomes. This liberates cadmium from metallothionein, and the liberated cadmium in turn induces local synthesis of metallothionein in the kidneys. Most of the cadmium reaching the kidneys is thus sooner or later bound to metallothionein. This bound cadmium is regarded as relatively inactive from a toxicological point of view; tissue damage, in kidney and liver as well as other organs, is assumed to be primarily due to the interaction between cadmium that is not bound to metallothionein and various tissue components such as membrane proteins. This is shown schematically in Figure 1.

Cadmium in the blood of occupationally exposed persons is mostly bound to the blood cells. When the halving time for cadmium in whole blood was studied in workers who interrupted their cadmium exposure, it was found that there were two components, one with a halving time of 75 to 130 days (probably reflecting the life span of the blood cells) and the other with a halving time of 7 to 16 years, which reflects cadmium accumulation in the body (52).

Depending on the route of uptake, some of the cadmium entering the body will initially be bound to tissues in lungs or digestive tract. After uptake, cadmium is

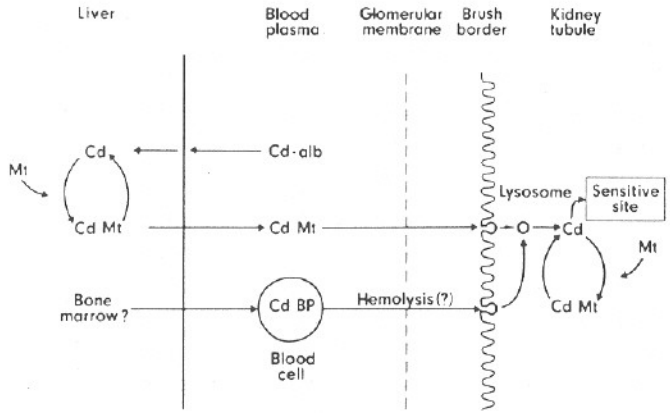

Figure 1. A schematic diagram of the transport and binding of cadmium in blood and tissues and the path by which cadmium reaches critical target structures in kidney tissue.

transported in the blood to various organs, at first mostly to the liver but also to the pancreas and some other organs. The cadmium is then gradually distributed further to kidneys and other tissues such as muscle. The distribution pattern is thus largely dependent on the time elapsed since uptake, or the duration of long-term exposure. In man, a long time after a single exposure or after exposure lasting several decades, most of the cadmium will be in the kidneys. A similar pattern is seen in experimental animals. The cadmium concentration is highest in renal cortex. As mentioned previously, cadmium in tissues is largely bound to a low molecular weight protein, identified in some tissues as metallothionein. In certain other organs, such as prostate and testes, cadmium is probably bound to both metallothionein and another low molecular weight protein. In testes, cadmium accumulates primarily in interstitial tissues.

Only limited amounts of cadmium pass through the placentas of experimental animals, but cadmium can be passed to the embryo before the placenta is developed. In rats, the proportion of injected cadmium transferred to the fetus depends on both the administered dose and the gestational age at which the dose is administered (108). In humans, there are somewhat lower cadmium concentrations in blood from the umbilical cord (from the baby) than in the mother's blood. In experimental animals, the cadmium content of the placenta is generally much higher than that of the young. For humans as well, the concentrations reported for placental tissue are somewhat higher than those found

in blood from the umbilical cord (see also the review in Reference 17 and the discussion in Section 9.2.).

After prolonged exposure to cadmium -- both industrial exposure and normal uptake from the general environment -- the highest concentration of cadmium is generally found in renal cortex. Concentrations in liver and pancreas are also relatively high, while those in other organs are lower.

In members of the general population, cadmium gradually accumulates with age up to about age 50, when concentrations in kidney tissue are at a maximum. The cadmium content then slowly declines as people get older.

3.3. Biotransformation

Properly speaking, there is no biotransformation of cadmium. However, as pointed out above, the binding of cadmium to metallothionein is of fundamental importance.

3.4. Excretion

Cadmium is excreted from the body very slowly, and as mentioned above, it gradually accumulates with age. Only 0.01 to 0.02% of the body burden is excreted per day in urine or feces. In man, excretion in urine is proportional to body burden and age up to the age of 50. Individual variations are considerable, however.

It is difficult to measure cadmium excretion in human feces, since most of the cadmium entering the mouth, as well as cadmium entering the digestive tract after mucociliary transport from the lungs, passes through the digestive tract without being absorbed (gastrointestinal absorption is about 5%). The cadmium content of feces can, however, be used as an indicator of both cadmium intake in food and cadmium cleared from the lungs. Fecal excretion of absorbed cadmium is probably dependent on both dose and body burden (83).

Metabolic model

A metabolic model has been developed which describes human uptake, distribution and excretion of cadmium in mathematical terms (64). The model describes the flow of cadmium between eight different tissues and gives the portions excreted in urine and feces. It can thus describe how cadmium is accumulated in these tissues and how tissue concentrations are related to uptake and excretion. Accumulation in renal cortex, which is the critical tissue, is of particular interest. With prolonged exposure (several decades), the cadmium in kidneys accounts for a third to a half of the body burden. The cadmium concentration in renal cortex is 1.25 times that in whole kidney. This model has been used to estimate cadmium accumulation in kidney tissue and the consequent medical risks (60).

In addition to the detailed metabolic model described above, simpler models have also been used --including one-compartment models. These simpler models can be valuable under specific conditions and for proscribed purposes. A one-compartment model that describes cadmium accumulation in renal tissue during

extremely long exposures (several decades) has been used for calculating concentrations in kidney tissue (47) and the associated risk of kidney damage.

3.5. Biological exposure indicators

A detailed review of the use of biological exposure indicators was made by Nordberg and Nordberg in 1988 (84). A summary in Swedish was published by Elinder et al in 1991 (25). Routine exposure monitoring is presently based on determination of cadmium concentrations in blood and urine samples. As mentioned above, cadmium in the blood of occupationally exposed workers is primarily bound to erythrocytes. Cadmium in plasma should be an interesting material for biological monitoring, but since concentrations are extremely low analytical problems have so far made it impractical to use this material. Since metalliothionine-bound cadmium in plasma is the main form of transport to the kidneys it would be interesting to be able to study this parameter (81, 84), but there are still no routine methods for doing so.

Non-invasive methods have been developed that allow determination of cadmium in various organs by in vivo neutron activation (28, 29, 73). These methods allow direct determination of cadmium content in the critical organ (kidney), and provide quite accurate information that can be related to the risk for cadmium-induced kidney damage. The methods are extremely complicated, however, and mobile equipment for use in the workplace is still not routinely available in Sweden.

Primarily because of analytical considerations, cadmium in blood has come to be the measure routinely used as a biological indicator of occupational exposure.The concentration of cadmium in whole blood from non-smokers who are not occupationally exposed to cadmium is generally between 0.2 and 1 µg/l; concentrations are higher for smokers, although still usually below 4 µg/l. As explained in Section 3.2, the halving time is short for a large proportion of the cadmium in blood, which reflects primarily current exposure. In Sweden there are regulations governing the use of blood samples to control exposures; see Appendix 1.

The Swedish regulations give detailed instructions on the interpretation of specified measured blood concentrations (see Appendix 1). In general, whole-blood cadmium values should be interpreted with consideration to the fact (Section 3.2) that cadmium in blood reflects two different "compartments," one with a halving time of 75 to 130 days and another with a halving time of 7 to 16 years. During chronic exposure the blood cadmium level reflects primarily the exposure level, while values found several months or years after termination of exposure reflect tissue deposits of cadmium.

Urine samples can also be used for biological monitoring of cadmium-exposed workers. There are a few problems involved with determination of cadmium in urine, but with modern atomic absorption equipment it can be done routinely even in the low-dose range. Another advantage is that early indicators of kidney damage (β_2-microglobulin, retinol-binding protein and metallothionein) can be monitored in the same sample. The cadmium content in urine increases if there is damage to kidney tubules. In a group of persons with the same cadmium

concentration in kidneys, those with kidney damage will excrete more cadmium in urine than the others.

With cadmium levels in the body that are below those that cause kidney damage, cadmium content in urine is correlated to the body burden of cadmium. However, there is considerable inter-individual variation in the relationship between cadmium in kidney tissue and cadmium in urine. One important factor is the dilution of the urine. This factor can be largely cancelled out by calculating cadmium excretion in relation to creatinine excretion. Another possibility is to take a urine sample that reflects a specific period, such as 24 hours. Cadmium concentrations in the urine of non-smokers who are not occupationally exposed to cadmium are usually below 1 µg/g creatinine. The cadmium concentration generally associated with risk of manifest kidney damage was earlier assumed to be 10 µg/g creatinine, but in order to protect a large majority of exposed workers from sub-clinical forms of kidney damage as well, this limit should be reduced to 5 µg/g creatinine (see also the discussion in Section 12). Data from Belgium (13) have indicated slight effects even at somewhat lower levels in a small proportion of people exposed in the general environment (see Section 5.4).

Cadmium content in hair has also been proposed as a possible subject of biological monitoring. Very little cadmium is incorporated into hair by the hair follicle, however, and concentrations are extremely low. They may be higher in cases of occupational exposure, but are then due to contamination from external sources. Hair concentrations may be used as a rough indicator of exposure, but analysis of blood samples is better; there is therefore no reason to use hair samples except in cases where only oral intake occurs and there is no risk that the hair has been contaminated from external sources.

Cadmium determination in placenta can also be used in special cases, when pregnant women are exposed. Concentrations in placenta probably reflect exposure conditions during pregnancy better than cadmium in a single blood sample, and can be useful in indicating whether there is a risk that the baby might be harmed by cadmium.

4. General toxicology

4.1. In vitro studies

The important role of metallothionein binding in the toxicology of cadmium was mentioned earlier (see Figure 1). Cadmium has been shown to induce metallothionein in several different kinds of tissues and cell types both in vivo and in vitro. Cadmium can inhibit a number of different enzyme systems in vitro and in vivo, and has recently been shown to cause damage to the cytoskeleton of cells (15). Cadmium can also induce transcription of certain oncogenes in vitro (49). This can be relevant to its carcinogenic effects (see Section 8).

A disturbance of the cell's calcium balance can help to explain several of the effects of cadmium, such as those on kidneys (50). The toxicology of cadmium is interesting, and differs from that of many other substances in that the effects of acute exposure are unlike those of chronic exposure. This discrepancy is

explained largely by the fact that metallothionein synthesis is constantly stimulated during long-term exposures, protecting the body from many of the acute effects.

4.2. Factors affecting toxicity

As mentioned previously, metallothionein induction is an important factor in determining the effects that occur and the tissue cadmium concentrations at which they occur. Other factors that affect toxicity are intake of other substances, such as zinc, which can also induce metallothionein and probably also compete with cadmium in relation to certain zinc-dependent enzymes, etc. The iron balance in the body has a pronounced effect on cadmium uptake, and is thus a major factor in the toxicity of oral intake. Intake of calcium and vitamin D are of central importance to effects on the skeleton and on mineral metabolism (83, 85).

4.3. General observations

Cadmium is a relatively toxic substance, particularly with inhalation. The air concentration given as the LD_{50} for rats, for example, is 500 minutes · mg/m^3 (e.g. 20 mg/m^3 for 25 minutes). The oral LD_{50} for rats is on the order of 50 to 400 mg/kg body weight for soluble compounds such as cadmium acetate, cadmium chloride or cadmium sulfate, while for insoluble compounds such as cadmium selenide and cadmium sulfide the LD_{50} exceeds 5 g/kg body weight.

Regarding exposure to cadmium in food or drinking water, concentrations exceeding 10 mg/liter in water or 10 mg/kg in food result in reduced growth in rats. The effect can be more pronounced with simultaneous calcium deficiency, and is also influenced by factors such as the amounts of zinc, copper or iron in food.

5. Effects on organs

5.1. Effects on skin and mucous membranes

A yellow discoloration of the gums and the teeth along the gumline was formerly common with cadmium exposure. It was probably due to high exposure to cadmium, on the order of hundreds of micrograms per cubic meter, in combination with poor dental hygiene. The condition is now extremely rare in Nordic countries.

5.2 Effects on respiratory organs

Welding or soldering with materials containing cadmium creates cadmium fumes, which can cause severe lung damage. Serious symptoms do not appear until several hours after exposures that at the time are only slightly irritating. Fatal cases of poisoning have occurred in such situations. Cases of this nature have not been reported in Sweden for several years, but still occur in other countries (129).

The initial symptoms resemble those of metal fume fever, but are followed by lung edema or chemical pneumonitis which can lead to death several days after the exposure. The exposure required to cause fatal effects of this type has been estimated to be 2500 min · mg/m^3, or 5 mg/m^3 for 8 hours (9). After lower exposures the condition is usually reversible. In some cases, massive, progressive lung fibrosis can appear several years after the initial incident (35, 118).

Exposure to lower concentrations can also have chronic effects on the lungs. An elevated frequency of chronic obstructive lung disease has been observed in cadmium-exposed workers. These chronic conditions take several years to develop, and increased mortality due to respiratory disease has been observed in workers exposed for long periods to relatively high cadmium concentrations in air. There is little information regarding microscopic examination of biopsy or autopsy material from man, but there is some from inhalation experiments with animals. One finding is emphysema-like changes, observed in microscopic examination of the lungs of rats (98).

There is reason to believe that cadmium oxide fumes are more harmful to lungs than cadmium oxide dust. The lowest concentrations of cadmium in industrial environments that have been correlated to effects on respiratory passages are around 70 µg cadmium/m^3 for dust and 20 µg/m^3 for fume.The effects of cadmium on the lungs are more pronounced in people who are also smokers (5, 63, 66).

5.3. Effects on liver

A person who swallowed 5 grams of cadmium iodide in an attempt to commit suicide survived for some days and developed anuria and clinical signs of liver necrosis; the latter was cited as the cause of death (128). Acute exposure of experimental animals, particularly parenteral administration, has acute effects on the liver which can lead to death. These effects are probably due mostly to cadmium that is not bound to metallothionein (87).

If adequate time is allowed for metallothionein synthesis to get started, which is the case with long-term cadmium exposure, effects on the liver are less pronounced. Chronic administration of relatively high doses has been observed to damage the livers of experimental animals (113), but such effects are extremely rare in man and have not attracted much attention. Studies of liver enzymes in workers with long-term cadmium exposures have generally shown normal values.

5.4. Effects on kidneys

In cases of acute cadmium poisoning from inhalation (see Section 5.2) or oral intake (Sections 5.3 and 5.5), local symptoms from the lungs or digestive tract are usually dominant. Kidney damage with anuria has been observed after extremely high (lethal) doses (128). It is clear, however, that symptoms involving the lungs or digestive tract appear at low doses in the absence of kidney damage, and these local effects are therefore the critical ones for short-term exposures. Since long-term exposure to cadmium is more common than short-term exposure, the rest of this section will be devoted to the effects of long-term exposure.

Table 1. Prevalence of proteinuria in cadmium workers (based on IPCS 1992)

Cadmium compound	Air concentration (µg/m3)a	Exposure time (years)b	No of persons	Prevalence of proteinuria (%)	Method of diagnosis	Ref.
CdO fume	40 - 50	controls	60	2	SA and TCA	11, 12, 58
		1 - 9	37	24		
		>9	63	46		
	64 - 241c	controls	11	0	TA	119
		<1	4	0	>100 mg/l	
		1 - 4	4	50		
	123c	5 -	4	100		
CdO dust	3000 - 15000	1 - 4	15	0	nitric acid (Heller's test positive in more than 50%)	33
		9 - 15	12	33		
		16 - 22	17	41		
		23 - 34	14	64		
CdO dust	31 (1,4)c	controls	31	0	Pathological electrophoresis pattern	65
		1 - 12 (4)	31	0		
		controls	27	4		
	134 (88)c	0.6 - 19.7 (9)	27	15		
		controls	22	0		
	66 (21)	21 - 40	22	68		
		controls	87	3.4	ß2-microglobulin (RIA) >290 µg/l (sg = 1.023)	62
	50c	0 - 3	50	6.0		
	50c	3 - 6	30	6.6		
	50c	6 - 12	21	19.0		
Cadmium stearate dust	30-690 (3)	controls	24	17	TCA	114
			19	58		
Cadmium sulfide dust	114d	<1 - 5	12	17	EP	40
		5 - 21	7	100		
		<1 - 5	12	8	TCA	
		5 - 21	12	43		

		controls	203	1	ß2-microglobulin	112
Cadmium		0 - 5	105	0	(RIA)	
sulfide	80	6 - 11	41	0	>765 µg/l	
dust	100	11 - 19	13	7.7	(sg=1.016)	
	100 - 600	20 +	14	57		
	100 - 600					
		controls	642	0 (0.8)	ß2-microglobulin	44
12 different	not given,	<18 mos	121	0 (10)	(RIA)	
industries,	Cd-B after	19 mos-5 yrs	168	1.8 (8.3)	>1000 µg/l	
mostly zinc	one year of	6 - 10 yrs	170	1.8 (16)	(or >200 µg/l)	
smelters	exposure=	11 - 15 yrs	82	7.3 (22)		
	15 µg/l	16 - 20 yrs	33	24 (45)		
		20 +	68	25 (56)		
					ß2-microglobulin	26
			16	18	>0.034 mg/mmol	
CdO	<1		22	32	creatinine	
fume	1-2		9	44		
	2-3		8	62		
	3-5		5	100		
	>5			6		72
	<1					
			75	58		
	1.5 - 3			86		
	3 - 5			100		
	>5					
			264	1.1		51
CdO	<0.4		76	9.2		
	0.4 - 1.7		43	23.3		
	1.7 - 4.6		31	32.3		
	4.6 - 9.6		16	32.2		
	9.6 - 15		10	50		
	>15					

a. Numbers in parentheses give the average values for the respirable particle fractions (<5µ)
b. Numbers in parentheses are average values
c. Measured in the breathing zone with personal monitor
d. Estimated exposure for workers with the most pronounced effect
SA = Sulfosalicylic acid test (qualitative)
TCA = Trichloroacetic acid test (qualitative)
TA = Tungsten acid method (quantitative)
EP = Electrophoresis
RIA = Radioimmunoassay

As stated in Section 3.2, with prolonged exposure to cadmium the substance accumulates selectively in kidney tissue. Mostly for this reason, the kidneys are the critical organs with regard to long-term exposure to cadmium. Kidney damage is usually tubular: glomerular damage is less frequent, but has also been reported. In vivo measurements of cadmium in the kidneys of workers with and without kidney damage (27, 28, 99) indicate that tubular damage occurs in about 10% of industrial workers who have a cadmium concentration of about 200 mg/kg in renal cortex. The relationship between cadmium concentrations in kidneys and the prevalence of β_2-microglobulinuria is shown in Figure 2.

Dose-response estimates based on the critical concentration in renal cortex are further discussed in Section 10. The amount of cadmium in urine that corresponds to about 200 µg/g in kidneys is about 10 µg/g creatinine (127). There have recently been reports that concentrations considerably lower than this are associated with an elevated incidence of tubular proteinuria in the general population. A cadmium excretion of 2 to 4 µg/24 hours was correlated to a 10% probability of tubular proteinuria, and diabetics were reported to be particularly sensitive to the effect of cadmium (13). Interpretation of this newly reported data is somewhat uncertain, however, since there is no way to be certain that the kidney damage is actually caused by cadmium. It is possible that certain individuals in the general population, diabetics for example, have kidney damage caused by some other agent and that this damage also results in increased excretion of cadmium. Tubular kidney damage is characterized by increased excretion of proteins, glucose and amino acids in urine; in more pronounced cases, function tests can indicate reduced tubular function. There can also be histological changes with degeneration of kidney tubules (60).
Cadmium-induced tubular proteinuria is characterized by increased excretion of plasma proteins in urine and particularly by a marked increase in the relative amount of low molecular weight plasma proteins. This proteinuria is a result of reduced tubular resorption of proteins, another expression of the same phenomenon that also causes increased excretion of glucose, amino acids, calcium, phosphate etc. There is also increased excretion of proteins and enzymes from the renal tubules themselves, indicated by elevated excretion of N-acetylbeta-d-glucosaminidase (NAG) (77).

The most frequently used indicators of tubular kidney damage are analysis of β_2-microglobulin or retinol-binding protein. Increased excretion of immunoglobulin chains, certain enzymes, riboneuclease and lysozyme, as well as metallothionein, has been demonstrated. Kidney damage has been correlated to the dose of cadmium absorbed via inhalation or food,which provided the basis for calculating cadium deposition in the kidneys, which in turn can be related to the occurrence of kidney damage (35). Kidney damage has also been correlated to cumulative absorbed dose calculated from cumulative blood cadmium values (51). Table 1 gives a summary of studies on the relationship between cadmium concentration measured in workplace air and the prevalence of proteinuria in exposed workers. Dose-response relationships are duscussed further in Section 10.

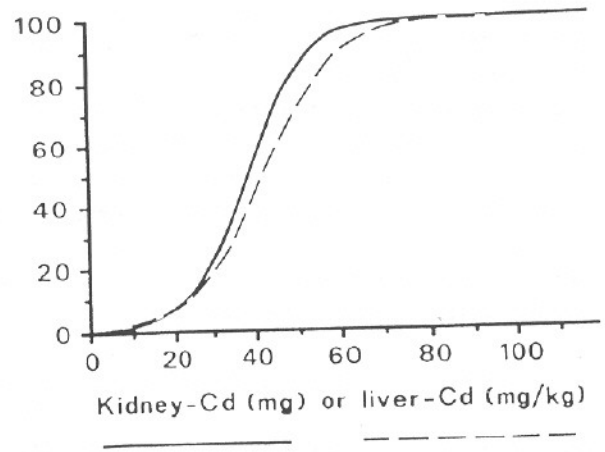

Figure 2. The percentage of workers with kidney damage in relation to the amount of cadmium in kidney tissue (mg in kidneys) or concentration in liver (adapted from Ellis et al, 1984). At a kidney content of 22 mg, which corresponds to a concentration of about 190 mg/kg in renal cortex, there is about a 10% prevalence of b_2-microglobulinuria.

A newly published study (100) (see also Section 5.6) reports that cadmium workers have an increased excretion of kallikrein. This has also been observed in rats given repeated subcutaneous doses of cadmium, which also probably causes some damage to distal renal tubules (36). The authors propose measurement of kallikrein in urine as a suitable indicator of damage to the distal portion of the nephron.

One question that has attracted considerable attention in the literature on cadmium is whether or not the kidney damage is reversible. Follow-up studies published earlier have generally indicated that the kidney damage, once it has become established with elevated total proteinuria, is permanent and may even be progressive despite termination of exposure. Some studies (39, 120) state that in some cases the kidney damage is reversible. Most studies of this problem, however, indicate that the kidney damage is usually permanent or even progressive. This is confirmed by a Belgian study (101), which reports a significant increase in serum creatinine and elevated excretion of β_2-microglobulin 11 years after termination of exposure.

Elevated mortality due to kidney disease was found in a study of causes of death in a cadmium-contaminated area in Belgium (67). This suggests that cadmium-induced kidney damage can be relevant in a wider context as well; see also the discussion in Bernard et al 1992 (8).

The elevated excretion of calcium and phosphorus and the consequent depletion of the body's reserves of these elements, combined with damage to renal tubules which reduces their ability to synthesize vitamin D metabolites, causes a

disturbance in mineral metabolism that can have effects on the skeleton. This reduced ability to regulate mineral metabolism will have different kinds of clinical manifestations, depending on food intake of calcium, vitamin D and phosphorus. In Swedish workers, it is primarily an increased occurrence of kidney stones (33), which has also been reported in other Western countries with similar dietary habits (106). Kidney stones have not been reported from Japan: there the disturbance in mineral metabolism is manifested instead as osteomalacia, with multiple fractures in extreme cases (see Section 5.10).

5.5. Effects on digestive tract

Intake of food or drinking water containing cadmium in concentrations above 15 mg/l (e.g. 15 mg/l in a 200-ml glass of water = 3 mg Cd) causes acute symptoms in the form of nausea, stomach cramps, vomiting and diarrhea (88). Extremely high (lethal) doses also have effects on liver and kidneys (see Sections 5.3 and 5.4), but these effects are not seen with oral intake of about 10 milligrams or less.

Experimental animals given high concentrations of cadmium in food or drinking water are reported to show chronic effects on the digestive tract, and such effects have also been associated with the Itai-itai disease in Japan (74). They do not occur with industrial exposure, where intake is primarily via inhalation.

5.6. Effects on heart and circulatory system.

Primarily on the basis of animal experiments in which some strains of rats given small amounts of cadmium in drinking water developed high blood pressure, it has been proposed that cadmium may be a cause of high blood pressure in humans as well. In a number of mortality studies of workers exposed to cadmium, however, deaths due to circulatory diseases were less frequent than predicted (4). This argues against the idea that exposure to cadmium at the levels found in work environments can cause clinically relevant hypertension . Well designed epidemiological studies of the general population have taken up the possibility of a correlation between high blood pressure and exposure to cadmium and have found no connection (111). There are macroepidemiological studies that report such a connection, but in these the control of confounding factors is inadequat

A recent finding of interest (100) is an increased excretion of kallikrein in the urine of cadmium workers in Belgium who had been exposed to cadmium for on average 11 years. A reduced aldosterone excretion in urine was also observed, as well as increased sodium excretion. The authors regard this as a compensation mechanism that works to prevent an increase in blood pressure. They consider that the study provides support for a recommendation that persons with hypertension should be protected from cadmium exposure.

5.7. Effects on blood and blood-forming organs

Some anemia has been reported in a number of studies of industrial workers exposed to high concentrations of cadmium in the work environment, above

several hundred micrograms per cubic meter (33). No clear reduction of hemoglobin levels was found in workers exposed to concentrations up to 67 $\mu g/m^3$ (7), and this effect of cadmium exposure is probably not a major problem at the cadmium concentrations now generally found in work environments. The effect of cadmium on hemoglobin concentration is due primarily to reduced iron uptake from the digestive tract rather than to direct effects on hemoglobin synthesis, and probably occurs regardless of the path of exposure.

5.8. Effects on central nervous system

Although large doses of cadmium during development have some effects on the development of the central nervous system in rats, there is no reason for concern that occupational exposure to cadmium might cause brain damage. The anosmia observed after high occupational exposure to cadmium (33) can be largely attributed to a direct effect of cadmium on the olfactory epithelium; an effect on the nerve cells in the corresponding section of the brain is also possible in these cases. A slight decline in performance on psychological tests has recently been reported in cadmium workers (41), but it is not possible to determine whether it is causally related to cadmium exposure.

5.9. Effects on peripheral nervous system

In animal experiments, injection of large doses of cadmium has caused necrosis in peripheral ganglia. This effect is observed in animals that have not been pre-treated with cadmium and therefore do not have previously induced metallothionein synthesis. The mechanism of cadmium-induced ganglial necrosis is probably damage to the blood vessels in the ganglia. No similar effects have been reported in humans, and there is probably no risk for effects of this nature with occupational exposure to cadmium, which does not involve injections. There is a study reporting changes in the peripheral nerves of rats after relatively high doses of cadmium in drinking water, but this is also irrelevant to occupational exposure (104).

5.10. Effects on other organs: bones

Skeletal effects have been reported in cadmium-exposed workers in a few cases (61, 75). The connection between cadmium exposure and the occurrence of bone disorders has attracted considerable interest because of Itai-itai, a disease which appeared in an agricultural area of Japan that had been contaminated by cadmium in irrigation water from a polluted river. The illness, which is a type of renal osteomalacia (and/or osteopenia), occurred primarily among women over 45 years old who had had several children. People in the area developed tubular dysfunction because of cadmium intake in rice, and this in turn caused disturbances in the metabolism of calcium, phosphorus and vitamin D (see also

Section 5.4), which led to bone disease in particularly sensitive members of this population (women), where calcium intake is lower than in the West.

A reduced level of vitamin D metabolites has recently been reported in cadmium-exposed workers (76): this supports the above hypothesis regarding the mechanism for development of bone disease. Recent studies by Kido et al (57) provide further support for the connection between tubular kidney damage and development of osteopenia in these cases.

6. Immunotoxicity and allergies

Contact allergy to cadmium is extremely rare. Of 1500 eczema patients given patch tests with cadmium chloride, not one had a positive reaction (125). When cadmium is used as a pigment in tattoos, however, there may be a phototoxic reaction causing the tattoo to swell (10). Studies of the immune function of cadmium workers have revealed no clear effects.

In some animal experiments, long-term exposure to cadmium in drinking water has resulted in lower numbers of antibody-forming cells in the spleen and reduced antibody production after stimulation with antigens. Some other experiments, however, have shown no such effects. Mice given intraperitoneal injections of cadmium have also shown reductions in cell-mediated immunity. Involution of the thymus has also been reported after injection of high doses of cadmium. The relevance of these findings to humans is unclear (21, 24, 47). The complicated nature of the connection is further emphasized in the studies reported by Cifone et al (16), in which in vivo exposure of rats caused both inhibition and stimulation of killer cells (NK cells) depending on the duration of exposure.

7. Mutagenicity, genotoxicity

Regarding the occurrence of chromosome aberrations in lymphocytes from cadmium-exposed workers and Itai-itai patients (cadmium exposure in the general environment), different studies have obtained different results. These results have been summarized by the IARC (46) and by Forni (32). The studies provide no support for a definite conclusion on the genotoxicity of cadmium. Contradictory results have also been reported from animal studies.

In vitro studies have shown that cadmium may affect primarily the cell spindle and chromosome contraction, which causes changes in chromosome length. Effects on chromosome length were observed in vitro after brief exposures to cadmium, but not after longer exposures which allowed time for the induction of metallothionein synthesis (3). Other in vitro experiments have shown that cadmium or zinc metallothionein can cause DNA damage. A summary and evaluation of available information from animal studies and in vitro experiments has been presented by Rossman et al (102).

8. Carcinogenicity

8.1. Human studies

Although our information on cadmium's carcinogenicity to man is incomplete, the studies presented in recent years have strengthened the suspicion that cadmium may be associated with lung cancers, though recent epidemiological studies have not supported the hypothesis of a similar connection with prostate cancer. Available data have been summarized by the IARC (45, 46), by the Scientific Committee on the Toxiciology of Metals (105), by the IPCS (47), and by Nordberg et al (82). A few of the most important observations on carcinogenicity are summarized below.

An elevated incidence of deaths due to prostate cancer was first observed among workers exposed to cadmium in a nickel-cadmium battery factory in England (59, 97) and subsequently in cadmium smelter workers in the United States (69). In later follow-up studies of the same groups as well as other groups of workers (5, 63, 109, 117), however, the initially observed clear increase of prostate cancer could not be fully confirmed. A newly published case-control study from the United States (23) reports a marginally higher odds ratio (OR) for aggressive forms of prostate cancer (OR 1.7, CI = 1.0 - 3.1) for persons who had had some form of occupational exposure to cadmium or a high intake of cadmium in food or cigarette smoke. The connection between cadmium exposure and elevated risk for prostate cancer must therefore still be regarded as tentative.

The suspicion of an elevated risk of lung cancer was not particularly emphasized in early studies of cancer mortality among cadmium workers. A statistically significant elevation in the risk of lung cancer was first reported in an American study by Lemen et al (69). In the Swedish studies (4, 26, 63) seven cases of lung cancer were found against four expected. This increase is not itself statistically significant, but should be assessed in the light of the results reported from other countries. A study by Sorahan and Waterhouse (110) reports a statistically significant increase in the number of lung cancer cases among workers who had been exposed in a nickel-cadmium battery factory in England. Other English studies (55) have also reported a significantly elevated risk of lung cancer in some exposed groups. A study by Thun et al (117), which was based on an extension of the above-mentioned study by Lemen et al (69), reported a dose-response relationship between cadmium exposure and the occurrence of lung cancer. The correlation was statistically significant for workers whose total exposure exceeded 2920 mg/m^3 · days. In a study by Thun (116) and in one by Kazantzis and Armstrong (55) workers were simultaneously exposed to other substances such as arsenic. The relevance of these confounding factors to the validity of conclusions regarding the correlation between cadmium exposure and lung cancer has recently been addressed in works by Kazantzis (54) and Doll (22).

8.2. Animal studies

In animal studies, local tumors have been induced by intramuscular injections of cadmium compounds (56). Leydig cell tumors can be induced in testes after parenteral injection of cadmium in doses of 1 to 3 mg/kg, which initially cause

necrosis in the testes (see Section 9.2); the tumors appear a long time after the initial injury (37). The formation of testicular tumors can be inhibited by administration of zinc, which also inhibits the formation of local tumors (sarcomas) at the injection site. An increased incidence of prostate tumors has been induced by injection of cadmium directly into prostate tissue and also by parenteral administration of cadmium (124). Rats treated with both cadmium and zinc, which counteracted degeneration of the testes, also had a higher incidence of prostate cancer (122). It is interesting in this context that the cadmium-binding low molecular weight proteins isolated from the prostate tissue of rats do not seem to be identical with metallothionein, and the content does not increase after treatment with cadmium (121). The authors propose that the absence of metallothionein binding can be the decisive factor for induction of tumors in prostate tissue (see also the survey by Waalkes (123) in Nordberg et al (82)).

In long-term experiments with rats, Takenaka et al (115) have shown that inhalation of relatively low concentrations of cadmium chloride (12.5 to 50 µg Cd/m^3) yields a dose-related increase in the occurrence of lung cancer. This has also been shown for other cadmium compounds such as cadmium sulfide and cadmium oxide. The effect has also been observed in other animal species, though it is less distinct (42, 43).

9. Reproduction toxicology

Single injections of high doses of cadmium have been shown to damage the reproductive organs of experimental animals. Long-term exposures have not been observed to have such effects, and they have not been seen in man.

Long-term exposure may possibly affect the metabolism of sex hormones: this effect has been observed in experimental animals. There are a few studies indicating that the effect may also appear among industrially exposed workers, but the data are uncertain; moreover, if such a risk exists, it probably requires exposure that far exceeds the occupational exposure limits for cadmium that were in force in Sweden during the 1980s (20 to 50 µg/m^3). A summary of reproduction toxicology data on cadmium is given below.

9.1. Human data

There are some extremely sketchy reproduction studies of both male and female workers exposed to cadmium. Unspecific histological changes in testicles have been observed in autopsies of deceased cadmium workers (107), but these changes were regarded as caused by the general condition leading to death rather than by cadmium exposure.

An Italian study reports some changes in the urinary excretion of testosterone metabolites in male cadmium workers (30). In a study from Great Britain (72), however, no effect on metabolism of male hormones could be observed despite the fact that the subjects had cadmium-induced kidney damage.

In a study from the Soviet Union (19) it is reported that female cadmium workers had babies with below-normal birth weights. Exposure to cadmium was reported to be up to 35,000 µg/m^3. Women who smoke cigarettes have elevated

concentrations of cadmium in blood and placenta. They also have children with lower birth weights than non-smoking mothers. It is unclear whether the histological changes observed in placentas from mothers who smoke (18, 126) can be attributed to cadmium accumulation or to other components in tobacco smoke. A newly published study by Berlin et al (6) of pregnant women occupationally exposed to cadmium, argues against the theory that cadmium is the cause.

9.2. Animal data

Injections of 1 to 3 mg/kg cadmium, clearly below the lethal dose, can cause testicular necrosis in animals (91). This initially reduces testosterone production, but when the testicles have been re-vascularized the Leydig cells regenerate and testosterone production resumes. The spermiogenic epithelium in the testicles usually does not regenerate, however, and a single injection of cadmium can thus cause permanent sterility in these animals. It is particularly interesting that pre-treating the animals with small doses of cadmium can protect them against the testes-damaging effects of cadmium, probably by induction of metallothionein-like proteins which protect the testes by binding cadmium (78). This would also explain why testicular necrosis does not occur even after prolonged exposures with heavy deposition of cadmium in testes. With this kind of exposure, however, there is an observable decrease of testosterone effects, probably because cadmium inhibits testosterone production in the Leydig cells (79, 86). This effect is probably reversible: in mice, the testosterone-dependent protein excretion in urine returns to normal after exposure to cadmium is terminated. These observations may be relevant to the question of cancer induction in testes and prostata (see Section 8.2).

A number of other metals, notably zinc, selenium and cobalt, can have a protective effect against the acute testicular damage caused by cadmium, if they are administered with or prior to cadmium (38).

As mentioned previously (Section 3.2), only small amounts of cadmium pass through the placenta. The effects of cadmium on the fetus depend on the size of the dose and the gestational age at which it is given. A survey was published by Clarkson et al in 1983 (17). Changes in placental transport of cadmium during the course of gestation are described by Denker et al (20). Deformities are primarily a result of exposure early in gestation, while fetal death is the dominant effect if cadmium is administered shortly before parturition. Teratogenic effects of cadmium were first reported in hamsters (31), but have since been confirmed in other experimental animals such as rats and mice (14, 48). All of these animal studies have involved injection of relatively large doses of cadmium, over 1 mg/kg body weight. The effects can probably be traced both to effects on the placenta and to cadmium's interaction with zinc and other nutrients transferred via the placenta. For example, it has been shown that zinc uptake by the fetus is inhibited by administration of cadmium (103). It has been proposed in a report on a study with mice (68) that induction of metallothionein synthesis in the mother (or in the placenta) is probably important in protecting the fetus against the teratogenic effect of cadmium, but these effects are still not clearly documented.

Injection of cadmium can also cause necrosis in ovaries of experimental animals. Ovaries of animals that have not reached full sexual maturity are particularly sensitive (53, 94). The doses necessary to induce this effect are in the range of 2 to 6 mg Cd/kg body weight. No such effects have been observed in long-term exposure experiments.

Large doses of cadmium late in gestation can cause a necrosis of the placenta which results in fetal death (92, 93). In experiments with rats, Levin and Miller demonstrated that the fetal death is caused by the effect of cadmium on the placenta and not by its direct effects on the fetus (70). The placentas of rats given repeated doses of cadmium show morphological changes resembling those seen in the placentas of human mothers who smoke (see Section 9.1).

10. Exposure-effect, exposure-response relationships

10.1 Effects of short-term exposures

Table 2 gives a summary of the effects that can be reasonably well quantified in relation to dose. The effects that appear at relatively low doses for each type of exposure are of particular interest. As mentioned earlier, the effects on the lungs that can result from acute exposure constitute a risk that must be guarded against with all welding or soldering of cadmium-containing materials. Most of the doses given are calculated on the basis of cadmium concentrations measured in lung tissue of deceased patients, and there is some uncertainty about them, but they may nevertheless be regarded as reasonable estimates in this context. Severe damage to lungs can result from 8 hours of exposure to 0.5 - 1 mg/m^3 cadmium. It can be safely assumed that less severe but clearly adverse changes can occur at lower concentrations. The effect on the lungs must be regarded as the critical effect of acute inhalation exposure. Some oral intake of cadmium can occur in work environments, from dust on food, for example (if the regulations published by the National Board of Occupational Safety and Health are not followed; see Appendix 1). Acute oral intake is probably of limited interest in the context of occupational exposure, since oral intake large enough to have acute effects is highly unlikely. The same is true for injection, which is not a form of occupational exposure. Because there are so little data, it is not possible to more closely describe the dose-effect relationship between inhalation of cadmium and effects on the lungs; as explained above, other acute effects are less relevant in the context of occupational exposure.

Table 2. Effects of short-term exposure to cadmium

INHALATION - HUMAN DATA **Effect**	**Dose**
Lung edema, pneumonitis leading to death	5 mg/m^3 cadmium fume, 8 hours
Lung edema, pneumonitis, generally reversible (but may in some cases lead to chronic fibrosis)	0.5 - 1 mg/m^3 cadmium fume, 8 hours (higher concentrations if cadmium is in the form of dust)
ORAL INTAKE - HUMAN DATA	
Effect	**Dose**
Liver damage, lethal kidney damage with anuria	5 g CdI in water (128)
Nausea, vomiting, stomach cramps, diarrhea (sometimes bloody)	15 mg/l or more in water (one 200-ml glass = 3 mg) or high concentrations in food
INJECTION - ANIMAL EXPERIMENTS	
Effect	**Dose**
Testicular necrosis (rats, mice etc.)	1 to 3 mg/kg (single dose)
Ovarian necrosis, particularly in juveniles (rats, mice)	2 to 6 mg/kg (single dose)
Deformity or death of fetuses, placental necrosis (rats, mice, hamsters)	1 to 6 mg/kg (single dose)

10.2. Effects of long-term exposures

Table 3 gives a summary of the effects of long-term exposure to cadmium, for humans as well as experimental animals. Quantitative estimates of the risks of inhalation exposure in industrial environments are given particular emphasis. At relatively high concentrations (70 µg/m^3 as cadmium dust or 20 µg/m^3 as fume) there is an increased risk of chronic obstructive lung disease.

In general, the effects on the kidneys have been regarded as the critical effects of inhalation exposure to cadmium dust in concentrations below 70 µg/m^3. These effects have therefore received closer quantitative analysis.

Two basically different analysis methods have been used for quantitative risk assessments regarding the effects of cadmium on the kidneys. The first method is based on epidemiological studies that describe the correlations between long-term air concentrations in work environments, cadmium levels in blood and urine, and the occurrence of kidney damage.

Table 3. Effects of long-term exposure to cadmium.

INHALATION - HUMAN DATA **Effect**	**Dose**
Chronic obstructive lung disease	Several years of exposure to cadmium dust levels above 70 µg/m^3 or cadmium fume levels above 20 µg/m^3
Lung cancer?	Dose?
Exposure estimated to cause kidney damage with proteinuria (β_2-microglobulin) in about 5% of exposed	Cd dust equivalent to 32 µg/m^3 during all working days for 10 years
Dose estimated to cause slight kidney damage in about 10% of exposed	14 µg/m^3 Cd dust during all working days up to age 50
INHALATION - EXPERIMENTAL ANIMALS	
Effect	**Dose**
Lung changes (rats)	25 - 50 µg/m^3, 24 hours/day, 90 days (98)
Lung cancer (rats)	12.5 to 50 µg/m^3 of $CdCl_2$
Tubular kidney damage with proteinuria	Inhalation exposures yielding 300 to 700 mg/kg cadmium in kidney
ORAL INTAKE - HUMAN DATA	
Effect	**Dose**
Estimated intake causing kidney damage with proteinuria (β_2-microglobulinuria) in 11% of exposed	Exposure equivalent to a daily intake of 200 µg from birth up to age 45

The second method is based on observed or estimated critical concentrations of cadmium in renal cortex, and uses a metabolic model in which the exposure required to reach the critical concentration is calculated from given assumptions.

10.2.1 . Assessments based on data from industrial workers.

Table 1, which is adapted from a similar table in the 1992 criteria document from the IPCS (47), lists observations on the prevalence of proteinuria in relation to occupational exposures. In several cases there is a considerable margin of error in the reported doses, but it is apparent from the table that several studies show a clear dose-response relationship between cadmium in air and the prevalence of proteinuria. With use of the classical criteria of total proteinuria, a dose-response relationship can be seen at 5 to 10 years of exposure to about 100 µg/m^3 cadmium. If excretion of low molecular weight proteins is used instead as the criterion for critical effect, it can be said that 10 to 20% of exposed workers show this effect after a cumulative dose equivalent to 10 to 20 years of exposure to 50

$\mu g/m^3$ cadmium. Thun et al (116) found a somewhat higher proportion of workers showing effects at this level, while the proportion with low-molecular proteinuria was in fairly good agreement with other studies of higher exposure levels.

As with most other substances in the work environment, there is limited information on the effects of exposure in the low-dose range, and dose-response estimates for low doses involve a considerable uncertainty.

10.2.2. Doses causing kidney damage in the general population

Studies of oral intake in the general population, primarily from Japan, indicate that either a daily cadmium intake of 140 to 260 µg up to age 50 or a cumulative cadmium intake of about 2000 mg during this period causes increased excretion of low molecular weight proteins in the urine of both men and women at age 50 (47).

Some newly published data from Belgium indicate that there might be slight damage at lower doses in about 10% of the population (5% over the background frequency) who have a cadmium excretion in urine equivalent to 2-4 µg per 24 hours (8, 13), but this is still unconfirmed.

10.2.3. Estimates based on metabolic models and critical concentrations

According to the IPCS (47), available information on critical concentration and kinetic models for cadmium can be used, with specific assumptions, to calculate the daily dose of cadmium in food, or concentration in air for occupational exposure, that is required to reach the critical concentration. Such calculations indicate that for a person weighing 70 kilograms, with one third of the body burden in the kidneys, 25 years of occupational exposure to 14 $\mu g/m^3$ is necessary to reach a concentration of 200 mg/kg in renal cortex. The halving time in kidney is assumed to be 17 to 30 years. As indicated in Section 5.4 and Figure 2, tubular kidney damage is considered to occur in an estimated 10% of industrial workers who have a cadmium concentration of 200 µg/g in renal cortex.This means that for 10% of industrial workers the critical concentration for kidney damage is below 200 µg/g.The cadmium concentration in renal cortex that is associated with a 50% prevalence of β_2-microglobulinuria in industrial workers can also be estimated from Figure 2: about 320 µg/g. Calculations have also been made by Kjellström (64) which take into account the distribution of critical concentration among exposed workers. From the information in Table 3 it can be estimated that tubular kidney damage severe enough to cause β_2-microglobulinuria in about 5% of exposed workers appears at an average occupational exposure equivalent to 32 $\mu g/m^3$ for 10 years. With longer exposures, this air concentration is lower. These calculations agree fairly well with the values given by IPCS for long exposure times.

OSHA (90), using a model developed from data published by Ellis et al, calculated that occupational exposure to 5 $\mu g/m^3$ for 45 years constituted a risk for kidney damage in 980 of 10,000 workers. These calculations indicate a somewhat higher risk than those cited earlier, and OSHA also pointed out that the model they used probably overestimated the risk in the low-dose area.

10.2.4. Assessment of risk for lung cancer

It is extremely difficult to quantify the risk of lung cancer from inhalation of cadmium in industrial environments. Some estimates have been presented by OSHA (90). These were based partly on the results of animal experiments, which generated relatively high risks in the low-dose area, while estimates based on epidemiological data yielded lower values. It is probably still too early to use this kind of estimate in discussions of occupational exposure limits. It should be pointed out, however, that the estimates indicate that risk of cadmium-induced lung cancer is low if exposure is held to a level that protects a large majority, say 97%, from the risk of developing tubular proteinuria (based on human data, which seems the most reasonable even though margins of error are considerable).

In general, cancer is often regarded as the critical effect even though there is still insufficient basis for a quantitative dose-response analysis (for more details see Reference 80). This is based on the assumption that cancer effects are stochastic, and in the low-dose area often have a linear component down to 0. Considering the fact that there is so far no satisfactory evidence that cadmium causes cancer in humans, it can still be debatable whether the "probably carcinogenic" (IARC group 2A) effect of cadmium should be regarded as the critical effect.

11. Research needs

The only research needs commented on here will be those where new research results may be relevant to the assessment of the risks associated with occupational exposure to cadmium, what kinds of exposure limits should be set, and how these should be monitored. A central concept in the discussion of exposure limits is the dose-response relationship for the critical effect. What effect is regarded as the critical effect is consequently of decisive importance. Present limits are based on a quantitative assessments of how cadmium can affect the kidneys, which are used to derive estimates of acceptable levels in the work environment. Various quantitative models have thus been used to calculate the risks for occurrence of kidney damage in industrially exposed populations. It is clear from the above discussion, however, that these estimates have considerable margins of error, particularly in the lower portion of the dose-response curve which is critical in the establishment of occupational exposure limits. The question of the relationship between metallothionein-bound and "free" cadmium in the kidney and the occurrence of kidney damage is of central interest in this context. There is reason to believe that metallothionein-bound cadmium is relatively inactive, while "free" cadmium can exercise its toxic effects with full power.

The relationship between these two forms of cadmium (bound and unbound) in the kidney and their relation to the occurrence of kidney damage should therefore be studied. If the circumstances that promote the appearance of unbound cadmium can be determined, and particularly sensitive situations or groups of people be identified, this can be quite important. Another important question is how the less severe kidney damage caused by cadmium affects calcium metabolism. This is of particular interest where female workers are exposed to cadmium, since women

have a greater tendency to develop osteoporosis after menopause (this disease has considerable practical importance in Sweden).

With regard to kidney damage caused by cadmium, it would also be interesting to find out whether there is reason to assume that persons with other diseases may be particularly sensitive to the harmful effects of cadmium exposure. Some data from epidemiological studies of the general population in Belgium indicate that diabetics may be one such group. Both further epidemiological studies and experimental studies would be of great value in casting light on this matter.

As indicated in the above discussion, effects other than those on kidneys may in the future be regarded as the critical effects of occupational exposure to cadmium. These effects include cadmium's possible carcinogenic qualities, particularly the risk of lung cancer from inhalation. Further epidemiological and toxicological studies on the possible relation between cadmium inhalation and lung cancer should therefore have high priority in the future. Another form of cancer being discussed is prostate cancer. Studies that could help to explain the mechanisms behind the occurrence of both lung cancer and prostate cancer in experimental systems after exposure to cadmium are also of great interest.

Other effects that should be studied further because of their potential relevance as critical effects for industrial exposure are effects of cadmium on the placenta and on androgen production in testes. Data from animal experiments indicate that cadmium can have such effects, but it is not yet clear whether they are relevant at the doses associated with occupational exposure. Data available so far do not indicate this, but further study is warranted.

12. Discussion and assessment

Available published correlations between exposure, effect and response for both short-term and long-term exposures were reviewed in Section 10. For short-term inhalation exposure, it is clearly the effects on the lungs that are the critical effects. These effects can be prevented by not allowing concentrations in the work environment to exceed peaks of about 1 mg/m^3 for 1 hour of exposure. If an eight-hour limit is set considerably lower, this should in theory virtually eliminate the risk of the type of exposure that can have acute effects on the lungs. There is aways a danger of acute exposure for people welding or soldering metals, who may not even know that the materials they are working with contain cadmium. There should therefore be regulations specifying that cadmium-containing materials be clearly marked, and the risks of handling them should be clearly described.

The effects of long-term exposure are those used to determine occupational exposure limits. The critical effect has long been regarded as the effect on kidneys, and it is still reasonable to use this as a basis for assessments. The critical concentration of cadmium in renal cortex that causes elevated excretion of low molecular weight proteins in the urine of 10% of exposed industrial workers has been estimated to be 200 µg/g. Biological monitoring of cadmium in blood and urine are reviewed in Section 3.5, and in Appendix 1. Cadmium levels in urine reflect concentrations in kidney, and can be used for dose-response assessments at

the group level. Urine concentrations of 10 µg/g creatinine correspond to about 200 µg/g in renal cortex. These levels in urine are correlated to some risk for the occurrence of kidney damage, and efforts should be made to hold levels below 5 µg/g creatinine in order to prevent kidney damage in the large majority of workers. As explained in Section 10.2, dose-response relationships for exposures via concentrations in workplace air have been calculated from direct epidemiological correlations between cadmium concentrations in air, exposure time and the occurrence of kidney damage, and also from calculations based on a metabolic model. In summary, it can be said that low-molecular proteinuria has been observed in 10 to 20 % of workers exposed to about 50 µg Cd/m^3 for 10 to 20 years. Estimates based on a metabolic model and critical concentrations of cadmium in kidney tissue arrive at similar results. It has been calculated, for example, that with occupational exposure to 14 mg/m^3 cadmium for an entire working life the concentration in renal cortex reaches 200 mg/kg, i.e. a level causing proteinuria in 10% of those exposed by the age of 50. Other calculations indicate that 5% of exposed workers will have an increased β_2-microglobulin concentration in urine after 10 years of exposure to an average 32 µg/m^3. These and similar extrapolations to low doses indicate that exposure for an entire working life to 10 µg/m^3 cadmium dust, or 5 µg/m^3 cadmium fume, should result in increased excretion of β_2-microglobulin in a few percent of those exposed.

Cadmium is carcinogenic in animal experiments, and an elevated risk of cancer in occupationally exposed workers has been substantiated by epidemiological studies. It is not yet possible to correlate a risk of lung cancer to particular exposure levels, but this risk should be borne in mind when occupational exposure limits are discussed.

13. Summary

Nordberg G. Cadmium 101.
Nordic Expert Group for Documentation of Occupational Exposure Limits
Arbete och Hälsa 1993:1, pp 85-124.

The document presents a literature survey and assessments to be used as a basis for establishing occupational exposure limits for cadmium. Cadmium is presently used primarily in the production of batteries. In Sweden, use of cadmium as a pigment, surface coating or stabilizer has been restricted by law. Occupational exposure to cadmium is primarily via inhalation. After uptake, cadmium is transported in the blood first to the liver, where it induces and is bound to the low molecular weight protein metallothionein. Thus bound, it is further transported to the kidneys, where it gradually accumulates. Cadmium is excreted from kidneys very slowly, and after some decades a critical concentration may be reached at which tubular kidney damage appears. Cadmium can also cause acute damage to the lungs, and in some less usual cases other organs as well.

The air concentrations of cadmium that can cause kidney damage after some decades of occupational exposure have been estimated to be in the range of 15 to 50 $\mu g/m^3$. With exposure to 10 $\mu g/m^3$ cadmium dust (or 5 $\mu g/m^3$ cadmium fume) during an entire working life, the risk of kidney damage is only a few percent. Cadmium is also carcinogenic in animal experiments, and some information indicates an increased risk of lung cancer in occupationally exposed workers.

In English, 129 references

Key words: Cadmium, exposure, kidney accumulation, kidney damage, lung cancer, metabolic model, β_2-microglobulin, tubular proteinuria, occupational exposure limits, prostate cancer.

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Appendix 1

Summary of the National Board of Occupational Safety and Health code of statutes: AFS 1989:3, Cadmium

This ordinance, with regulations on cadmium and general guidelines for the application of the regulations, contains first a section with general regulations and the area covered by the regulations. It treats the labeling of cadmium materials as well as the regulations applying to certain types of work, where for example ventilation hoods or face masks are necessary. It points out that equipment and working areas shall be so designed that spreading of airborne cadmium is limited as much as possible, by enclosing machines, for example. Work areas must be adequately cleaned, and the ventilation system is to be inspected regularly. With regard to personal protective equipment, the regulations on measures against air contaminants for prevention of detrimental effects on health (AFS 1980:11) shall be followed. If a face mask is required it must be at least a half mask, with a filter that effectively protects the wearer from cadmium dust.

Protective work clothes for personnel working with cadmium shall be stored separately, so that dust from this clothing does not spread to street clothes or the clothing of other employees. Cadmium-contaminated protective clothing is not to be taken or worn into cafeterias or other localities where food is consumed. Food and drink, and the use of tobacco or cosmetics, are prohibited in areas where cadmium work is done. Employees who work with cadmium are to wash before meals and before any smoking or snuff taking, and shower immediately after work.

Air contaminants are to be monitored regularly in accordance with the National Board of Occupational Safety and Health ordinance on monitoring of air contaminants in work environments (AFS 1988:3). Exposure monitoring is to include determination of cadmium in both total dust and respirable dust.

The section on medical monitoring contains guidelines for the initial physical examination before employment to work with cadmium, and covers in addition to analysis of cadmium in blood and urine also determination of creatinine in urine and β_2-microglobulin in urine (see Section 5.4 in this report). Periodic health examinations are to be made at six-month intervals (six-month checkups) and must include determination of cadmium in blood. If the cadmium concentration exceeds 50 nmol/liter (5.5 µg/l) the employer must investigate the cause of this and where necessary take measures to reduce cadmium uptake. Workers who on any occasion have blood cadmium levels exceeding 150 nmol/l (16.5 µg/l) are not to work with cadmium until a new medical examination is made and a new control shows that cadmium in blood has dropped below 100 nmol/l (11 µg/l).

If an employee has a blood cadmium level below 100 nmol/l (11 µg/l) at three consecutive six-month checkups, the periodic examinations may thereafter be made at 12-month intervals (annual checkups). If at any subsequent annual examination the employee is found to have a blood cadmium level exceeding 100 nmol/l (11 µg/l), six-month examinations must be resumed.

Appendix 2

Permitted or recommended maxima for concentrations of cadmium and inorganic compounds (as Cd) in air in work environments.

Country	mg/m^3	Comments	Year	Reference
Denmark	0.01		1988	1
Finland	0.02		1987	2
	0.01	Cd oxide		
Iceland	0.05		1978	3
	0.02	Cd oxide		
The Netherlands *	0.02		1989	4
	0.05	Cd oxide		
Norway *	0.05		1989	5
	0.02	Cd oxide		
Sweden * **	0.05	total dust	1990	6
	0.02	respirable dust		
USA (ACGIH) * **	0.05		1991-92	7
(NIOSH) **	C	fume, dust	1992	8

* Ceiling value
** Possibly carcinogenic to humans
C Lowest possible concentration (detection limit = 0.01)

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Inorganic lead

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Contents

Abbreviations

AAS	Atomic absorption spectrosscopy
ALA	∂-amino levulinic acid
ALAD	∂-amino levulinic acid dehydratase
B-Pb	Blood lead level
B-ZPP	Zinc protoporphyrin level in blood
$CaNa_2EDTA$	Calcium disodium edetate
CAS	Chemical Abstract
cf	see further
CNS	Central nervous system
CP	Coproporphyrin
CRC	Chemical Rubber Company
DMSA	Dimercaptosuccinic acid
EEC	European community
EEG	Electroencephalography
FAO	Food and Agrulture Organization
FEP	Free erythrocyte protoporphyrin
GABA	Gamma-aminobutyric acid
Hg	Mercury
HPLC	High performance liquid chromatography
IARC	International Agency for Research on Cancer
Na^+,K^+-ATPase	Na^+,K^+-adenosinetriphosphatase
NAG	N-acetyl-ß-D-glucosaminidase
P5N	Pyrimidine 5´-nucleotidase
Pb	Lead
PNS	Peripheral nervous system
PP	Protoporphyrin
RBP	Retinol binding protein
U-ALA	∂-amino levulinic acid level in urine
U-CP	Coproporphyrin level in urine
U.K.	United Kingdom
U.K. MRC	Medical Reasearch Council
U.S.A.	United States of America
U.S. ATSDR	Agency for Toxic Substances and Disease Registry
U.S. CDC	Center for Disease Control
U.S. EPA	Environmental Protection Agency
U.S. NIOSH	Occupational Safety and Health Administration
U.S. NRC	National Research Council
U.S. OSHA	U.S. Occupational Safety and Health
WHO	World Health Organization
XRF	X-ray fluorescence
ZPP	Zinc protoporphyrin

Background

The literature on the toxicology of lead is enormous. Lead intoxication was descibed already in antiquity (274,563,564,838). A large number of reviews have been published, some of them recently (13,96,215, 290,342,441,461,481,521, 522, 555,563-565, 591,592,729,730,732,758,767,792,798,801-804,808,810, 842-845). Particularly comprahensive is the review by the U.S. EPA 1986 (806).

In this review, only data of immediate relevance for the possibilities for biological monitoring of lead exposure and risk of lead toxicity will be surveyed.

1. Physical and chemical properties

Lead (Pb; CAS 7439-92-1)

Molecular weight: 207.19 (4 isotopes: 204, 206, 207 and 208).
1 µg=0.004826 µmol

Density: 11.3 g/cm^3

Melting point: 327.5° C

Boiling point: 1,740° C

Valences: In its inorganic compounds, lead usually has the oxidation figure +2, but +4 also occurs.

Solubility: Metallic lead is very insoluble, but will dissolve in nitric acid and concentrated sulfuric acid. Most lead(II) salts are difficult to dissolve (e.g. lead sulphide and lead oxides), with the exception for lead nitrate, lead chlorate, and - to some extent - lead chloride. In additon, some salts with organic acids are insoluble, e.g. lead oxalate.

Further information on physical and chemical properties of lead compounds may be obtained in e.g. CRC Handbook of Chemistry and Physics (182).

2. Occurence, uses and exposure

2.1. General environment

2.1.1. Sources

Humanity has always been exposed to lead, as it is ubiquitously present. There is no evidence that the human body requires lead (806). Lead is a multimedia pollutant, i.e. several sources and media contribute to the exposure (189,804,806; Figure 1).

It is the net body burden produced by the sum of the different sources that constitute the risk of adverse health effects.

Lead carbonbate and hydroxide has had a widespread use as pigment in house *paint* in some countries, and weathering, chalking, and peeling paint may cause

exposure (146; 804). In such paint lead may constitute up to 40% of the final dried solid. In the Nordic countries, lead paint has had a very limited use for painting of buildings. In Sweden, use of lead paint inside buildings was restricted by a law issued in 1926 (a result of an international agreement in Geneva 1921 on the use of white lead paint; ref. 554); in 1984 there was a definite prohibition (541).

Organolead compounds are added to *petrol*. During combustion in the engine, organic lead is transformed into inorganic lead, and is emitted almost entirely as such. This causes exposure to inorganic lead, in particular in subjects living in areas with heavy traffic (48,157,238,470,473,571,632,635,692,694, 737).

Also, *industrial emissions* may cause exposure in neighborhood populations (48,432,621,692,694,737).

These sources may cause exposure *via* inhalation and ingestion.

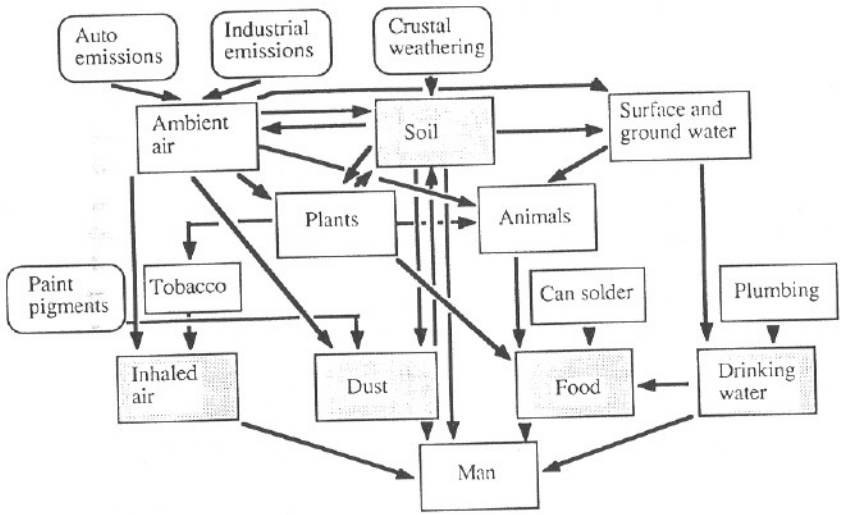

Figure 1. Sources and routes of lead exposure in the general population. Modified after U.S. EPA (806).

2.1.2. Exposure routes

2.1.2.1. Inhalation

The exposure through *ambient air* is also low in most areas, the average levels being 0.1 μg/m^3 or less (433,814), corresponding to an inhaled amount of less than 1-2 μg/day. In some areas it may be much higher, up to about 10 μg/m^3, corresponding to a daily inhalation of about 200 μg (792,806). Of the lead, a few percent is organic lead, the rest inorganic (302). The indoor/outdoor ratio is 0.6-0.8 (137,806).

The different sources of ambient air lead are discussed in Section 2.1.3.

The particle size distribution may vary considerably between different areas. For example, in London, U.K., 60% of the particles were less than 0.3 μm and only 1% above 10 μm. In Los Angeles, U.S.A., only 30% of the particles were less than 0.3 μm, and a considerable fraction more than 10 μm (136). The size distribution is of great importance for the deposition in the airways (see below).

In addition, inhalation exposure occurs through cigarette *smoking* (53,213,295,576,617,627,628,753,765), although the association may, to some extent, be confounded by alcohol intake (295). There is even an effect on cord B-Pb of the smoking pattern of the pregnant woman (235, 633). The lead content in a cigarrette is 3-12 μg. About 2% of this is inhaled into the active smoker. Further, in children, there is an exposure associated with environmental tobacco smoke (passive smoking; 21,48,54a,157,190,468,472,861). Lead exposure has also occurred through contaminated snuff (249).

Some *hobbies* may cause lead exposure. Such are indoor shooting (550,766), tin soldier moulding (694), ceramic work, employing lead-containing glazes, and motor sports involving work with exhaust system. There is exposure through inhalation, but in addition, oral intake may occur. Further, long-distance running may be associated with lead exposure (314), probably from petrol lead.

2.1.2.2. Ingestion

Soil and street and home *dust* may thus contain high lead levels. In Sweden, the average lead level in soil from fields and meadows is 16 μg/g (538), but in soil from cities it may be twenty times higher (825). In children, hand contamination and mouthing behaviour may thus be important for the exposure (435, 632, 780,804,825), as well as pica (468). The maximum uptake in infants seem to occur around 2 years of age, and is higher in the summer than in the winter (54,166), probably because of the playing and mouthing behaviour of children.

The lead content of the *drinking water* may vary considerably. Of course, the lead content in the surface or ground water is of importance (806). This may be contaminated, e.g. by industrial discharges or highway runoff. However, plumbosolvent (in particular acid and soft) water may be contaminated with lead from lead pipes, lead soldered copper tubes, or from other parts of the water system (514,806). The level is then dependent upon the time during which the water did dwell in the pipe. Further, the lead content is often higher in the first flush than later (524). Moreover, intake of contaminated rain water may cause exposure (53,54). It

has been proposed, that the well-established relationship between soft water and ischemic heart disease is due to lead contamination.

The intake through drinking water is low in many areas, about 1 µg/day or less (765), but it may be high in other regions (221,428,524), sometimes as high as 3 mg/day (792,804). Drinking water with levels 0.05 mg/l, or higher, are considered unsuitable for consumption (540,843a).

Also, lead exposure occurs through *foods* (591,806). The intake of lead through diet is low in certain areas of the world. In Sweden, an average of 20-30 µg/day has been reported (4,71a,110,690,738,812-814,890), in Finland 66-70 µg/day (465, 819), and in Denmark 77 µg/day (19). The intake is considerably higher in many other areas, amounting to a few hundred µg/day (465,792,804,806; Section 2.1.3). This is in accordance with the differences in B-Pbs in different areas (Section 3.7.1.3). The diet is usually the dominating source of lead exposure.

Most of the lead in food is inorganic; however, in some foods, e.g. fish (725), a fraction may be organic. In Sweden, the allowed levels of lead in different foods varies between 0.02 and 3 mg/kg (539).

Some foods take up lead from the water during cooking (526). A significant amount of the lead content in foods may originate from lead-soldered tin *cans* (19,393,474,690,804,890). In addition, very high oral intake of lead (several mg/day), even leading to clinical intoxication, may originate from acid foods contained in *lead-glazed* or lead-painted *pottery*, earthenware, or *pewters* (462,866). Even crystal glass may cause contamination (196, 309).

Food and Agricultural Organization and World Health Organization have a provisional tolerable weekly intake of 25 µg/kg for infants and children (244) and 3 mg/person in adults (243).

Also, *alcoholic beverages* may cause lead exposure (213,216,295,392,576,617, 627,628,753,890). There is even an effect on cord B-Pb of the drinking pattern of the pregnant woman (234,633).

Earlier, lead acetate was used as a sweetener in wines (60). Heavy exposure may also occur through homemade alcohol, produced by use of automobile radiators with lead solderings as condensators ("moonshine whiskey" in the "Moonshine belt" in Southern U.S.A.; 325, 645). Even less spectacular alcoholic beverages, especially wines, may contain considerable lead concentrations, partly due to use of lead arsenate as a fungicide on grapes and to contamination from containers (392, 462). Alcohol may also increase the absorption of lead (Section 3.1.2); alcohol beverages stored in crystal glass containers may be contaminated (see above), which, however, should be of limited importance. Thus, alcoholics, in particular wine drinkers, may have a significant exposure (101,186,216,418). Possibly, a disulfiram treatment causes a reduction of B-Pb (299). Lead contamination of wine (563,564), in combination with other lead exposure (274) has even been claimed to have caused the fall of the Roman empire.

Considerable exposure may occur from intake of leaden things. This is a special problem in playing children (229,257,263,360,697), but lead shots in game food may also cause exposure, if they are retained in the appendix (208,478).

2.1.2.3. Other

Since ancient times, lead has also been used in *cosmetic preparations* (25, 838). This is still the case in e.g. Indians. This may reasonably cause exposure, probably mainly through the gastrointestinal tract. *Aphrodisiacs* (107) and other herbal medicines (742) for oral use used by Asians may also contain lead.

Considerable exposure may result from gunshot bullets retained intraarticularly (71,445,457,704).

2.1.3. Geographical differences

The lead exposure is quite varying in different areas of the world. The lead exposure in industrialized areas (*Germany:* 724,831,876; *Italy*: 238,276; *U.K.:* 217,218,222,224,627,628; *U.S.A.:* 24,636; *New Zealand:* 346,486; *Greece:* 140,332; *South Africa:* 314; *India:* 403; *China:* 886; *Canada:* 571; *Australia:* 865; *Belgium:* 194) is generally higher than in areas remote from industries and traffic (220,614,620). In the industrialized world, the Nordic countries have a very low exposure (*Sweden:* 21,48,261,307,694,737,861, 862,885; *Norway:* 157; *Denmark:* 296,474,513).

Within the Western countries, the relative importance of different sources of lead exposure varies; in Scotland lead exposure through plumbosolvent drinking *water* is prevalent (524), in other areas, *petrol* is a major cause of exposure (636,775), in some areas of the U.S.A. and in some states of Australia lead-based house *paint* (625,865,881), and in other local areas *industrial emissions* (53,432,621). Children in urban areas have higher exposure than those living in rural areas (48,109,275,435,571,692,694,737). There have been major changes of the importance of the lead sources.

In many countries, there has been a major reduction of lead in petrol (48,694, 737), which has resulted in a reduction of air lead levels in urban areas (337), and is probably also the explanation of the decreasing lead exposure in many countries (Section 2.1.4).

The geographical variation in exposure is reflected by large differences in B-Pbs in different areas (Section 3.7.1.3).

2.1.4. Time pattern

The exposure to lead has increased from the preindustrial era (258,292,304,328), in some areas more than one order of magnitude (608).

In several industrialized countries, the lead exposure in the general population now seems to decrease rather rapidly (*Germany:* 205,724,831; *Italy:* 238,276; *U.S.A.:* 24,636; *U.K.:* 218,222,224; *New Zealand:* 346, 486; *Sweden:* 48,214,692,694,737; *Greece:* 140; *Denmark:* 296; *Belgium:* 194; *South Africa:* 314a), probably as a result of actions taken against such sources as lead in petrol (337), lead in canned food, lead contamination of drinking water, and/or industrial emissions.

2.2. Occupational settings

In addition to the exposure from the general environment, many *occupational settings* imply exposure to lead. Between 100 and 200 diffrerent lead-exposing occupations have been listed. Some of those are found in Table 1.

Table 1. Work tasks which cause or may cause risk for lead exposure (after 341,554,555, with additions).

High risk	Moderate/low risk
Primary and secondary lead smelting	Lead mining
Production of lead paint	Plumbing
Spray painting with lead paint	Cable industry
Flame welding and cutting in lead-painted metal	Type casting in printing shops
	Stereo-type composing
Blasting or scraping of lead-painted metal	Lead casting (tin casting)
	Lead soldering (tin soldering)
Ship breaking	Car repairing
Brass foundry work (including bronze)	Porcelain manufacturing
Storage battery manufacturing	Earthenware manufacturing
Addition of lead stabilisator or lead pigment to polyvinylchloride	Crystal glass manufacturing
	Glass painting
Car radiator repairing	Electric welding in lead-painted metal
Annealing of enamel	
Ammunition work	Sulfuric acid production
Indoor shooting	Application of lead arsenate pesticides
Aluminum forging	
	Wire-drawing
	Rubber-tube drawing
	Tool hardening

Lead paint for anti-corrosion purposes often contains much more lead than house paint, up to 70-80% lead (146). Flame-cutting in metal painted with such paint causes a considerable risk (63).

Most lead workers are males. This is illustrated by the fact, that at the Institute of Occupational Health in Helsinki, in the period 1973-83, over 55,000 B-Pb determinations were made in males, against only 7,464 in women (455,771). The latter group contained 2,068 samples obtained from 802 women, who had been pregnant during the period.

Rather few women have a high exposure. Among 206 women, who were studied in a (inconclusive) case-referent study of spontanous abortion, B-Pb determinations had been made within one year before or during pregnancy in 49. Out of those, only six had levels $\geq$1.4 (up to 3.1) µmol/l (771).

In the occupational setting, exposure occurs both through inhalation (air and contaminated tobacco smoking; 346b,606) and through ingestion of contaminated food, drink, and snuff (500a).

It is out of the scope of this paper to give an account for lead levels in air in different occupational settings. However, it may be mentioned, as an example, that average concentrations in the range 0.05-0.2 mg/m^3 (647) and 0.01-0.03 mg/m^3 (346b) were found in different parts of a U.S. storage battery plant. In a brass foundry, the mass median diameter of the particles was 3-12 µm (about 5% $\leq$1 µm) in different operations, in a primary lead smelter 2-7 µm (25-46% $\leq$1 µm; 264) and in two battery-plants 11-23 µm ($\leq$11 % $\leq$1 µm; 346a).

Children to lead workers have, in several studies, had higher blood lead levels than other children (109,141,146,294,399,414,646, 694,865). Occupational lead exposure in pregnant females is associated with increased lead levels in cord blood (886). Also, increased lead levels have been found in blood from pregnant women (886) and cord blood from newborn infants (53) in the families of male lead workers. Even lead toxicity has been claimed to have occured in children to lead workers (146). Of particular importance for this indirect exposure is bringing home and washing of work clothes ("carry-home exposure"; 886).

2.3. Methods for evaluation of inhalation exposure

Air levels of lead may be estimated by use of area sampling or personal sampling; the latter gives a more reliable estimate of the individual exposure than does the former, and should thus be preferred (448,842).

At personal sampling, the lead particles are collected on a filter, through which the air is drawn by use of a pump. The air volume sampled is adapted from the sensitivity of the analytical method, which will be used; at sampling in the occupational setting, about 100 l is usually fully adequate.

In the Nordic countries, atomic absorption spectrometry (AAS) is the most widely used analytical method. It may have a sufficient sensitivity (about 1 µg/sample) and precision (448,807); this corresponds to about 10 µg/m^3 in a 100 l air sample. Earlier, the colorimetric dithizone method was widely used, and it is still employed in some areas of the world. Non-destructive metods, as X-ray fluorescence (XRF; 313) and particle induced X-ray emission (PIXE; 433), require more expensive quipment.

3. Kinetics

There are several recent reviews on the metabolism (pharmacokinetics, toxicokinetics, biokinetics) of inorganic lead in man (135,136,352, 806).

3.1. Absorption

3.1.1. Airways

The pattern of deposition of inhaled lead in the respiratory tract is affected by the particle size of the inhaled aerosol and the ventilation rate (see below).

Particles with an aerodynamic diameter above 5 µm are mainly deposited in the upper airways, cleared by the mucociliary mechanism, and swallowed. Some of

this lead is then absorbed from the gastrointestinal tract. Particles with a diameter below 1 μm are, to a large extent, deposited in the alveolar region of the lung.

For particles inhaled via the mouth, and with a size in the range 0.01-5 μm, 10-60% are deposited in the alveolar tract (121,136,137,314b,400,401,806). At a particle size of 0.05 μm and a respiratory rate of 15/min, about 40% of the inhaled lead is deposited in the airways; at a particle size of 0.5 μm, the deposition is lower, about 20% (136). For particles inhaled via the nose, the fractions are lower. A major fraction of larger particles is deposited in the nose, mouth, and upper parts of the airways; a large part of this is cleared and swallowed. It is possible that subjects breathing mainly through the nose have a deposition in the nose, thus avoiding exposure in comparison with subjects breathing mainly through the mouth.

Most of the lead deposited in the alveolar part of the lung is absorbed. The rate of absorption is dependent upon solubility of the chemical species of lead. In human radiotracer experiments, the absorption has usually been completed within 24 hours (136,361,529). Such a rapid absorption is in accordance with the lack of accumulation as regards pulmonary lead content in deceased lead workers in comparison with subjects without occupational exposure (64). On the other hand, increased levels of lead has been found in dead lead workers, who had been exposed to a lead compound with low solubility (lead sulfide; 111,269).

3.1.2. Gastrointestinal tract

Lead is absorbed from the gastrointestinal tract. In radiotracer experiments in fasting subjects, the absorption was 37-70% (average about 60%) according to different investigations (91,252,335,383,634). Of soluble lead salts taken with meals, 4-21% (average about 8%) have been resorbed (90,383,528,634).

From studies of the uptake of stable lead in adults, an average absorption of 15-20% may be estimated (136,314b,400).

There are indications of a higher gastrointestinal absorption in children than in adults (16,887). In adults, there seems to be a considerable inter-individual variation in lead uptake from the gut (89,361). In rats, very large doses were absorbed less efficiently than small ones (52). In humans, there was no effect of moderate lead doses on the fractional uptake of lead (136,252,335).

Effect of nutritional status on the absorption will be discussed in Section 3.6.

3.1.3. Skin

A fraction of *inorganic lead* salt applied on the skin is absorbed (254,453). In one study, the absorption was only 0.06% in one month (528).

Probably, the absorption of *lead soaps* (lead naphtenate and lead stearate) is considerably higher (675). One case of toxicity has been attributed to percutaneous absorption of a lead soap (18). In the industrial setting, lead absorption has been reported in subjects exposed to lead soaps (69,128,279,580). However, probably, at least part of the lead was absorbed through inhalation.

3.2. Distribution

3.2.1. Blood

Lead is absorbed into the blood *plasma* (and the lymph, which is later emptied into the blood plasma). Little is known about the binding of lead in plasma at "realistic" concentrations. In lead workers, 5-25% of the plasma lead was ultrafiltrable (33). The rest of the lead may be bound to proteins, mainly albumin (523). Some of the plasma lead probably represents very recent absorption. Lead rapidly equilibrates between plasma and extracellular fluid.

More slowly, but within minutes, lead is tranferred from plasma into *blood cells*. Within the blood, 99% of the lead content is in the red cells, only from less than one to a few percent in the plasma (26,38,126,129,130,163,199,379,401,490, 492,580,584). There are some indication that the relative plasma level is higher in workers exposed to lead stearate (127) and lead naphtenate (580) than to other forms of lead.

Lead to some extent binds to the erythrocyte membrane (523,582). However, in the red blood cells, a large fraction of the lead is bound to hemoglobin (582), but also to a 10,000 molecular weight protein, which is possibly induced by lead exposure (280,463,641,642), and to a protein fraction displaying ∂-amino levulinic acid dehydratase activity (ALAD; 671; Sections 3.6 and 3.7.3.1). Fetal hemoglobin has a higher affinity to lead than adult (582). The relative distribution within the blood cell seems to be dependent upon individual factors and the intensity of the exposure.

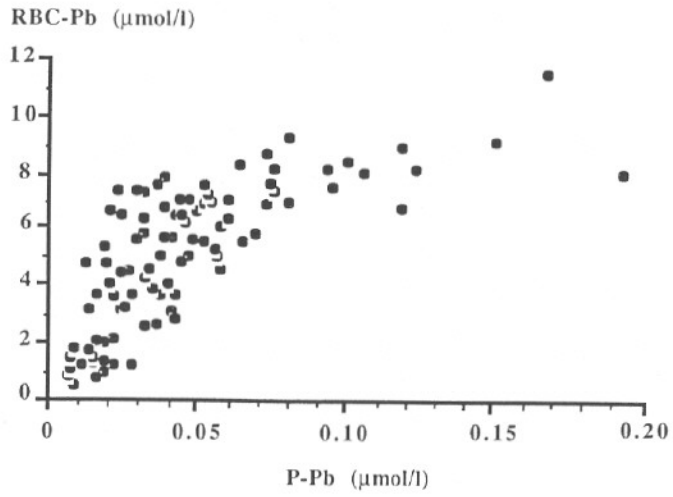

Figure 2. Relationship between lead levels in plasma (P-Pb) and blood cells (Ery-Pb) in 103 lead workers. Data from De Silva (199).

It should be noted, that the binding of lead in erythrocytes may vary between different species, which may affect the relationship between B-Pb on the one hand, and exposure, organ levels, and effects, on the other.

The ratio of lead content in red cells and plasma is *not* constant over varying total blood-lead levels. Thus, the fraction in plasma rises with increasing blood lead concentration (199,490; Figure 2). This is probably due to a saturation in blood cells. It is thus reasonable to assume, that the lead level in whole blood, over a wide range of concentrations, not has a constant relation to levels in other organs (55).

Lead is also distributed to the *bone marrow*. The levels at that site seem to be similar to those in blood (734).

3.2.2. Soft tissues

From the blood plasma the absorbed lead is distributed to other organs. Among the soft tissues, the *liver* and the *kidney* attain the highest concentrations (55,64,111,382,734). In the kidney and liver, lead occurs as intranuclear inclusion bodies (88; Section 5.3.).

Lead does, to some extent, pass the blood-brain barrier (64,734). The distribution within the *nervous system* is uneven, with high levels in the hippocampus and the amygdala (289). Particularly high levels are present in the choroid plexus (262,490). Judging from animal experiments (480), the degree of passage of lead into the nervous system is probably higher in children than in adults. The lead level in cerebrospinal fluid is very low (162,490,492,757); it is correlated with plasma lead (though even lower), but not with B-Pb (128). In the brain, there are high-affinity lead-binding proteins (259). Also, possibly, there is a binding of lead to melanin (438).

In animal experiments (52,345,436), there is no constant relationship between levels in blood and in soft tissues. Thus, the accumulation in liver and kidney is higher than in blood, while it is lower in the central nervous system (CNS). The peripheral nervous system (PNS) may accumulate considerably more lead than the CNS.

Lead is distributed to the *gonads* (806). Also, lead accumulates in the male reproductive tract (testis, epididymis, seminal vesicles, and prostate; 389). Also, there is an incorporation in the *seminal fluid*.

Lead is also transferred into the *fetus* and *milk* (Section 3.4.3).

3.2.3. Skeleton

A large proportion of the absorbed lead is incorporated into the skeleton (64,205, 207,297,317,878). About a fifth of a single dose was deposited in the skeleton (336). The skeleton contains more than 90% of the body burden of lead; in lead workers, that fraction may be even higher (64).

The lead content in the skeleton is not a homogenous pool. By analogy with calcium, there is probably a small but rapidly exchangeable skeletal lead pool. In addition, there are at least two other pools: One is contained in *trabecular bone* (64). In addition there is a lead pool in the *cortical bone* (152,153,459,549,638,734,747-

750,774). The skeleton contains about 20% trabecular and about 80% cortical bone, but the surface area of the two types of bone is similar. Thus, the turnover of the trabecular bone lead pool is much faster than that of the cortical one (698; Section 3.5.3.).The turnover rate of lead in the skeleton is probably higher in infants than in adults (136).

The lead content in the skeleton in subjects *without occupational exposure* varies in different areas of the world. It was very low, probably a few milligrams in prehistoric subjects living in a world without traffic and industries (231,292), about 10 mg in contemporary Scandinavians (288,297,698), and it is about 100 mg in subjects from the U.K. (64) and the U.S.A. (231,315,373,400).

In *lead workers*, the lead levels in bone are high (8,9,64,152,153,268,270,271, 281,297, 406,458,459,549,698-700,734,747-750,774,841,856). High levels have also been found in subjects with extreme lead exposure from *other sources* (209,625), including persons who died with lead toxicity (253,281,376,689). In heavily exposed subjects, the skeletal lead content may be in the order of magnitude of one gram.

There is a continuous turn-over of the skeleton. This causes a release of lead from the skeleton, and an endogenous lead exposure (Section 3.7.1.2).

3.2.4. Chelatable lead

After administration of a chelating agent, there is an increase of excretion of lead in urine (699,772,774; Section 3.7.4.5). The lead excreted has been referred to as "chelated lead" (772), and is a reflection of a body burden of chelatable lead (41). The anatomical position has not been fully elucidated. Probably, it is mainly located in the soft tissues (699,774), but it may also include a fraction of the skeletal body burden (699,774,818,856).

A dose of 20 mg calcium disodium edetate ($CaNa_2EDTA$) per kg body weight in lead workers, washed out 14% of the body burden of chelatable lead (which was about 10-20 mg; 27,41), which, in turn, however, is only about one percent of the total body burden (64,734).

3.3. Biotransformation

There is some circumstantial evidence that inorganic lead may be methylated by microorganism, but there is no conclusive evidence (173). It is not known whether this may occur in the gastrointestinal tract. There are no indications of methylation or any other biotransformation in the tissues.

3.4. Elimination

Lead is exreted from the body mainly through the urine and the feces, but there are also other, minor routes of elimination, which have a practical importance.

3.4.1. Kidneys

The excretion into urine is through glomerular filtration (32,37), probably followed by partial tubular reabsorption (37).

There is a circadian rythm in urinary lead excretion rate, both in unexposed subjects (40) and in lead workers (28), with a decrease during the night. Further, the excretion rate is affected by urinary flow (Section 3.7.2).

There is a correlation between lead levels in urine and whole blood (490,696, 733,774,785). However, the association is not linear; the urinary lead level increases relatively more than the blood lead concentration, probably exponentially. A possible explanation of these observations is a dependence of urinary lead primarily upon plasma lead, which, as said above (Section 3.2.1), seems to increase relatively more than the whole blood lead level. Indeed, there seems to be a linear relationship between plasma lead and urinary lead (490). There may be a considerable inter-individual variation in the urinary lead excretion at a certain B-Pb (733). In one study, there was an inverse relationship between B-Pb and renal lead clearance (123a).

3.4.2. Gastrointestinal tract

Lead is also excreted throug bile (378) and pancreatic juice (377), and apperas in feces (638). Possibly, the excretion in bile is in the form of a lead-glutathione complex (17). At low exposures, the excretion in the feces is about half that in the urine, at higher levels probably relatively smaller.

3.4.3. Other routes of elimination

Lead is also, to some extent, excreted in sweat (401,638). Amounts without practical importance (besides, possibly, for biological monitoring, see Section 3.7.4.2) are excreted in nails and hair (637).

Low levels of lead have been found in the semen in males without particular exposure (119,615,666,806). It seems, that a significant fraction of the lead originates from the prostate or the seminal vesicle (119). Further, lead workers have increased lead levels in the seminal fluid; the semen levels were about one tenth of those in blood (47).

Lead is deposited in the placenta (359,405,416,680). There was a correlation between levels in maternal blood and in placenta (680). The levels in placenta were higher in occupationally lead-exposed women than in non-exposed ones (405,833). Further, the lead concentration increased with time of exposure. Low level of lead are present in amniotic fluid (412).

Also, lead passes the placental barrier causes exposure of the embryo and the fetus in experimental animals (114,187,198) and in man (62,99,405,502,609, 864). There was a correlation between lead levels in placenta and in cord blood (680). The distribution in the fetus seems to be similar to that in the adult organism (62,405,502, 864). However, in this connection, it should be mentioned, that least in experimental animals, the growing organism accumulates higher levels of lead in the CNS than does the adult animal (520). Also, results of experiments with lead

treatment before mating, indicated a mobilisation of the lead stores during pregnancy, and transferrence to the fetus (114).

The blood-lead level in the child at birth is associated with that in the mother; the concentration in the child is somewhat lower than in the mother, in whole blood (15,62,235,359,405,416,422,428,513,524,583,672,782,793,883,885), as well as in red cells and plasma (130) and serum (363; though the levels in this study seem high).

There is usually a decrease of B-Pb in the beginning of the pregnancy (15,97), probably mainly because of expansion of the plasma volume. This change may perhaps be counteracted by a mobilization of lead from the skeleton during pregnancy, which may cause a transfer of lead to the fetus (672,806). After delivery, there was an increase of B-Pb, which indicates that this skeletal mobilization is at least limited (232).

In addition, there is lead excretion in milk, probably of lead mainly bound to casein (70). In the cow (596,773 and rat (604), there is an exponential increase of lead levels in milk with increasing B-Pb. In the rat (604) and mouse (402), there is a linear relationship between lead levels in plasma and milk. In the rat, the ratio of lead in milk and plasma is 8 (604), in the mouse 25 (402). Calcium has a similar high ratio. In the mouse, the elimination of lead from the dam was increased during lactation (402). Lead in the milk is absorbed by the offspring. Further, in the rat, the lead transferred from mother to offspring during lactation probably exceeded transfer during gestation (420). Moreover, in rats exposed before mating, there were indications of a transfer of lead from the dam´s skeleton to the suckling pups (114). However, coprophagia by the pups may have caused an overestimate of uptake through milk in some animal studies (535), especially at oral exposure of the dam.

Low levels of lead are found in human milk, generally in the order of 10 nmol/l (184,422,428,429,437,524,633,652,680), possibly higher in colostrum than in mature milk (756). In some studies, higher levels have been claimed (358,583), possibly because of analytical problems; analytical quality control data was not reported. The concentration is associated with, but considerably lower than the level in the woman' s whole blood (2-9%; 422,428,524,652,680; a considerably higher fraction was reported in ref 583). The levels in milk are certainly higher than in blood plasma. There was a correlation between lead levels in milk and B-Pb in the breast-fed infant (428,633).

The levels of lead in breast milk from women without particular exposure to lead do not differ significantly from levels in milk formulas (184,422,429). Accordingly, B-Pbs did not differ between breast-fed and formula-fed infants (466,665).

3.5. Compartment model

3.5.1. Number of compartments

Already from a theoretical point of view, it may safely be assumed that the metabolism of lead involves a large number of different compartments with varying lead and kinetics. However, from a practical point of view, it is important to find a

sufficiently simple model, without disregarding completely the possibility of reasonably accurate predictions.

Different authors have argued for one (251), two (8,630,700,754), three (154,373,549,638), four (85,136,251,731,733), five (84,413), and seven (496) compartments, in models of human lead metabolism.

Rabinowitz et al (638) analysed data from experiments in humans exposed to relatively low dietary doses of labelled lead. They found a better fit of a three-compartment linear model, as compared to a two-compartment one. On the other hand, another group tried one, two and three compartments on sets of curves for blood lead decrease in former lead workers. They found a good fit for a two-compartment linear model (700,734). However, three compartments gave a slightly better fit (549).

Based upon the above-mentioned information, at least four compartments must be assumed: Plasma and extracellular fluid, soft tissues (including blood cells and probably a small, rapidly exchangable fraction of the skeleton), trabecular bone, and cortical bone (Figure 3).

From a practical point of view, a two-compartment linear model may be useful, especially for evaluation of B-Pb data.

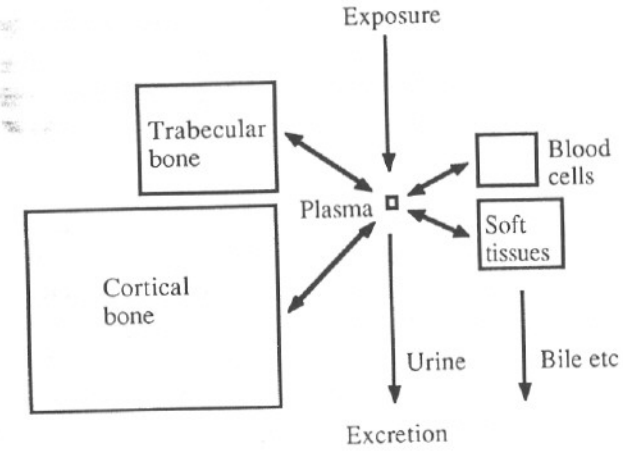

Figure 3. Metabolic model for inorganic lead in man (733). "Plasma" denotes blood plasma and extracellular fluid.

3.5.2. Mathematics

The next problem is to choose suitable mathematical expressions for the transfer of lead into and out from the different compartments. Sometimes non-linear power functions have been employed. However attractive mathematically, as regards possibilities to obtain a nice fitting to empirical data, power functions have a limited value from a conceptual point of view. In that sense, linear exponential models are more useful.

Is a linear model applicable to lead metabolism? There are data indicating non-linearity, e.g. as regards the relationship between lead levels in air on the one hand and lead levels in blood on the other (Section 3.7.1.4), as well as between lead levels in erythrocytes and plasma (Section 3.2.1) and blood and urine (Section 3.4.1).

On the other hand, data on blood lead does not indicate concentration-dependent kinetics, as similar elimination rates have been noted both at very low and very high levels (126,638,700,734). Thus, a linear multiexponential model may be used practically.

3.5.3. Turnover rates

The turnover rates in a linear exponential model may be expressed as transfer constants, mean residence times, or half-lives. Here, half-lives will be used.

The turnover of lead in blood plasma is very rapid; the half-life after intravenous administration was about one minute (124).

The half-life in the blood/soft tissue compartment(s) of adult man is 3-4 weeks (549,638,700,734). The kinetics for blood lead is also discussed in Section 3.7.1.2.

The half-life of lead in finger-bone (mainly cortical bone) about a decade (153, 549); in vertebra (mainly trabecular) it is considerably shorter (698). A few months after end of lead exposure, the lead levels in blood mainly indicate the decrease in the skeleton (298,549,700). Such data are also in favour of an average half-time for parts of the skeleton of about one decade (356,549,700, 734), for other parts about a year (549).

This suggested turnover fits with a series of other estimates, by use of a metabolic model (794), and data on decrease of radiolead (158,879), lead in bone biopsies (281,841), and blood lead (36,356). However, it is faster than has earlier been estimated (biological half-lives of 8-71 years) on the basis of bone remodeling (384), various metabolic models (84,251,352,754), and *in vivo* measurements of decrease in radiolead (160). Recent data indicate that the calcaneus and tibia may have half-times of 2-3 decades (231a,268).

The slow turnover of the skeletal lead pool is also shown by the relatively slow rebound of blood lead after chelation therapy, which has radically reduced the soft tissue pool; the doubling time is about one month (356). The chelatable lead also decreases only slowly after end of occupational exposure (36). This is probably due to the fact that it is dependent upon the bone-lead pool (699,774).

The data on the elimination of lead from blood during a long time after cessation of exposure indicate an inter-individual variation in skeletal lead kinetics (700). Indications of such a difference has also been reported in dogs (251).

The inter-individual variations in kinetics of lead metabolism, both in soft tissues and in bone, probably means a large difference between individuals in soft tissue and skeletal lead levels at a certain rate of absorption, and an accordingly different risk of adverse effects. Subjects who have a high elimination from the body are of course favored. However, it is not possible to define, at this stage, whether a rapid turnover of the blood lead is an advantage. It could mean a rapid elimination from the body, which, of course, is an advantage, but it may also mean a high degree of incorporation of lead into the skeleton, which will mean a detoxification on a short-term perspective, but will cause a higher endogenous lead release in the future.

As to kinetics of B-Pb, see also Section 3.7.1.2!

3.6. Factors which affect the metabolism and effects

Age is an important determinant of lead metabolism (806). Thus, as said above (Section 3.1.2) infants *absorb* lead from the gastrointestinal tract to a much larger degree than older subjects. Also, in infants the lead probably passes the blood brain barrier easily (Section 3.2.2).

In humans, simultaneous intake of lead on the one hand, and *calcium* or *phosphate*, on the other, may cause a reduction of gastrointestinal lead absorption (90,91,136,335,336,383). In a small study, supplementation with calcium caused some decrease in the B-Pb in lead workers (527).

Milk is a major source of calcium and phosphorus. For over a century, milk was recommended as a prophylatic for lead toxicity in industry. However, milk increases the lead uptake to a higher level than is expected from its content of calcium and phosphate (91,383). Lead salts and milk lead are absorbed in different modes (340). In the rat, during lactation, there is a sevenfold increase of gastrointestinal lead absorption (420).

Milk is a complicated food. It contains several components that may account for the enhancement of lead absorption. It is not known which factor is responsible for the increase of lead uptake. The uptake from skimmed milk is as good as from whole milk (383). Lactose has a limited effect (252,383). Lactoferrin may have an increasing effect (626).

Phytic acid decreases the absorption (383,791). Uptake of lead is increased by *alcohol* (383).

In animal experiments, *iron* decreased the absorption of lead (479,792,806). In man, there was no such inhibition (252). In man, a deficient iron status seems to increase the gastrointestinal absorption (479,792,806) and blood levels (53,513) of lead, although this has not always been found (252,344). The lack of iron in milk is not the reason for its effect on lead absorption (421).

Further, in animal experiments, *vitamin D*, *protein*, and *fat* increased, and *zinc* decreased, the absorption of lead (479,792,806).

In addition to an effect on the gastro-intestinal absorption, low dietary calcium, and certain other nutrients (iron, zinc, selenium, and fat) may affect the *distribution* of lead in the body in animal experiments (479).

The effect of the *selenium* status on the lead metabolism seems to be limited in man (319).

A release of lead from the large skeletal pool may occur during *pregnancy*, *lactation*, and *menopause*, and because of other conditions causing a breakdown of bone tissue (see Section 3.7.1.2).

Also, concommittant exposure to *other chemicals* may probably affect the metabolism of lead. Dithiocarbamates, a group of chemicals used as fungicides and in rubber processing, and as a drug in the treatment of alcoholics (disulfiram, Antabus®), in experimental animals markedly affected the distribution of lead (562,586-589,595,597,599). There was a decrease of lead levels in blood and bone and an increase in the brain. Further, the transplacental passage of lead increased, as did the lead levels in the CNS and the fetus. Disulfiram, in rats, decreased the lead excretion in milk. This can be explained by *in vivo* formation of a lipophilic lead-dithiocarbamate complex. Ethylenediaminetetraacetic acid (EDTA), which has a wide industrial use, affects the metabolism of lead (551).

Moreover, the *effect* of lead may be affected by dithiocarbamates. Thus, in *animal experiments*, disulfiram plus lead induced marked behavioural and neurochemical effects (599) and increased the effect on hem synthesis in the bone marrow, although ALAD in blood, liver, and kidney was not affected (590). However, ALAD in rat hepatocytes was inhibited by a lead-dithiocarbamate complex (594) Further, formation of intranuclear inclusion bodies in proximal tubuli of the kidney was inhibited (595).

Iron deficiency aggravates the effect of lead on heme metabolism (Section 3.7.3.4).

Zinc does, to some extent, affect the inhibiting effect of lead upon the zinc-containing enzyme ∂-aminolevulinic acid dehydratase (ALAD activity; 2,3,5,82, 324). A lead-induced blood-cell ALAD-depression may be partially reversed *in vitro* by addition of zinc. Thus, theoretically, the zinc status of the lead-exposed individual might be of importance. Further, simultanous zinc exposure might affect the dose-response relationship between lead and ALAD.

However, occupational zinc exposure causes only minor effects (510). Of the other metals, mercury compounds (methylmercury: 82,695) and aluminum (82) seem to have a slight effects on the ALAD activity.

The ALAD activity is also affected by ethanol intoxication (101,324).

Selenium decreases the cytogenetic effect of lead in lymphocytes *in vitro* (72).

In *humans*, based upon studies of nerve conduction velocities in lead workers, it has been claimed that zinc absorption decreases the negative impact of lead (42,43).

It has been proposed, that there is an inter-individual variation in induction of a lead-binding red-cell low molecular weight protein, which might explain some of the difference in effects (641,642; Sections 3.2.1 and 3.7.3.1).

There are species differences in the effects of lead on heme synthesis (788). Certain unusual *inborn errors of metabolism* may increase the susceptibility to lead (781). Thus, heterozygoty for ALAD porhyria causes a disturbance of heme metabolism (202). Such subjects have only half the ALAD acticity and predisposes for lead toxicity (203,204). The prevalence of this condition is less than 1% in Germany (203). Probably, also other acute hepatic porphyrias predispose in a similar way (65).

Further, it has, on the basis of a few case reports (12,142) been claimed that glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and the thalassemic syndromes may increase the susceptibility at lead exposure, mainly by causing an increased risk of hemolysis and anemia. However, very limited firm information is available. It has been claimed that the G-6-PD activity influences the lead absorption in children (505). However, in a study of lead workers, G-6-PD deficiency did not affect B-Pb or protoporphyrin response, while ß-thalassemia carriers had higher lead levels in erythrocytes (possibly because of a higher content of fetal hemoglobin, which has a high affinity for lead, Section 3.2.1), and a lower protoporhyrin response at a certain B-Pb (142). Further, it has been claimed that the hemoglobin disorder sickle cell anemia predisposes for lead neurotoxicity (374). These genetic traits may perhaps be one reason why there is a striking inter-individual difference in susceptibilty to lead exposure (Section 3.7.1.5). It is interesting to note, that there is a striking similarity in the clinical picture between acute hepatic porphyria and acute lead toxicity.

3.7. Biological exposure indicators

There are several recent reviews on biological monitoring of lead exposure (342,729,806).

3.7.1. Lead level in blood

3.7.1.1. Sampling and analysis

Blood lead levels are usually determined from analysis of venous blood (248). Sometimes capillary blood has been employed. The level in capillary blood may be higher than in venous blood (483), due to higher packed cell fraction and contamination from the skin, the difference being dependent upon the sampling technique. It is important that the skin is carefully cleaned before sampling.

As lead in blood is mainly present in the blood cells, levels in blood cells would be a suitable measure. But for practical reasons, levels in whole blood are usually employed. Levels in plasma may contain information of the most recent lead absorption (see above). However, the very low levels cause serious problems, mainly through contamination. Thus, plasma-lead levels have no practical use.

The packed cell volume may vary, as a result of lead exposure, or for other reasons. To be able to make a fully accurate evaluation of a whole-blood lead level, it is thus advisable to determine the packed cell volume (hematocrit) or hemoglobin level in connection with the blood-lead analysis. However, in practice, this is seldom done as a routine. However, in conditions with increased packed cell volume, such as heart or lung diseases, it may be advisable, as otherwise too high readings may be obtained (769).

Nowadays, blood-lead levels are usually analysed by atomic absorption spectrometry, either flame or flameless (electrothermal). Also, anodic stripping voltametry is employed widely. The colorimetric dithizone method was widely used earlier, but is very time consuming, and has thus been abandoned.

The analysis may cause considerable errors. A precision of 10% (coefficient of variation) is not unsusual, at least at low levels. It is important to employ a rigid quality control program, both internal and external (169,260,454).

Traditionally, blood lead levels are given as µg/100 ml (µg/dl). This way of expressing concentrations is obsolete. Thus, in this paper, µmol/l will be used (1 µmol/l=207 µg/l, 200 µg/l=0.96 µmol/l).

3.7.1.2. Kinetics

In subjects without occupational exposure, the whole blood lead levels may be remarkably stable over time (197). After a rise of the exposure intensity, the lead level in blood increases gradually, usually to reach a steady state after weeks to months (152,314b,401,447,546,785). However, after a heavy exposure, the level may rise by ten-fold within a few hours (199,696).

As mentioned above (Section 3.5.4), after cessation of exposure, the blood lead level decreases. There is an *initial* rather rapid decrease, later on the decrease is slower (Figure 4). In *adults*, the average decline rate is compatible with an initial phase with a half-life of about one month, if a second, slow phase is taken into consideration (8,137,199,314b,395,400,401,467,549,570,638, 700,734).

Data on the elimination of lead from whole blood after cessation of exposure indicate an inter-individual variation (549,700,734), which exceeds that of the uncertainty in the estimates of the true slopes. There are some indications, that the elimation rate may decrease with increasing age (356,700). Further, the elimination of blood lead may decrease in subjects with renal impairment (356). During treatment with the chelating agent $CaNa_2EDTA$, the half-time of blood lead is only about one week (356), at treatment with a combination of $CaNa_2EDTA$ and hemodialysis for a few hours (500,741; but not with dialysis alone). Also, the scarce data on hand may indicate, that the half-life in blood is somewhat longer in infants and children (664,691,759).

The decay rate of the *slow phase* has a half-life of about half a decade years in adults, again with inter-individual variation (694). Analysis by one-compartment kinetics may thus give an entirely misleading picture of the blood-lead kinetics. Probably, the slow decade has two components, one with a half time of about a year, the other one about a decade (549). A similar decay rate may be assumed from limited data in children (518).

The slow phase is dependent upon release of lead from the skeleton into the blood stream (152,549,700,734). This causes an endogenous lead exposure, which is dependent upon the skeletal lead pool (152,153,698,700), and which may be both considerable and long-lasting (14,152,153,170,298,546,624,698,700,734).

In a group of lead workers, the impact of the slow compartment corresponded to an average of 1.8 µmol/l, about 64% of the total blood lead level, and it ranged as far as up to 2.7 µmol/l (700,734). The relative importance of the skeletal lead pool is, of course, also dependent upon the rate of recent absorption. Thus, the fraction is usually higher in retired workers than in active ones (8,700). In subjects without occupational lead exposure, fractions of 10-70% have been estimated (136,352, 488,489). Probably, the true figure is closer to the latter than to the first one. In children, in whom the turnover of the skeleton is about ten times faster than in

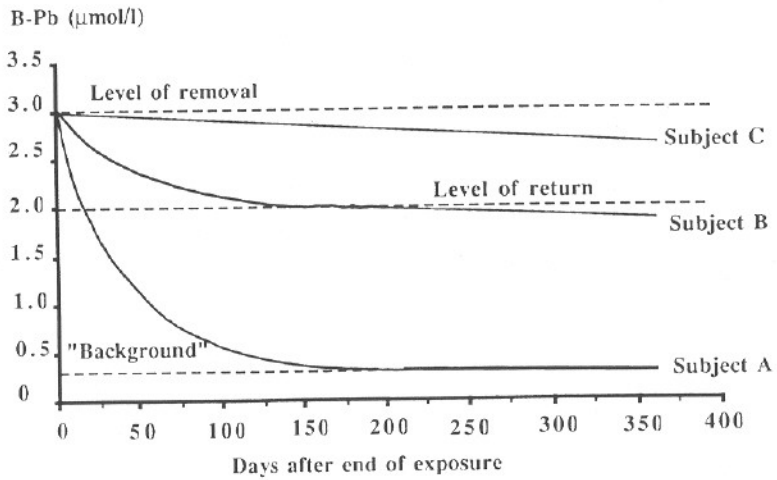

Figure 4. Decrease of blood lead (B-Pb) after end of occupational exposure. It has been assumed that workers are removed at a B-Pb of 3.0 µmol/l. Subject A has a very low skeletal lead burden, Subjects B and C have skeletal burdens giving B-Pbs of 1.8 µmol/l and 2.7 µmol/l, respectively. A B-Pb of 2.0 µmol/l has been indicated ("return level"). A "background" B-Pb, caused by non-occupational exposure, of 0.3 µmol/l, has been assumed. The estimates are based upon data from Schütz et al (700); it has been assumed that the elimination has two components with half-times of 30 days (soft tissues) and 5 years (skeleton), respectively.

Sweden has, as from January 1 1993, a level of removal, for men and women under 50 years of age of 2.5 and 1.5 µmol/l, respectively. Level of return is <2.0 and 1.2 µmol/l, respectively (43a).

adults, the impact of skeletal lead should be considerably larger; the problem has not been studied.

The endogenous exposure from the skeletal pool, and thus the B-Pb, may increase during periods of skeletal break-down, such as pregnancy and, in particular, lactation (animal experiments: 114; human data: 489,664,718,778), and menopause (720; Section 3.7.1.2.). In lead workers, in theory, bone destruction may cause a substantial exposure (8). It has even been claimed, that extensiv destruction of the skeleton of lead workers, e.g. by bone tumours (316,691) or progressive osteoporosis (711) have caused "endogenous" lead toxicity.

The decrease pattern of blood lead after end of occupational exposure depends on the skeletal lead burden and the "background" of non-occupational exposure (569,700). If a worker is removed at a level of 3.0 µmol/l, if the background is low, and if the skeletal lead level is low (short duation and/or low intensity of the exposure), the worker may reach 2.0 µmol/l already after about three weeks (Figure 4). A worker with a skeletal lead burden causing a blood lead level of 1.8 µmol/l, would reach 2 µmol/l after about 5 months, while in one with a skeletal impact of 2.7 µmol/l it would take years. The estimates are based upon data from Schütz et al (700); it has been assumed that the elimination has two components with half-times of 30 days (soft tissues) and 5 years (average of the two skeletal compartments), respectively.

One possibility, in epidemiological studies of long-term effect of lead exposure, is to use the time-integrated blood lead level as an exposure index (152,268,270, 271,365,698,700).

3.7.1.3. Reference values

It has been estimated, that the B-Pb in early, preindustrial human was only in the order of 0.025 µmol/l (608).

Today, B-Pb in subjects without occupational exposure varies with age (children, especially 1-3 year olds, have higher levels than adults; for data see ref 135), sex (males have higher levels than females; postmenopausal women higher than premenopausal ones; 753), drinking and smoking habits (drinkers and smokers have higher levels; ref 214), and with area of living.

In areas without industry and traffic, the average level is about 0.15-0.25 (614,620).

In Sweden, the average level is about 0.4 µmol/l in males and 0.3 µmol/l in females (Figure 5; 20,94,110,214,261,765). In children, the B-Pb is lower, in average about 0.2 µmol/l (21,48,307,692,694,737). Among children, those below one have a higher levels than the older ones (135,804,806).

Similar levels have been recorded in other parts of Scandinavia (157,474,513, 576). In Denmark, there was a seasonal variation, with a winter maximum and a summer minimum (576).

In other areas, the levels may be considerably higher, up to in average 1 µmol/l (261). In some population strata, almost one fifth have had levels above 1.5 µmol/l (483).

The blood lead levels are rapidly decreasing over time in many countries (Section 2.1.4).

3.7.1.4. Relationship between lead exposure and blood lead levels

A long series of studies, both experimental and epidemiological, have been devoted to the relationship between lead exposure and lead levels in blood. Several detailed reviews have been published (112,135,136,138,219,327,803). The matter is far from simple. As mentioned above (Section 2), exposure may occur from various sources: air, food, and drinking water. Especially in children, lead in dustfall, house dust, and soil may be important.

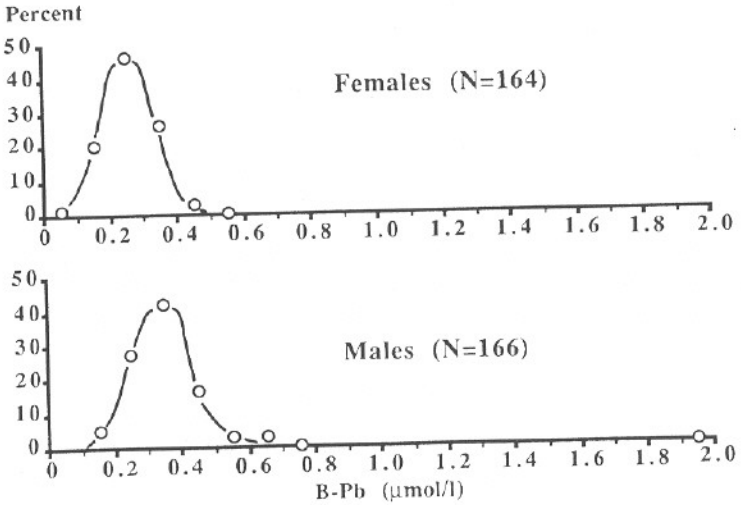

Figure 5. Blood lead levels 1984 in adults (age 20-66) from the county of Blekinge, Sweden. Data from Svensson et al (765), with additions. The mean level in females is 0.27 µmol/l (geometric mean 0.26; median 0.26; 95th percentile 0.53; range 0.10-0.58), in males 0.37 µmol/l (geometric mean 0.35; median 0.34; 95th percentile 0.58; range 0.14-2.0). The male with the highest level had occupational exposure as an auto mechanic.

Simultaneous estimates of all these factors have never been performed in one study. Moreover, in studies where exposure via inhalation has been assessed, area sampling has usually been used, instead of personal sampling in the breathing zone. This may cause problems, e.g. because the difference in air lead levels outside and inside houses. Also, the particle size and solubility of the aerosol, and the pulmonary ventilation affects the absorption. Similarly, relevant sampling of food and drinking water is not easy. Intake may alos occur through contamination of hands and further transferal of lead into the gastrointestinal tract, by "mouthing behaviour" (especially in children), or indirectly by successive contmination of foods. Also, cigarettes and pipe tobacco may be contaminated, directly or through dirty hands, and the lead may be inhaled as a small particle aerosol at the smoking.

However, generally, the studies published have shown a relationship between absorption of lead, both through inhalation (112,135,327,346b,810), through gastrointestinal intake (110,566,716,799), or through both (443, 814). In both cases the relationship is nonlinear, with a slower increased rate of blood lead as the absorption increases.

A U.K. Royal Commission on Environmental Pollution (803) has, on the basis of a survey of available information by Chamberlain (138) summarized the relationship between total amount of lead taken up by the body and B-Pb in adult humans (Figure 6). The conclusions are in agreement with later information. Most of the data comes from population surveys, in which the B-Pb in individuals or groups was correlated with locally measured lead concentration in air and water, experiments in which volunteers are exposed to controlled air lead concenteration and their B-Pb measured, and studies of the lead balance of individuals, estimating the contribution of air and measuring the intake of lead in food and drink. It is not possible to describe the exact form of the curve. Also, there is a considerable range of interpretation of the available information.

In Sweden, the intake through food is about 30 µg/day and through water less than 1 µg/day, of which about 15% is absorbed (Section 3.1.2). The lead level in environmental air is 0.1 $\mu g/m^3$ or less, with a considerable small size fraction (Section 3.1.1.2); it may be assumed that roughly 50% is absorbed (Section 3.1.1.1). It is generally assumed that the ventilation is 20 m^3/day. This corresponds to a total uptake of about 5 µg/day. In studies of populations, the average B-Pb in Swedish males is about 0.4 µmol/l (Section 3.5.1.3), which is within the range given in Figure 6.

In the industrial setting, the several studies which have been devoted to the relationship between air and B-Pb, have shown only poor correlations (346b,810). This may be due to lack of relevance of the air measurements (time, site of sampling, and particle size and solubility). Especially, particle size distribution is important for the absorption (264). Also, the impact of a certain occupational exposure is dependent upon the background exposure from food, drink, and environmental air.

WHO (843) stated that, at air lead levels up to 50 $\mu g/m^3$ (particle size unspecified), and exposure for 40 hours per week, an increase of 10 $\mu g/m^3$ would cause an increase of B-Pb by about 0.25 µmol/l. This is compatible with other estimates (346b,810). It is also in general agreement with the association in Figure 6, if it is assumed that the ventilation is about 10 m^3/work shift, the lead content of food is 100 µg/day (relevant for many countries), the intake through water 1 µg/day, of which 15% is absorbed, the lead level in environmental air is 0.1 $\mu g/m^3$, the ventilation (outside work) 12 m^3, the pulmonary absorption of which is 50% (e.g. the background uptake is about 15 µg/day), and if the absorption of air lead in the occupational setting is 30% (larger average particle size than in the general environment). The impact of the occupational exposure is somewhat larger in the lower range, somewhat less in the upper range. In Sweden, where, as said above, the background exposure is lower (about 5 µg/day), the general impact should be somewhat higher.

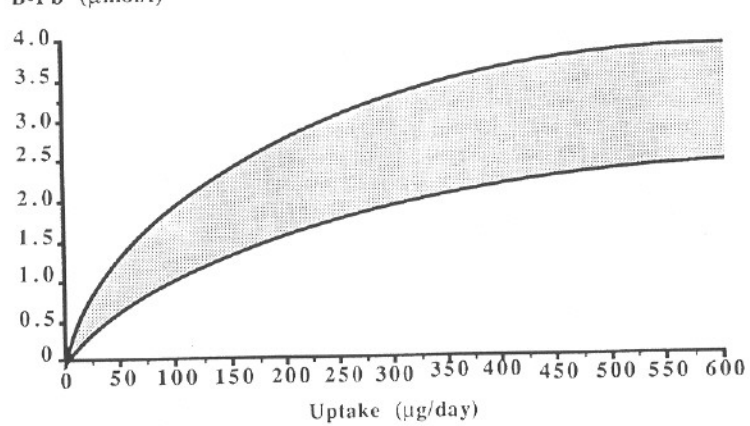

Figure 6. Relationship between total uptake of lead and blood lead levels (B-Pb) in adults (modified from U.K. Royal Commission on Environmental Pollution ref. 803). The considerable range of possible interpretation of the available information is shown.

However, there are also wide variations, due to differences in the exposure pattern and variations in the metabolism of lead. Thus, according to one estimate (810), by use of a theoretical model, at a time-weighted average air level of 25 µg/m^3 (5% of the time above 50 µg/m^3), 0.5% of the workers would have blood levels above 3 µmol/l and two thirds below 2 µmol/l. This is compatible with the data given in Figure 6.

As to exposure (in the general environment) in infants and children, the information is scarcer, but the corresponding B-Pb increase seems to be steeper than in adults, both with regard to gastrointestinal (799) and inhalation (112) exposure.

3.7.1.5. Relationship between blood-lead level and response

In estimates of exposure-respons relationships, B-Pb is often used as an indicator of exposure. This implies two problems. *First*, due to the nonlinear behaviour of B-Pb, the relationship between B-Pb and at least some effects, is not linear. This holds for effects on heme metabolism (see Section 10.3). *Second*, there is obviously a considerable inter-individual variation in effects at a certain B-Pb. Thus, in some cases, subjects may suffer toxicity at low B-Pbs (789), while others may have extremely high B-Pb with few symptoms (139). The reason is not clear; it may be due to variations in binding of lead in the red cells, or to inherited differences in heme metabolism (Section 3.6).

Still, depending mainly on the welth of information, the best estimates of dose-respons relationships are based upon B-Pb (see Section 10).

3.7.2. Lead level in urine

As mentioned above, lead is excreted in the urine. Thus, urinary lead levels have been used for biological monitoring of lead exposure and risk, particularily in occupational exposure.

After an increase of lead exposure, the urinary lead level rises gradually, to reach an apparent steady state after weeks (314b,401,785). The increase is faster than that of blood lead (314b,400). As said above (Section 3.4.1), there is a non-linear correlation between lead levels in urine and whole blood, but with a considerable inter-individual variation in the urinary lead excretion at a certain whole blood lead level.

After a decrease of lead exposure, the urinary lead level decay (314b,401,733), but remain enhanced for a long time. At the same B-Pb, women have higher U-Pbs than males (519,654).

The urinary lead concentration is dependent upon the urinary flow rate, which may vary considerably. At a high urinary flow, the level is lower than at a high one. This requires a correction. One way of allowing for this is to relate the excretion to time; often, 24 hour urinary samples have been employed. However, this is impractical, as all urine is often not sampled, and as the need to sample during working hours causes risk of contamination. Thus, samples voided during a specified period outside working hours may be employed. They may be related to time; alternatively a correction for urinary flow rate has been advocated (31,37). However, often spot samples are used. Then, the lead content should be corrected for the degree of dilution of the urine. This is of course particularly crucial when relating levels of lead to the level of an effect parameter in urine. Correction can be made by recalculating the lead content to a certain urinary density (usually 1.020) or by relating lead level to urinary osmolarity. Alternatively, the lead content may be related to the urinary content of creatinine. This is particularly useful in cases with glucosuria. However useful, these corrections does not fully compensate for variations in urinary flow rate (11,31,32,37). The problems are particularly great in very diluted (density <0.010; creatinine <0.3 g/l) and very concentrated (density >0.010; creatinine >3 g/l) urine (11,822).

3.7.3. Effects on the heme metabolism and the erythrocytes

Inorganic lead has an inhibiting influence on several steps in the chain of reactions which lead to formation of heme (Figure 7; Section 5.2). These abnormalities may be used for biological monitoring.

3.7.3.1. ∂-amino levulinic acid dehydratase activity

As briefly mentioned above (Section 3.6), lead inhibits the enzyme ALAD (=porphobilinogen syntethase), which may be determined in red blood cells (322,323a,324). The ALAD activity is determined as the amount of PBG formed

per time unit in the presence of an excess of ∂-amino levulinic acid (ALA). The analysis does not require expensive equipment, but determinations should be performed within a few hours after sampling (695).

An inhibition can be demonstrated at exposures associated with very low blood lead levels (about 0.5 µmol/l), and is directly parallel in time to changes in blood lead level (82,556,696; Section 5.2). There seems to be a closer association between heme synthesis and B-Pb than with plasma lead (129,580), possibly because of closer relation in kinetics in the former case.

At lead exposure there seems to be a compensatory increase of the amount of ALAD enzyme (82). The activity can be partially restored *in vitro* by addition of i.a. zinc, which allows an evaluation of the true degree of inhibition. A disadvantage in using ALAD as an exposure index is that total inhibition occurs already at blood lead levels of about 3.0 µmol/l.

There is a rare hereditary condition with a decrease of ALAD activity (Section 3.6). There is a genetic polymorphism for ALAD. However, the response of blood cell ALAD activity to lead is independent of the ALAD phenotype (888).

The ALAD activity may be affected by a few other metals and by ethanol intoxication (Section 3.6). Normal ALAD activities may be found in subjects with reticulocytosis, even when there is lead exposure (12).

In rats, the brain ALAD parallells peripheral blood activities (512). In man, there was an association between blood cell ALAD and liver ALAD (702).

3.7.3.2. ∂-amino levulinic acid

The inhibition of ALAD leads to a metabolic block, with accumulation of ALA in the blood plasma, which in turn leads to an excretion of the metabolite in the urine (176,320,703). Also, the lack of heme causes an induction of ALA syntethase (the rate limiting enzyme) in the liver, which results in an increase of the ALA production. There is a time-lag of only a few hours after changes of the lead absorption rate (696). Levels of ALA in urine (U-ALA) has been used extensively for biological monitoring of lead exposure.

There is a non-linear relationship between B-Pb and U-ALA (14,696, 843; Section 5.2), probably mainly because of the non-linear behaviour of B-Pb discussed above (Sections 3.2.1 and 3.7.1.4). After end of exposure, U-ALA remains increased for a long time, proportionally to the B-Pb (14).

The classical method for determination of ALA is that developed by Mauzeral and Granik (5,696). It does not differ between ALA and aminoacetone, which, however, only is of importance at marginal increases of ALA. There are many modifications of the method (696). Recently, a much more specific method, employing high performance liquid chromatography (HPLC), has been published (770,877).

There seems to be a considerable inter-individual variation of excretion of the metabolites at the same lead absorption. If used, the urinary levels should be corrected for dilution of the urine, by relation to creatinine, or to a defined density (Section 3.7.2. Alternatively, it may be related to a defined time period.

There are other kinds of interference. Thus, ALA is increased in hepatic porphyrias (481; Section 3.6).

3.7.3.3. Coproporphyrin

Lead exposure causes an inhibition of coproporphyrin oxidase (806). This lead to an accumulation of coproporphyrin (CP) and excretion of this metabolite in urine (826). The concentration of CP in urine (U-CP) has earlier been used extensively for biological monitoring of lead exposure. Analysis of CP in urine is usually by extraction with diethylether or ethylacetate/acetic acid, and spectrophotometric determination after oxidation.

Recently, a much more specific method, employing HPLC, has been published (578; Section 5.2).

Coproporhyrinuria may also be caused by a number of hereditary (erythropoetic protoporphyria) and attained conditions, i.a. alcohol intoxication (781).

As to corrections for urinary flow rate, see Section 3.7.2.

3.7.3.4. Protoporhyrin

Lead also inhibits ferrochelatase (heme synthetase). Further, lead interferes with the mitochondrial energy metabolism, which is necessary to reduce iron [Fe(III) to Fe(II)] before insertion in the porphyrin ring (806).

These effects causes an accumulation of protoporhyrins (PP; zinc protoporphyrin=ZPP; free erythrocytic protoporphyrin=FEP) in the red blood cells (826). These changes are extensively used for biological monitoring of lead exposure (293,323a,450; Figure 8; 806,857).

There is a non-linear relationship bewteen B-Pb and ZPP, probably mainly because of the non-linear behaviour of B-Pb (Sections 3.2.1, 3.7.1.4 and 5.2).

Some methods measure specifically PP IX , while others do not differ between PP, CP and uroporphyrins. However, this is of limited practical importance, as more than 90% of the total FEP in the red cells is PP. The PP IX in the red cells at lead exposure occurs as ZPP, which may be determined by a fluorometric method, which is specific, simple, and rapid, and which requires only small amounts of blood (293,323a,857).

Further, an additional advantage is the time pattern of the effect; it integrates the exposure over several months. The level is affected by the life-span of the red blood cells, i.e. about 120 days. After an increase of exposure, the level increases more slowly than does the blood lead level, and after cessation of exposure, the level decreases more slowly than the B-Pb (355,447,679,857). However, after end of exposure, a new steady state is gradually attained; at that, there is a protoporphyrine increase, which is roughly proportional to the B-Pb (14,170).

Moreover, there are some indications that the erythrocyte protoporphyrin level correlates better with certain effects, on the kidney function (451) and nervous system (293,452), than does the B-Pb. Whether this is due to the time pattern discussed above, or to the fact that the protoporphyrin level reflects a metabolic effect, and not only an accumulation of lead, is not known.

But there are problems in connection with erythrocyte protoporphyrins as a mean for biological monitoring, both in the analysis (820), and in the interpretation of results. Iron deficiency causes an increase of erythrocyte protoporphyrin

(145,321,482,497, 857), which may be a problem, especially in women, though rarely seen in healthy male workers. Also, the inter-individual variation at a certain lead absorption seems to be considerable, resulting in a low sensitivity and specificity in adults (323a) and in children (482,504,613,792), especially at low exposure. Thus, a pre-exposure determination is of value. A rare inborn error of metabolism, erythropoetic protoporphyria, produces markedly elevated erythrocyte protoporphyrin level (781). Further, the hemoglobin disorder ß-thalassemia may affect the relationship between B-Pb and protoporhyrin levels (Section 3.6).

3.7.3.5. Pyrimidine 5´-nucleotidase

Lead inhibits the activity of the enzyme pyrimidine 5´-nucleotidase (P5N), which is present in the red cell cytosol and catalyses the hydrolytic dephosphorylation of pyrimidine 5´-monophosphates (23,164,371,372,519,669,670,786,787,816). The decrease is proportional to the B-Pb. The decrease of P5N on B-Pb is non-linear; it starts already in the B-Pb range 0.5-1.0 µmol/l and continues up to about 5 µmol/l (Section 5.2).

The activity of P5N is fairly stable in samples stored in refrigerator (372,670). The P5N has been used in several studies as an index of lead exposure. Also, pyrimidine and purine nucleotides in erythrocytes have been proposed (668).

3.3.3.6. Other indicators

Lead exposure results in reticulocytosis and stippled erythrocytes in peripheral blood (806). Further, the life-span of circulating erythrocytes also becomes shortened (cf Section 5.2).

The combined effects of lead on heme synthesis and on life-span of the blood cells results may result in anemia. Neither is adequate for biological monitoring, as they represent adverse effects.

3.7.4. Other indices

3.7.4.1. Fecal lead excretion

Excretion of lead in feces may be used as an index of dietary lead intake (110). However, due to obvious practical difficulties, it is seldom useful.

3.7.4.2. Hair-lead levels

Lead is incorporated in hair (637). Several studies have shown a correlation between lead levels in blood and hair (801). Analysis of a strand of hair (291) may give a time-integrated index of the exposure for several months back. Scalp hair has been used for biological monitoring of lead content in the body at the time of formation of the part of the hair analysed.

However, there are problems. Lead levels in hair in an individual can vary, even between hairs obtained from the same region of the scalp. Further, the levels in subjects with similar exposure may vary with sex and hair colour. In addition, the level in hair is a result not only from endogenous incorporation, but also from

external contamination, which of course may be substantial, especially in subjects living near lead works or in lead workers (291). Accordingly, many authors have tried to wash the hair prior to analysis to get rid of the contamination. However, the washing may cause loss of endogenous lead. Also, washing of the hair while still on the scalp of the exposed subject may cause a loss of endogenous lead, which then is more pronounced in long hair, which has been washed many times, thus causing a spuriously low index of the body burden at the time of hair formation.

Because of these difficulties, lead level in hair have, in spite of its obvious advantages in terms of easiness at sampling and its character of a time-integrated index, not attained but a rather limited use (776).

3.7.4.3. Teeth lead levels

Lead is incorporated in teeth. The lead level in teeth has been used as an index of lead exposure, especially the shedded decidious teeth in children (105,300,303, 537,545,568,739). But methods have also been developed for determination of lead in teeth *in situ* (95). The tooth lead level may perhaps be a cumulative index of the lead exposure from the prenatal period, when the teeth are formed, up to the time of shedding (801). There is a poor correlation between lead levels in blood and teeth, probably because of their different time perspectives.

However, there are problems. Within one tooth, there is a considerable variation of lead level between enamel and primary and secondary dentine. The lead level in teeth is probably not an ideal time-integrated exposure-index, as the incorporation is highest in connection with the prenatal formation of the tooth, and much lower later on. It is possible, though, that circumpulpal dentine may accumulate lead continously (303). Further, considerable variation in tooth-lead concentration has been noted in the same child, especially when the teeth are of different types, or from different jaws. Moreover, it is difficult to make a homogenate from a tooth, and to do that without loosing materials, and inter-laboratory variation has been reported at analyses of lead in teeth.

Lead levels in teeth has some practical limitations when used for biological monitoring. However, it may be used, perhaps especially as an index of integrated exposure during the prenatal and early extrauterine life in groups of individuals, provided the sampling and analysis is well controlled.

3.7.4.4. Skeletal lead levels

It is possible to use the skeletal lead level as an index of exposure. It reflects earlier exposure.

In archæology, analysis of bone from toombs have been used for assesssment of historical lead exposure (7,50,51,288,292,297,304).

Also, in epidemiological research, bone lead levels at autopsy have been used as an index of exposure (339,376).

In children heavily exposed to lead, radiographic lead lines develop at the metaphyseal ends of growing bones (93,640). In particular cases, the skeletal lead level has been estimated in bone biopsies from ileum (68,253,281,489,638,818,

841), vertebrae (698,699), or even skull bone (376). But this is, of course, not a practical possibility for biological monitoring.

However, the lead level in bone may also be measured in vivo by XRF technique (357). The measurements have been performed in finger-bone by use of K X-rays (8,9,151-153,180,209,549,625,736a,777), or tibia (44,68,144,217,268, 270,271, 312,391,528a,659,701,747-750,774,818,834,856), calcaneus (268,270,271, 749,750,774,784), *ulna* (231a), *sternum* (231a), or *temporal bone* (744). The measurements take about half an hour and causes only a low radiation dose.

For the tibia, both L X-rays, which measure the lead content of superficial bone (180,659,660,856) and K X-rays, which also measure lead in deeper parts of the bone (44,68,144,217,268,270,271,391,701,747-750,774,818,834) have been employed.

The detection limit in finger-bone is about 20 µg/g wet weight, which is much higher than the levels found in subjects without particular exposure (698), but sufficient for use in the occupational setting (8,9,152,153,549) and in other particular exposure (209,625). At measurements in the tibia, the detection limit is similar (747-750). The method error in finger-bone is about 15% (coefficient of variation), which is sufficient for many purposes.

As said above (Section 3.2.3), in lead workers, there is an increase of skeletal lead levels with increasing time of exposure (152,698,736), although the inter-individual variation in bone-lead concentration at a certain exposure time is considerable. That variation is, at least to a great extent, dependent upon variations in intensity of exposure, and accordingly in lead absorption, in different individuals occupied in different working environments. The skeletal lead level is thus considerably better associated with blood lead level integrated over time of occupational lead exposure.

As mentioned earlier (Section 3.2.3), the rate of turnover of lead differs between different parts of the skeleton. It is considerably faster in trabecular bone than in cortical bone (698). The rate of turnover of lead in the finger-bone, which contains both trabecular and cortical bone, corresponds to a half-life of about a decade (153,549). This means that, in this species of bone, a steady state is reached after a couple of decades of exposure (736). The finger-bone lead level can thus be expected to give a picture of the time-integrated lead absorption during a decade back. It is possible that use of a more typical cortical bone, such as the tibia (747-750), may give a picture of the lead exposure even further back in time. But that possibility remains to be investigated.

3.7.4.5. Lead mobilization test

Lead is chelated by calcium-disodium-ethylenediamine-tetraacetate (calcium disodium edetate; $CaNa_2EDTA$) and d-penicillamine (see also Section 3.2.4.). If those substances are administered, the lead level in plasma increases for a few hours ($CaNa_2EDTA$: 26) and the excretion in urine rises (24 h excretion about 10 times; 38), which may be used for biological monitoring of lead exposure and risk of toxicity. $CaNa_2EDTA$ (624,772) is a more potent chelating agent than penicillamine, and has thus been used more frequently, but on the other hand, it has

to be given parenterally, while penicillamine may be given orally (176,574,699). Both compunds have side effects at prolonged administration, but none have been reported at single dose administration.

$CaNa_2EDTA$ is given either as an intravenous infusion (104,170) or as a single or twice-repeated intramuscular injection (148,499), in the latter case mixed with procain to reduce the pain. The dose administered has varied considerably, but is usually about 25 mg/kg body weight. The dose of chelating agent is almost completely eliminated during the 24 hours following injection, and urine is accordingly usually collected during that period. However, the long period of urine collection causes considerable problems, in non-hospitalized individuals. It has been shown that a period of 3-8 hours is sufficient (26,499,699,743). The result (chelatable lead) is either expressed as the total amount of lead excreted during the defined time period or as the amount of lead excreted in relation to the amount of chelating agent administered.

After an increase of lead exposure, there is a gradual increase of chelatable lead, which reaches a steady state after approximately a year (104). The shape of the accumulation curve is similar to that of blood lead, but seems to level-off later. There is a correlation between B-Pb and chelatable lead; the increase of chelatable lead on B-Pb is exponential (41,38,148,699,774,856). If this is not taken into consideration, spurious conclusions may be arrived at (14). The chelatable lead is correlated with urinary lead (38,699).

After end of infusion, the chelatable lead is "refilled" from the non-chelatable pool, by about 20% during the first 24 h. During $CaNa_2EDTA$ infusion, there is a transient decrease of ALAD activity in blood cells (379). After end of lead exposure, the chelatable lead remains increased for several years (14,170,624,699).

It has been claimed that the chelatable lead is a better index of the metabolically active lead pool than is blood lead. The reason for this is mainly the linear relationship to urinary excretion of ALA (Section 5.2). Also, an association with renal dysfunction (66,67,178,179,836; Section 5.3) and neurophysiological effects (39; Section 5.1) have been recorded.

Lead mobilization tests are too complicated for use in routine biological monitoring. The tests mostly give little information in addition to that obtained by determination of the blood lead level. It may be of some use, though, in subjects who have previously been exposed to lead, but who have recently been suffering only low exposure. In those, the blood lead level may be only slightly increased, but the mobilization test may be significantly elevated. Its main use has been in children with suspected or threatening lead toxicity, mainly to determine whether prolonged chelation therapy should be embarked upon or not.

In subjects with decreased glomerular filtration, the excretion of the chelate is very prolonged (226,837); mild renal insufficiency does not seem to affect the excretion (743). Thus, urine sampling for several days is needed. Then, the total induced lead excretion is increased, as a result of the slower excretion of edetate, which gives it longer time to chelate lead (601). Even in uremia, chelation has been employed, with measurement of lead in hemofiltration fluid (500). Further, the lead excretion after chelation is raised at increased bone cell activity (as indicated by alkaline phosphatase activity; 181).

In this connection, it should be mentioned, that even a single dose of $CaNa_2EDTA$, by redistribution, may increase the lead concentration in the brain (147,172). Also, parenteral administration of $CaNa_2EDTA$ may increase the absorption of lead from the gastrointestinal tract. Futher, it has been claimed, that even a single dose of $CaNa_2EDTA$ in heavily exposed subjects may result in renal failure (882).

The chelating drug 2,3-dimercaptosuccinic acid (DMSA), which has been used to treat childhood lead poisoning (310) does not seem to have been employed yet in lead mobilization tests. It does not cause a redistribution of lead to the brain (171), neither increase gastrointestinal absorption of lead (397).

In summary, lead mobilization tests give information on the chelatable lead, which probably reflects the metabolically active lead pool. However, it is not recommended, as it does not supply more infomation than U-Pb or B-Pb, and as it may possibly cause a rise in lead levels in CNS, which might be adverse.

3.7.4.6. Other

Determinations of function of the nervous system or the kidneys have been used for surveillance of lead workers. Neither is adequate for biological monitoring, as they represent adverse effects.

4. General toxicity

Rather little is known about the basic mechanism behind lead toxicity (plumbism or saturnism). However, it is well established that lead binds to the sulphydryl groups of proteins. If this occurs on an enzyme, its function may be inhibited, which may result in toxic effects.

Lead *inhibits the enzymes* ALAD, ferrochelatase, and probably also coproporhyrinogen oxidase, three enzymes involved in the formation of heme (Sections 3.7.3 and 5.2; Figure 7). In this case, the mechanism may be an interaction with the zinc in the enzyme (Section 3.6). The lack of heme induces an increase of the ALA syntethase in the liver. This leads to an accumulation of the metabolite ALA, which is neurotoxic, possibly by interaction with the gamma-amino-butyric acid (GABA) system (82,155,522,525). Lead also interferes with other neurotransmitters (49,516,715, see also Section 5.3).

The lack of heme causes a deficiency of hemoglobin, and accordingly anemia. Lead also causes an inhibition of the enzymes P5N and Na^+,K^+-adenosine-triphosphatase (Na^+,K^+-ATPase) in red cells, which causes hemolysis, and thus adds to the anemia (Section 5.2).

Further, heme is a constituent of several hemoproteins, including a number of enzymes (cytochrome oxidase, catalase, peroxidase, tryptophane pyrrolase, and cytochrome P450) in all cells of the body (525,806,842,843).

Several of these enzymes are involved in the energy metabolism. Thus, a deficiency in the energy production disturbs the function of the cell (118). Also, the tryptophan (increase of 5-hydroxytryptamine) and steroid metabolisms are derranged, these effects may, in turn, cause various symptoms and signs from

different organs, e.g. the nervous system (525). Disturbances of the heme metabolism in the nervous system has been seen in newborn rats, but was not present in adult animals (436). An interaction with energy metabolism is also a probable result of the morphological and functional changes in mitochondria induced by lead (175,593). This may be of importance for the effects of lead on the kidney, and also with the energy metabolism of the blood-brain barrier (155).

Lead exposure has also, through the effect on heme synthesis, been shown to decrease the cytochrome P-450 containing mixed function oxidases of the liver (10,806). As a result, the body becomes less able to detoxify various organic foreign substances, as has been shown in lead workers (525).

Lead exposure also seems to affect the serum levels of lipid peroxides and blood superoxide dismutase (SOD) activity (381), indicating lipid peroxidation in the tissues by disruption of the metabolism of activated oxygens, possibly caused by the inhibtion of SOD.

Also, lead *alters calcium-mediated cellular processes*. It inhibits the movement of calcium into the cell through calcium channels (155,622,722,806). Further, lead enters the cell through those channels and may mimic calcium in binding to regulatory proteins. Thus, lead binds to calmodulin, which may interfere with the intracellular metabolic events, in which calcium serves as a "second messenger", e.g. release of acetylcholine. Also, lead mimics calcium in the activation of protein kinase C (498), which phoshorylates various critical cell membrane and transport proteins, and thus is a major site for regulation of cellular growth and differentiation.

The interaction with calcium may lead to malfunction of smooth muscle cells, e.g. in the gastrointestinal tract, which may be the mechanism behind the symptoms from this area in lead toxicity. Also, this may be the background behind some effects of lead upon nervous cells. Moreover, lead affects the metabolism of vitamin D into metabolites active in the calcium metabolism, probably by an effect on the kidney.

One possible mechanism behind effects of lead is also an interaction with the essential element selenium (Section 3.6).

Lead also interacts with the genetic material. This is discussed in Section 7.

Protection of the cell by formation of inclusion bodies is discussed in Section 5.3.

5. Organ effects

Inorganic lead can affect the body in several ways. A clinical lead toxicity often disturbs the heme synthesis, the erythrocyte survival, the nervous system, kidneys, and the gastrointestinal tract. Lead also affects the reproduction, and possibly also causes cardiovascular and mutagenic effects, and cancer (843).

Almost all information on relationship between exposure and effect/response is based upon B-Pb. Thus, mainly such data will be discussed here. The relationship between exposure and B-Pb has been discussed above (Section 3.5.1.4), and will

be further treated below (Section 11). In addition, spome comments will be given on other information, mainly relationship between U-Pb, protopophyrins, and organ lead levels on the one hand, and various effects on the other.

5.1. Nervous system

Exposure to inorganic lead can *damage the PNS* and in rare cases cause peripheral motor neuropathy with paralysis ("wrist drop" and "ancle drop"; 707,806,842,843). This is due to demyelination, axonal degeneration, and possibly also presynaptic block. In lead-exposed subjects without clinical signs of peripheral neuropathy, neurophysiological examinations may reveal disurbancies of motor nerve conduction velocity and electromyographic abnormalities. Also, pain in the extremities, especially arthralgia, which is a common symptom in lead toxicity (618), is probably usually a result of an injury of the sensory PNS (but see also saturnine gout; Section 5.3).

There are several recent reviews on dose-response relationships for neurotoxic effects of lead exposure, both in adults (707) and in children (306,739,801,802).

Clinical symtoms and signs of motor and/or sensory PNS affection seem to generally occur only at B-Pbs of about 3.0-3.5 µmol/l, or more (56,450,548).

Several studies have shown that chronic lead exposure reduces conduction velocity in peripheral nerves in adult subjects without clinical symptoms or signs of disease (34,42,43,46,98,116,333,334,386,390,450,509,657,707,708,710,723, 790,806,889). The effect seems to occur first in motor nerves in the arms (median nerve first), later in sensory nerves of the arm and in motor and sensory nerves of the leg.

In some studies of such subclinical effects, there was a dose-response relationship. Even so, it is difficult to define the lowest effect level. However, discrete effects in adults probably occur at blood lead levels as low as about 2.0-2.5 µmol/l (42,43,98,334,386,533,534,657,708,710,790,889), even though, in some studies (548,610,611,677,752), levels as high, or even higher, have not been associated with detectable functional disturbances. However, the discrepances may, to a large extent, be due to differences in exposure patterns and/or methodology [e.g. nerve(s) studied]. In a study of children, the treshold for effects on the motor conduction velocity was estimated at a B-Pb of 1.5 µmol/l (686).

In a small prospective study, in which workers were followed for up to four years, there were statistically significant effects at even lower blood lead levels; deviations were noted within two years in workers with B-Pbs in the range 1.5-2.3 µmol/l, while workers below this level did not deteriorate, even during four years of exposure (709). This study is the most important one as regards conclusions on the lower range of the dose-response curve. However, it is not without problems, mainly due to a considerable loss in follow-up, which was not random.

It should be mentioned that Sweden, as from January 1 1993,introduces a level of removal from work with lead exposure, for men and women under 50 years of age, at B-Pbs of 2.5 and 1.5 umol/l, respectively. Return to work which causes lead exposure is allowed when the B-Pb has diminished below 2.0 and 1.2 umol/l, respectively (43a).

The significance of such neurophysiological disturbancies is not clear. They may be considered an early sign of neuropathy, or an innocent functional disturbance of the nervous membrane, without relationship with the "true" neuropathy (211). Also, there are conflicting results as to their reversibility (35,170,334,532), perhaps due to dependence upon the exposure level and duration. However, it seems that they may be at least partly reversible. In light of the fact that more excessive lead exposure may cause severe nervous tissue damage, also early effects should be regarded as adverse.

Lead exposure has also been claimed to cause effects on the optic nerve (131) and the auditory system (351,688). In children, an increase of B-Pb from 0.3 to 0.9 µmol/l corresponded to a 2-dB decrease of hearing at all frequencies (687).

Slight effects on the *autonomic nervous system* were recorded in a group of workers with an average B-Pb of 1.6 µmol/l (534). The clinical importance of the findings is not clear.

Lead exposure may also cause *encephalopathy*, in experimental animals (87,347, 760-764) and in man, especially in acutely poisoned children (806,842,843), but also in adults (81,246). The classical signs in severe toxicity are ataxia, coma, and convulsions. After recovery from acute encephalopathia, residual clinical signs may sustain.

In subjects without obvious clinical signs of encephalopathia, subjective, and non-specific symptoms (e.g. fatigue, impaired concentration, loss of memory, insomnia, anxiety, and irritability) may occur (365), as well as impaired performance in psychometric tests (Section 10.1.1). Similar symptoms have been recorded in welders exposed to lead (726). Corresponding effects in fetuses, infants, and children will be discussed below (Sections 9.2 and 10.5).

Increased prevalences of symptoms suggesting affection of the central nervous system were recorded in lead workers with B-Pbs of about 3.0 µmol/l, or higher (58,430). In two studies, in which the average B-Pb was about 2.5 µmol/l, one reported an increase of symptoms (385), while the other one did not (410,411).

Slight effects on the CNS are difficult to measure (211). In psychometric tests, it has been possible to demonstrate minor effects on mainly visual intelligence and visual-motor coordination in groups of lead workers with average B-Pbs of 2.0-2.5 µmol/l, or higher (42,45,56,61,86,92,212,277, 293,350,364,385,390,618, 751,806,815,840,863). However, in one large and carefully analysed study, of workers with B-Pbs in the same range, only marginal effects were found (663). In Several studies, there were no effects in different tests in workers with average B-Pbs of 2.0 µmol/l or lower (131,364,606).

In a small prospective study of 24 newly employed lead workers, of whom, 11 were followed for 4 years, when they had an average B-Pb of 1.4 µmol/l, there were indications of a slight decline of the performance in some tests (487); however, the conclusions are hampered by the large loss in follow-up.

This kind of studies involve several methodological problems, in terms of selection of a proper reference group, control of confounding and multiple inference, because of the large number of tests usually employed.

Effects on somatosensory-, visual- and auditory-evoked potentials in the EEG have been reported in workers with average B-Pbs of 2.0-2.5 µmol/l (39,351,707), or higher (333).

It seems, that the effects on CNS cognitive function are, at least in some cases, and at least partially, reversible (59,181a,183). The same seems to hold for latencies of visual and somatosensory-evoked potentials (39). However, not enough is known about the prognosis.

As said above (Section 3.2.2), there are indications from animal experiments that there is no close relationship between B-Pb and lead levels in the nervous system, the latter having a greater tendency to accumulate lead. There are some indications that the erythrocyte protoporphyrin level correlates better with certain effects on the nervous system (86,293,815), than does the B-Pb. Whether this is due to the fact that B-ZPP reflects the exposure during a longer period back in time, or because the protoporphyrin level reflects a metabolic effect, and not merely an accumulation of lead, is not known.

In rodents, CNS effects were associated with brain-lead levels in the order of 1-10 µg/g (460,806). U.K. subjects without occupational exposure seem to have about 0.1 µg/g, occupationally exposed subjects about 0.6 µg/g (64,289). In subjects with severe lead poisoning, the levels may be more than ten times higher (689).

Vascular disease in the CNS will be discussed below (Section 5.5), as will effects on the hypothalamus-pituitary (Section 5.5. and 9.2), and effects on the CNS of fetuses, suckling infants, and children (Section 9.2).

Patients with amyotrophic lateral sclerosis have an increased level of lead in plasma (but not whole blood; 163). Thus, lead has been suspected to have an etiological role in that disease. However, the explanation is an increased tendency of hemolysis in ALS patients. In case-referens studies, there was no association between Alzheimer´s disease and lead exposure (308). Lead exposure has in some reports been associated with multiple sclerosis, while others have failed to demonstrate such a relationship. A recent Finnish case-referent study showed no evidence of a lead-associated risk (394).

5.2. Blood och blood-forming organs

As said above (Sections 3.7.3 and 4; Figure 7), inorganic lead has an inhibiting influence on several steps in the chain of reactions which lead to the formation of heme, a constituent of hemoglobin. About 80% of the heme synthesis occurs in erythroid tissues.

The metabolic interactions lead to an accumulation of ALA and CP in the blood plasma, which in turn leads to an excretion of those metabolites in the urine. Also, there is an accumulation of protoporhyrins (PP, ZPP, and FEP) in the red blood cells). Lead also inhibits the enzyme P5N in red cells (Section 3.7.3.6 and below). Hereditary deficiency of P5N results in non-spherocytic anemia with basophilic stippling (816). This is similar to the hematological findings in lead toxicity.

Thus, heavy lead exposure is associated with reticulocytosis and occurrence of stippled erythrocytes in peripheral blood (806,842,843), possibly mediated through the effect on P5N. In a Danish study of smelter workers with an average B-Pb of 2.5 µmol/l, there was an association between B-Pb and reticulocyte counts (411).

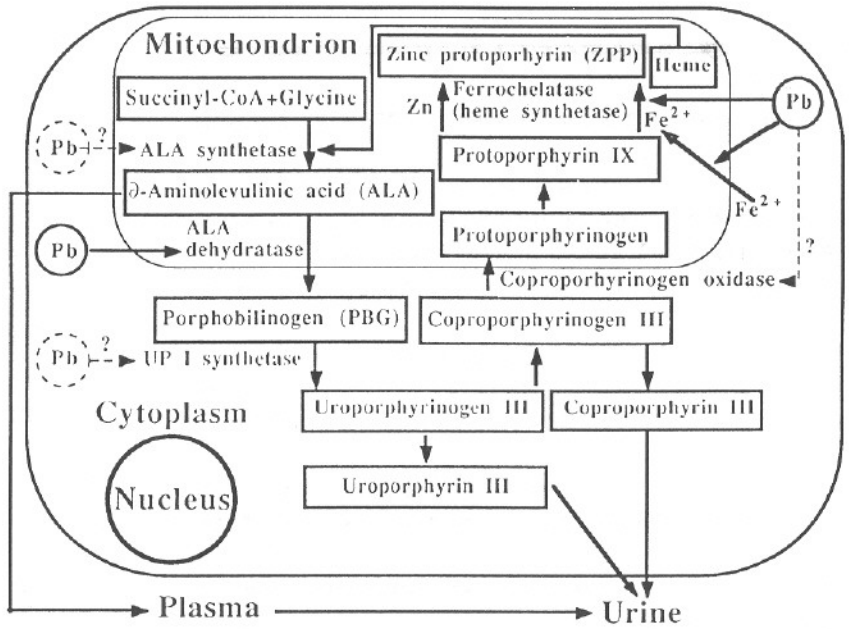

Figure 7. Heme metabolism. Known and suspected interactions by lead (Pb) are indicated (After Moore, ref. 523).

The blood regeneration after bleeding is delayed in lead workers with a blood lead level of 2.1 umol/l (297a). Also, the life-span of circulating erythrocytes becomes shortened, probably because an inhibition of the red cell membrane Na^+,K^+-ATPase (331,642), possibly also of the erythrocyte P5N, and through changes of membrane proteins (30). Changes of erythrocyte microviscosity and phospholipid composition has been recorded in lead workers (165). There might also be an effect mediated via erythropoetin, possibly via an effect on kidney tubuli (310a). There are also other possible mechanisms of the anemia (523).

The combined effects of lead on heme synthesis, red cell formation, and life-span of the blood cells may result in an anemia, which is normocytic and sideroblastic (523).

Even a very small increase of the blood lead level causes an inhibition of the enzyme ALAD in blood cells (322,323,695,806; Sections 3.7.3 and 5.2). Inhibition occurs already at low B-Pbs (about 0.5 µmol/l), and is total at not extremely high B-Pbs (about 3.0 µmol/l).

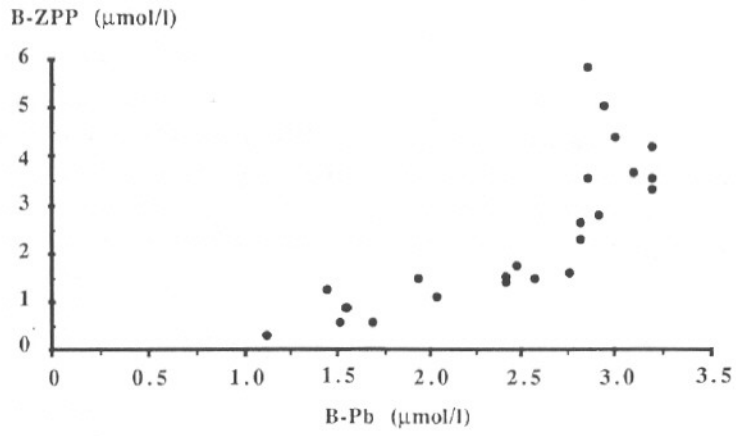

Figure 8. Relationship between blood levels of lead (B-Pb; mean during the last 4 months) and zincprotoporphyrin (B-ZPP) in 23 lead workers. Data from Haeger-Aronsen and Schütz (323a).

As said above, lead inhibits the enzyme P5N in red cells. Such an effect may occur even at low B-Pbs (in the range 0.5-1.0 µmol/l; 23,164,372,669,670). Inhibition of other enzymes have been seen at similarly low B-Pbs (380).

The effects on ALAD and P5N in red cells cannot, in themselves, be considered detrimental to health, because no associated pathology has been discovered.

Somewhat higher B-Pbs are associated with an increase of protoporphyrin in blood cells. The increase of protoporphyrin on B-Pb is exponential (14,58,170, 293,450,806, Figure 8). It is steeper in females than in males, and steeper in children than in females. At a level of 1.5 µmol/l, about 50% of the females and about 15% of the males display an elevation (323,806,844). This effect cannot, in itself, be considered detrimental to health. Even in severe lead toxicity, the amount of ZPP corresponds to less than 1% of the hemoglobin. But the protoporphyrine level in blood may be used as an index of exposure (Section 3.7.3.4.).

Also, there is an increase of ALA levels in plasma and raised excretions of ALA in urine. The increase of ALA on B-Pb is exponential (148,696,770; Section 3.7.1.5). The effect in females and children is more pronounced than in adult males. Employing colorimetric method, it has been found that in the B-Pb range 1.5-2.0 µmol/l, about 40% of the females and 15% of the males display an increase of ALA (843). However, by use of a more specific HPLC method, a 50% response was found in males already at a B-Pb of 1.3 µmol/l (770).

CP in urine increases at higher exposures. By use of a new HPLC method, an effect B-Pb level of about 2.5 µmol/l has been reported (578; Section 3.7.3.3).

Again, the effects on ALA and CP excretion in urine may not *per se* be detrimental to health, although the fact that ALA accumulation may have neurotoxic effects suggests that future studies in this area are important. However, ALA and CP levels may be used for monitoring of exposure (Section 3.7.3).

At high B-Pbs (about 3 µmol/l in males, somewhat lower in females, and especially in children; 58,450,523,785,806), the disturbance of the heme synthesis, in combination with - and probably as important - the shortened life span of the erythrocytes, causes a reduction of the hemoglobin level in blood, resulting in anemia ("lead pallor"). This is, of course, a definitely adverse effect. A slight decrease of hemoglobin level in blood was noted in a group of smelter workers with an average B-Pb of 2.4 µmol/l (411).

Very little information is avaiable on the level of lead in bone marrow. In one dead lead smelter worker, the level was 0.8 µg/g (probably containated with trabecular bone, which had 110 µg/g); the level in blood was 2.3 µmol/l (0.5 µg/g; 734).

5.3. Kidneys

Lead exposure may also cause kidney damage (80,83,177,285,370,430,649,806, 835,842,843,846,888).

5.3.1. Tubular effects

In *acute* lead toxicity, there is *proximal tubular damage* with eosinophilic nuclear inclusion bodies (88,595), which consist of a lead-protein complex, possibly as a result of protective sequestration of lead by a cytoplasmatic protein, and transport into the nucleus (259,278,600). The inclusion bodies are removed by chelation (595). Characteristic inclusion bodies may be excreted in urine during occupational exposure to lead (682). The formation of lead-protein complexes is not specific for the kidney, since it may occur in other tissues, including the nervous system (259). Also, there is alteration of renal mitochondrial morphology (593).

In acute toxicity, the tubular damage may result in a reversible Fanconi syndrome-like condition (with aminoaciduria, glucosuria, and hyperphosphaturia). Such has not been reported in lead workers, although defect reabsorption of glucose (353) and aminoaciduria (286) has occassionally been reported. Defective tubular reabsorption of low molecular weight proteins (retinol binding protein, RBP; $ß_2$-microglobulin), filtered through the glomerulus, leading to urinary excretion of such proteins, is an early sign of toxicity by other heavy metals, but is apparently a rather late sign of lead-induced renal damage (115,678,735,811,821). In cases, in whom such has been found, confounding by other exposures must be considered, especially in smelter workers (115,312).

Further, tubular damage may cause leakage of enzymes (e.g. the lysosomal N-acetyl-ß-D-glucosaminidase, NAG; enzymuria; 168,228,511,581,735,821) from the cells. It is unclear whether slight enzymuria represent a cytotoxic effect. It

seems to be reversible (168). Also, it seems that lead may impair its own excretion (123a).

An increase of the urinary excretion of the tubular enzyme NAG has been noted among workers having a median blood lead level of 1.5-2.5 µmol/l, or higher (168,228,511,581,735,821). There were no effects in workers having an averge B-Pb of 1.5 (270,271) or 2.4 (267a) µmol/l.

Further, an effect on the kidney is possibly the cause of the reduction of serum levels of 1,25-dihydroxycholecalciferol (the major actieve form of vitamin D), which occurs in *children* at even lower lead absorption (484), but seems to be rather unusual in considerably more exposed lead workers (312). The relevance to health of these findings is not clear.

Rats developed proximal tubular damage at a lead level in the kidney of about 45 µg/g (287). U.K. subjects without occupational exposure seem to have about 0.8 µg/g in kidney cortex, occupationally exposed subjects about the same concentration (64). In subjects with severe lead poisoning, the levels may be more than ten times higher (689).

As said above (Section 3.2.2.), there are indications from animal experiments that there is no close relationship between B-Pb and levels in the kidney, the latter having a greater tendency to accumulate lead.

5.3.2. Interstitial nephritis

In experimental animals, *prolonged exposure* to lead may cause progression irreversible nephropathy (285). In man, the corresponding condition, after years of heavy exposure, is chronic interstitial nephritis, with interstitial fibrosis, tubular atrophy, and arteriosclerotic changes, but with only occassional nuclear inclusion bodies (175,837). The kidney disease sometimes results in granular contracted kidneys. The changes are not specific for lead nephropathy.

Functionally, the chronic kidney damage results in a decrease of renal plasma flow with a reduction of glomerular filtration rate, resulting in azotemia (increase of blood urea nitrogen, BUN, and serum creatinine; 58,123,451,452,493,581,612, 643a,837; above the upper reference limits only when about two thirds of the kidney function is lost), and in increase of tubular reabsorption of uric acid (227), resulting in an increase of serum levels of uric acid (eventually hyperuricemia; 126,267,493,612), which is probably the cause of gout (Section 5.3.3). Even in advanced renal disease, the proteinuria is mild and unspecific. Chronic effects of low-level lead exposure may thus go unrecognized, until irreversible kidney disease exists.

Effects on the glomerular filtration rate (as indicated by increase of blood-urea nitrogen or serum-creatinine levels; 58,411,451,452,493,581,612,678,836, 837,842) and uric acid excretion (126,493,612) occur in groups of workers with average B-Pbs of about 2.5-3.5 µmol/l, or higher, but not at lower exposures (115,195,619,735,820).

One problem in the interpretation of data on kidney damage, is the lack of clear dose-response relationship. This may be due to the fact that disturbance of renal function may remain for a long time, the effect thus possibly being associated with earlier, higher exposures.

There are some indications that the erythrocyte protoporphyrin level is closer associated with certain effects on the kidney function (451), than does the blood lead level. It is not known, whether this is because it reflects lead absorption for a relatively long time, or to the fact that that the protoporphyrin level is a metabolic effect, and not only an accumulation of lead.

5.3.3. Saturnine gouty arthritis

Also, lead toxicity may result in saturnine gouty arthritis (67,76,126, 161, 179,180,226, 267,325,339,531). As gout from other causes seldom results in renal insufficiency, it has even been proposed, that gout appearing after onset of uremia, which is rare, should rise suspicions of lead toxicity, especially in patients with a history of ingestion of lead-containing wine (Romans: 563,564; port wine in 18th and 19th century England: 60) or illicit alcohol ("moonshine whiskey"; 325). However, the suggestion of a high prevalece of an association between lead and renal failure/gout has also been challenged (645,880). Changes of this type have been recorded in adults in Queensland, Australia, who had been lead poisoned as children (226,339,376); in U.S. have, for unknown reasons, no similar late renal effects been found (517).

Several groups have studied *clinical cases of renal disease* (without or with gout), and found an association with lead exposure. Thus, a considerable part of adult patients with uremia had a history of lead exposure, as indicated by *chelation test* (collection of urine for several days needed, as the renal failure retards the excretion of the complex; 67,76,161,178-180,226,418,649) and shown by increased *bone-lead* levels (180,181,339,818). Similarly, an association between abnormal renal function and *B-Pb* has been found in some studies (123,418,769,779), but not in other (616a), probably because the latter were performed in an area where the exposure was rather low. In contrast, *soft-tissue lead* levels were not associated with renal disease (375).

It has even been suggested (837), that long-term chelation therapy may be of value in some patients with renal failure, although certainly not always (273).

The extent to which environmental lead exposure contributes to the cause of renal disease is still uncertain. It may, of course, vary between areas with different prevalence of heavy lead exposure (179). Also, renal disease may mainly be the result of long-term exposure, as in a follow-up of U.S. cases of childhood lead toxicity, there was no indication of late kidney effects (667). Moreover, the clinical entity of renal disease studied may be crucial. It may be, that lead does not precipitate the disease, but rather cause a deterioration of kidney disease from other causes.

Also, the available information presents several other methodological problems. It has e.g. been suspected, that the renal disease was the cause of lead retention, rather than the result of an exposure. Some data (179) may suggest, that renal failure with gout may cause a high lead excretion at chelation. Further, the use of the usual criteria for chelation test (even with prolonged urine sampling time) as an index of lead retention may not be relevant in subjects with renal failure and osteodystrophy (601). However, several studies indicate, that although there is a decrease of lead excretion with decreasing glomerular filtration, this is probably not

sufficiently large to explain all of the association (67,123,418,617), particularly not of the accumulation of lead in bone in uremic patients in Queensland, Australia (180,181,339).

5.3.4. Mortality

There was a considerably increased risk of death in renal disease in subjects, who had, as children, been treated for lead toxicity (226,338). In epidemiological studies of lead workers, there were increased incidences of deaths from kidney disease in workers in battery factories (167,485), smelters (167,506,705), and in lead pigment works (191). The workers have probably had B-Pbs above 3.0-3.5 µmol/l. Also, in some of these settings, there may have been exposure to confounding agents, e.g. cadmium. Increased mortality has not been seen at lower exposure (272).

As to hypertensive nephropathy, see also Section 5.5!

5.4. Gastrointestinal tract

Lead exposure may result in precipitation of dark bluish lead sulfide in the gingiva ("lead line", "Burtonian line"), particularly if there is paradentosis, with bacterial infection. Lead affects the gastrointestinal tract, causing constipation or diarrhoea, epigastric pain, nausea, indigestion, loss of appetite, and colic (58,450,451, 618,842).

Data on relationship between blood lead levels and gastrointestinal symptoms are limited; they are common with blood lead levels higher than about 3.5 µmol/l (58,450,842), but seems to occur even at lower B-Pbs (618).

5.5. Cardiovascular system

5.5.1. Cardiotoxicity

Animal experiments have displayed toxicity of lead on the *heart* (415). Effects on both the myocardium and the propagation system, causing both cardiac failure and arrythmia has been recorded in clinical cases of lead toxicity. Environmental and occupational exposure that raise the B-Pb above about 5 µmol/l in adults and 3 µmol/l in children are frequently associated with heart effects. At lower B-Pbs, effects have not been firmly established. Patients with heart disease may have a rise of B-Pb as a result of an increased packed cell volume (769).

5.5.2. Blood pressure

5.5.2.1. Animal studies

Lead exposure may cause an increase of blood pressure (83,285,425,712), as has been shown in both experimental animals (823) and humans.

The mechanism is unknown. Exaggerated alpha-adrenergic responses with changes in sympathetic tone and disturbance of calcium metabolism with affected smooth muscles in the end-arteriola and thus an increased vascular reactivity have been proposed as mechanisms (684,712). It has been suggested, that lead acts as a potentiator, or effect modifier, of a causal relation between a triggering agent and the blood-pressure response (134,713,714).

Also, there are indications of effects mediated via the renin-angiotensin-aldosteron system (125,817). Possibly, this effect is biphasic, with an increase of plasma-renin activity early during moderate exposure, and normal or depressed activities following more chronic, severe exposure. The effect on blood pressure is thus probably more pronounced with low doses than with high ones (823).

5.5.2.2. Human data

An association between excessive lead exposure and hypertension in man was reported by Lorimer already in 1886 (464).

In lead workers, there was an increase of plasma renin levels at B-Pb above 1.5 µmol/l (125).In lead-exposed children, there are indications of disturbed catecholamine metabolism (719). In on study of lead workers, there was no increased excretion in urine of catecholamines or the metabolite vanillylmandelic acid (VMA; 102), while in another, there was a certain increase of VMA and an B-Pb associated increase of another catecholamine metabolite, homovanillic acid (HVA), in the B-Pb range 1.0-3.6 µmol/l (579). There are conflicting results as to effects on the kallikrein-kinin system in lead workers (103,149, 656), possibly because of confounding cadmium exposure, which is associated with an effect.

Also, several large studies of samples of the *general population* or subgroups in the U.S. (683,684,839), the U.K. (225,617,753), the Netherlands (427), Canada (547), Denmark (296), and France (585) provides reasonably consistent evidence that a similar effect may occur, already within the B-Pb range of the general population in those countries.

In the B-Pb range in the general population, there is an increase of systolic and diastolic blood pressure by 1-2 mm Hg for each doubling of B-Pb (617). A similar effect has been reported in pregnant women (631; see also Section 9.2).

All positive correlations were weak. Also, a causal relationship has not been firmly established. For example, age and sex may be confounders. Further, hemoglobin level is associated with both B-Pb (Section 3.7.1.1) and blood pressure (296), and thus is a possible confounder. Moreover, the alcohol intake may affect both lead exposure (Section 2.1.2.2) and blood pressure, and may thus be a confounder (296; assuming that the effect of alcohol on blood pressure is not mediated through lead, and thus a factor in the chain of causality, and not a confounder). But there are studies, in which there was an effect even after allowance for alcohol intake (585,683). Some data indicate that smoking may negatively confound the relationship, as smokers tend to have higher B-Pbs, but lower blood pressure (713). Also, the possibility of reversed causation has been raised, as blood pressure is negatively associated with glomerular filtration, which might decrease lead excretion, and thus increase B-Pb. However, lead excretion

was, in one study, not affected by decreased glomerular filtration (123a), while others have shown increased B-Pb in patients with chronic renal failure (769,779).

Hypertension is associated with atherosclerosis and cardio- and cerebrovascular disease. In case-referent studies of essential hypertension, cases had higher B-Pb and U-Pb than referents (66,75,404), and autopsy cases with atherosclerosis higher bone lead than others (1). In another case-referent study, there was an association between lead levels in aorta at autopsy and "heart-related disease" (830). However, in all these four studies, confounding is a possible explanation of the findings. In a U.S. population study, there was an association between B-Pb and signs of left ventricular hypertrophy in the electrocardiogram (684). However, there was no indication an increase of chelatable lead in cases of hypertensive nephropathy (602). Further, in a U.K. prospective general population study, *no* association between B-Pb on the one hand, and ischemic heart disease and stroke on the other, could be firmly established (617). Possibly, the effect of beta-blocker therapy is less effective in patients with increased B-Pb (714).

There are thus indications of a levelling off of the effect as B-Pb increases. This may be the explanation of the fact that the information on blood pressure in *lead workers* is conflicting. Increase of blood pressure has been reported in early studies of heavily exposed workers. This has often been considered to be secondary to lead-induced renal disease. In later studies, of less exposed lead workers, there has only seldom been indications of an increase of blood pressure, and then only a slight raise (450), while, in other studies, no blood pressure effect was found (174).

Out of three recent studies, one reported a blood-pressure effect in workers with an average B-Pb of 2.3 µmol/l (195), while a second one showed a slight increase of blood pressure and ishemic electrocardiographic changes in workers with an average of 2.5 µmol/l (410,411), and a third one, with better control of confounding, did not find such an effect in workers with a current level of 1.9 µmol/l (time-weighted average 2.4 µmol/l; 605).

Moratality studies in lead workers have indicated an increased incidence of deaths from "other hypertensive disease", which, however, was mainly secondary to renal disease; there was no clear increase of hypertensive *heart disease* (167). In accordance with this, in another study, heart disease was not increased (705). In a series of studies of causes of deaths among heavily exposed lead workers, there were increases of deaths from *cerebrovascular disease* in some (191,242,485,506), but not in others (167,705). These cohorts had a heavy exposure (many had mean U-Pb over 0.5 µmol/l and B-Pb over 3.5 µmol/l).

In a Swedish study of lead-smelter workers, who probably had a lower exposure, there was no increase of neither cardiovascular, nor cerebrovascular disease (272). In recent studies of Swedish glassworkers, there were increased risks of cardiovascular and cerebrovascular disease (869,870,871). Glassworkers are exposed to lead, but also to a series to other agents.

5.6. Endocrine system

There are some indications of endocrine effects by lead exposure in humans on the hypothalamus-pituitary-thyroid/adrenal axes (283,362,650, 783,796). However, the effects reported are not consistent, and in other studies (318,644, 717), no

effects were noted, perhaps due to variations in exposure. The reported observations may indicate effects on the hypothalamus or the pituitary, on the iodine uptake by the thyroid, and/or on the thyroid-hormone binding serum proteins.

Effects have also been noted on the serum levels of prolactin (283,661) and cortisol (318) in man. Neither in this case, is the anatomical level of the effect known.

There are some indications of endocrine effects by lead exposure on the hypothalamus-pituitary-thyroid/adrenal axis, in groups of lead workers with average B-Pbs of about 2 µmol/l, or higher (283,318,650,661). However, the data does not allow a close definition of an effect level.

Effects on gonadotropins have also been noted; such effects will be discussed below (Section 9.2).

6. Immunotoxicology

6.1. Animal studies

Available information regarding immunotoxic effects of lead is limited (407,806). However, it is clear that in experimental animals, lead has an immunosuppressive action, parcticularly affecting the humoral immune system and macrophage function (423,424). Lead-exposed animals have an increased susceptibilty to infections, both by bacteria and viruses.

6.2. Human data

As to man, there is limited information (407). Lead workers (average B-Pb 2.7 µmol/l) suffered an increased incidence of colds and influenza infections (237). Also, the workers had suppressed levels of serum levels of immunoglobuline IgM, and of secretory IgA in saliva, and negative correlations between B-Pb (median 2.8 µmol/l) on the one hand, and serum levels of complement C3 and IgG on the other. In a similar study of immunoglobulins in workers with lower intensity of exposure (average B-Pb 1.8 µmol/l), there was no effect (408). However, tendencies of suppression of immunoglobulins IgM and IgA were found in children living in the vicinity of a smelter (832). Further, there was a disturbance of suppressor-cell activity in lead workers with B-Pbs in the range 1.9-2.5 µmol/l (159), and of leukocyte chemotaxis in workers with B-Pbs above 3 µmol/l (282). In Swedish smelter workers, exposed at a similar intensity, there was lymphocytosis (727).

It has been claimed that lead exposure was the cause of the high incidence of deaths from lung disease in printers in earlier centuries, allegedly due to a decrease of the resistance against tuberculosis (577). However, the basis for this view is weak.

Lead does not induce allergic contact dermatitis or other allergic disease.

7. Mutagenicity

In general, experimental *in vitro* and *in vivo* tests on genotoxicity, lead has not caused effects (367-369,884).

Urinary mutagenic activity, as assayed by bacterial fluctuation tests was not affected by occupational lead exposure (29).

Thirteen cytogenetic effects on chromosomal aberrations and sister chromatide exchanges in peripheral lymphocytes were found in 13 studies of lead-exposed populations, whose average B-Pbs ranged 0.3-4.8 µmol/l (73,255,305,366-369,446,552,674), but not in nine studies of these parameters (367-369), or of micronuclei (348) in populations with B-Pbs in the range 0.2-2.8 µmol/l .

The varying results may be due to relevance of referent groups, lymphocyte culture time, intensity and duration of lead exposure, and - above all - simultaneous exposure to other clastogenic compounds. The signficance of chromosome aberrations, as far as health is concerned, is unclear. Cancer and chromosome aberrations in the offspring have been proposed.

In one study, the fetal death was more prevalent in wives of smelter workers, exposed to *i.a.* lead, which was suspected to be due to a genetic effect on the male germ cells (74). However, there are several possible explanations, biases as well as carry-home exposure.

Lead workers had an increased urinary excretion of ß-aminoisobutyric acid (245), indicating an effect on the thymine metabolism in DNA.

Some other effects (especially the possible lead-associated abortions), discussed under reproduction (Section 9), might be of genotoxic origin.

8. Carcinogenicity

8.1. Animal studies

Lead acetate and lead subacetate caused kidney and brain tumours, lead phosphate kidney tumours, in rodents, following oral or parenteral administration (367-369). The doses were high and caused gross morphological changes in the kidney. However, there were dose-repsonse relationships, and the interval from onset of exposure to tumour formation was shorter in the the more heavily exposed animals. Metallic lead, lead oxide, and lead arsenate could not be evaluated.

IARC in 1987 concluded that the evidence for cacinogenicity to animals was sufficient for inorganic lead compounds (369). The overall classification of inorganic lead and lead compounds was "possibly carcinogenic to humans" (group 2B).

There seems to be a synergistic carcinogenic effect between lead acetate and organic carcinogens (e.g. nitrosamines; 369).

8.2. Human data

Even though some animal experiments provide indication that inorganic lead can be carcinogenic, epidemiological studies of workers exposed to lead do not support the existence of such an effect in man (167,242,272,367,369,478a,485,705), in spite

of the fact that the exposure in several of the studies corresponded to B-Pbs well above 3.0 µmol/l.

A lack of demonstrated carcinogenicity seems to be relavant also to lead arsenate and lung cancer (847). There are occassional case reports on renal cancer in lead workers (57,449), but this may be due to chance. In a Finnish study of renal cell adenocarcinomas, there was an elevated, but statistically nonsignificant increased risk associated with exposure to lead (607).

IARC in 1987 concluded that the evidence for cacinogenicity to humans was inadequate (369).

In recent studies of glassworkers, there were increased risks of stomach, colon, and lung cancer (868-871). Glassworkers are exposed to lead, but also to a series to other agents.

Of two case-referent studies of tumours in children and lead work in their fathers, one has indicated such an effect (396,574a), while the other did not (425a,859, 860).

9. Reproduction

Reproduction toxicology may include any effect, which affects the fertility or the progeny. Such effects are disturbance of the endocrine basis of fertility in males and females, i.e. the spermatogenesis and the estrous cycle, and effects on the gonads, the ovum, or the sperm cell, the embryo and fetus, and the neonate. Further, the placenta may be damaged.

The end points may - in theory - be decreased libido, menstrual disorder, reduced fertility, fetal loss, stillbirth, malformation, low birth weight, perinatal disease, developmental disturbance (physical or mental), or childhood cancer. Some of these effects will be discussed in this section.

There are several recent reviews on the reproductive toxicology of lead (156, 806).

The effects on the germ cells or the early embryo may have a genotoxic basis (point mutations or chromosome aberrations). Such events may, theoretically, result in i.e. abortion, malformation, tumours in the progeny, or genetic diseases in later generations. The knowledge as to genotoxic effects of lead have been discussed above (Section 7).

In addition, because of a general feeling of disease in a severly poisoned person, the libido in males or women may be affected, as well as the potency in males; such effects will not be discussed in this section.

9.1. Animal studies

Reproductive effects of lead have been studied i several studie. The doses employed have not been excessively high. Lead exposure may impair the endocrine function of *male* animals, probably through disturbance of the hypothalamic-pituitary function (653,745,746).

Probably mainly as a concequence of this, but also because of a direct toxic effect on the testis, lead has been shown to induce testicular atrophy, and to reduce

spermatogenesis (150,326,676,746). Also, lead is known to affect the spermatozoa (387,388) and to reduce sperm motility (806). Thus, it is not surprising, that lead exposure of male animals decreased their fertility and caused reduction of birth weight and survival (389).

Pre- and/or postnatal exposure of *female* animals to lead can probably disturb the hypothalamus-pituitary-ovarian-uterine function (284). Probably as a result of this, long-term lead exposure in nonhuman primates caused altered menstrual cycles (439).

Further, in exposure of pregnant rodents to lead in caused implantation failure, probably due to interference with the ovary-uterus endocrine interaction (848,849,851,853-855). Moreover, exposure of pregnant rodents to high does of lead by injection caused resorption of embryos, and offspring showed low weight, malformations, and increased perinatal mortality (417,867).

Lead-exposure may decrease the blood flow through the placenta and may cause disturbances of the heme metabolism of the fetus (806). Further, long-term low-dose exposure affects the CNS development (806). Thus, morphologic effects in the fetal nervous system (476,477) and behavioural changes (354) have been reported in nonhuman primates at exposures not affecting the pregnant mother (192).

Interestingly, exposure *in utero* caused reduced fertility in the female mouse, probably due to damage of the primordial germ cells (850,852).

Suckling animals recieve lead via breast milk from exposed dams (Section 3.4.3).

9.2. Human data

Few areas are more resistant to scientific study than human reproduction. Thus, there are many caveats. However, there are sufficient evidence that lead may cause reproduction effects in man. These are even thought, by some, to have contributed to the fall of the Roman empire (274).

As to effects on the *male* reproduction, there are some indications of effects of occupational lead exposure on the hypothalamic-pituitary-testis axis (106,318). Such effects have been found in groups of lead workers having an average B-Pb of 1.9 µmol/l or higher (318). This might affect the male fertility, but proof of this mechanism lacks. A similar effect was not observed in another study; however, the reference group had high blood lead levels (267a)

Decrease of libido, erectile dysfunction, ejaculation problems, and sperm disturbancies have been reported in lead workers, as has an increased rate of abortions in their wives (431). There are methodological problems, especially as the results were not consistent.

Although in one recent study of subjects without known occupational, or other particular, lead exposure, there was an association between lead levels in the semen and sperm qualities (666), other studies have not displayed this (806).

There are data from lead-poisoned males that may support lead effects on testis and spermatogenesis (47,106,183,250,431,650,828,858), but not all studies have displayed such an effect (795), perhaps due to the methodological problems

involved in this type of investigations. One difficult problem is the low participation rate and the selection of an adequate reference group.

Sperm abnormalities have, on rather weak data, been claimed to have occurred in lead workers with an average B-Pb of 2.0 µmol/l, or more (431). In one study, subtle changes of some semen parameters (with unknown functional significance) were noted in a group of lead workers with an average B-Pb of about 2.2 µmol/l (858), in another changes of sperms in a group with an average B-Pb of 2.9 µmol/l (47). Also, damage of testes and sperm changes have been reported in workers with other symptoms and signs of clinical lead toxicity, having higher B-Pbs (106,183).

In a recent, important Danish study, in which a long series (up to 11) of blood lead determinations and semen analyses were made in 19 workers in a lead storage battery factory during one year, there were significant associations between B-Pb (average 2.0 µmol/l) on the one hand, and sperm vitality, motility, and morphology on the other (828). It was estimated that a decrease of B-Pb from 2.2 to 1.7 µmol/l corresponded to an increase of the number of living sperm cells by 9%, of moving cells by 9%, and of normal cells with 7%. A no-effect level cannot be judged from these data.

In a Danish case-referent study, there was no association between lead exposure on the one hand and infertility or semen abnormalities on the other (530).

In a study of workers in a Swedish smelter, women employees were reported to have higher spontaneous abortion rate if their husbands were also working at the smelter (559). This study has methodological problems. Results in a Finnish case-referent study suggested a possible dose-response relationship between measured or estimated B-Pbs of males and hospital-treated abortion in their wives (odds ratio 1.6, confidence interval 0.6-3.9 in males with B-Pb ≥1.9 µmol/l), but the data did not allow firm conclusions (456). In a population study of medically diagnosed spontaneous abortions in Finland, lead exposure in the husband was not a risk factor (455). The findings are in general accordance with other, older data (806). Studies in fertile and infertile males in the general population have not revealed differences of B-Pb levels (806).

Regarding possible *genotoxic* effects on germ cells, see Section 7.2.

There are no studies on possible effects of lead on the *female* hypothalamic-pituitary-ovary-endometric axis, or directly upon ovaries (806). A Danish study suggests a possible association between female occupational exposure to "lead, mercury, and cadmium" and *infertility* (639). However, further data is needed to allow firm conclusions.

There was a small but definite association between B-Pb in pregnant women and *blood pressure* at delivery (but not preeclampsia; 631; see also above). The effect was in the magnitude of 6 mm Hg/µmol/l. It is wellknown that hypertension may affect the fetus.

As said above, lead passes the placental barrier and thus causes exposure of the *embryo* and the *fetus*, including its CNS. Some aspects of such effects are discussed in recent reviews (193,542,804).

Already in 1860, Paul reported that severely lead-poisoned pregnant women were likely to *abort*, while those less severly intoxicated were more likely to deliver stillborn infants (609). Lead compounds have even been used as abortifacients.

There is a paucity of information on exposure (806). However, it can safely be assumed, that the exposure was very high.

In a Finnish study of spontaneous abortion among occupationally exposed women, there was no clearcut association with B-Pbs (individual values up to 3.1 µmol/l), although the confidence limits were very wide (771). In the Australian Port Pirie study, abortions were not associated with B-Pb (average 0.5 µmol/l), although the study was not designed to detect effects early during pregnany (54).

Other studies in the general population of perinatal infant health and lead exposure have given varying results (806). In the Port Pirie study, the stillbirth rate was doubled in a lead-exposed group (54). In an English study, placentas from *stillbirths* and infants with a record of "fetal distress" possibly had higher lead levels than those from other pregances (405). There are some indications that there is an association between lead levels and enzyme activity in placenta (398). Moreover, another English study possibly indicated, that skeletal lead levels were increased in stillborn babies (113).

The most reliable data on the fetus and infant come from well-controlled prospective epidemiological studies in Australia (Port Pirie and Sydney), the U.S. (Cleveland, Ohio; Cincinatti, Ohio; Boston, Masachusetts), and Scotland (Glasgow) of women without occupational exposure and their offspring (802,804). In those studies, extensive efforts have been paid to identifying and controlling possible confounding variables (*i.a.* socio-economic factors) and the possibilty of reversed causality, which are major problems.

In some prospective studies, lead-associated reductions of *gestational age* (Glasgow: 524; Port Pirie: 507) and *birth weight* (in term deliveries; Boston: 79; Cincinatti: 100) have been documented, though not in all studies (22,311,655). The reduction of gestational age is also in agreement with cross-sectional studies of populations with high exposures in Missouri, U.S. (240), but not in another U.S. population (22), which had, however, a lower exposure. In a small study in Sweden and Poland, the lead levels were higher in the myometrium in preterm delivery than in term deliveries (239). Further, there are some data supporting an association between high B-Pbs and premature membrane ruptures in term deliveries (240).

In the Port Pirie study, the relative risk of pre-term delivery at maternal B-Pb of 0.7 µmol/l, or higher, was 3.4 times the risk at levels up to 0.4 µmol/l (54). In the U.S. Cincinatti study, for approximately every 0.5 µmol/l increase of B-Pb, the decrease in birth weight was from 58 (18-year-old mothers) to 601 g (30-year-old mothers; 100). In a Californian study, a cord B-Pb of 2.4 µmol/l was associated with a relative risk of 2.9 for prematurity (population attributable risk 47%; 673).

In a retrospective study, there was also some indications on minor *congenital malformations* (545). However, the study does not allow firm conclusions on this point. Other studies have not displayed such effects (15,234).

In a study of Swedish female smelter workers, there was an increased frequency of spontaneous abortion and a decrease of birth weight if the woman was employed at the factory, or had been so employed earlier, and still lived near the smelter (559,560). Also, women, who worked in polluted areas of the smelter had a higher risk than the others. Moreover, it was claimed, that both single and multiple malformations were increased, if the mother had worked in the smelter during

pregnancy (560). Both studies are open to criticism from a methodological point of view, because of possible selection and observation biases, as well as confounding problems because of mixed exposure. In a Finnish case-referent study, there was no significant association between spontaneous abortion and B-Pb (771); however, the lead exposure was low, and the confidence intervals wide.

In a study of the population around a Swedish smelter, there was claimed to be an increased frequency of miscarriges and birth-weight reduction in females living close to a smelter (557,558). Later studies, by the same group, of the population living around another smelter, gave similar results, with decreases of birth weights and increases of malformations in females living close to the smelter (256,561). However, there are several major methodological objections to these studies.

An effect of lead on the offspring is not obligatory; even at very high exposures, women have given birth to apparently healthy infants (806,867).

Further, lead has caused metabolic effects on *heme* synthesis in the fetus, as reflected by ALAD activity in red cells and urinary ALA excretion in the newborn infant, in groups with average maternal B-Pbs of 0.5 µmol/l, or higher (442,804).

It is not known to what extent effects in infants or children are due to prenatal exposure, to exposure via breast milk, or to later exposure, including indirect exposure in lead worker´s children. The information will be discussed in one context here.

There are some indications, that infants, who suffered from *sudden infant death syndrome* had somewhat higher lead levels in blood (206), teeth (469), and different tissues (230) than other infants. It is not known whether this is due to prenatal or postnatal exposure, and whether the association is a true causal one.

Also, *growth and stature* of the child may be reduced, at least during the first years of life (440,468,685), although not all studies have shown such an effect (311). An effect on growth is intersting, because effects on osteoblasts have been reported (623,658).

Further, three of the above-mentioned, large prospective studies in the *U.S.* (*Cincinatti:* 201; *Boston:* 77,78) and one of the *Australian* (827), have shown lead-exposure associated developmental effects on *cognitive abilities* and *behavioural* functions (193,542,802,804).

In summary, response rates of these effects on the child have been to dependent upon the B-Pbs in the pregnant woman, the newborn infant, and the young child. Taken together, the data indicate, that slight effects *may* be present already at B-Pbs in the pregnant woman, newborn (cord blood), and/or infant in the range of 0.5-0.75 µmol/l, *perhaps* even lower (306). An example: For every increase of B-Pb by 0.5 µmol/l, the 24-month the mental development index score decreased by about 2 points (the scale has an average of 100, and a standard deviation of 16; ref. 54).

However, in a fourth prospective study in the *U.S.* (*Cleveland:* 233) there was no clear lead-associated effect, and neither in a second *Australian* one (*Sidney:* 503). No effect was seen in a study in the *U.K.* (*Glasgow:* 523a). In the non-positive Cleveland study, the average cord B-Pb was about 0.3 µmol/l, the B-Pb at 3 years 0.8 (range up to 2.0) µmol/l (233). The acceptance of low-exposure effects on child development has not been unanimous (233,740).

The effects on CNS are in general accordance with findings in recent mainly cross-sectional studies of young children from the *U.S.* (*Boston:* 544; *Chicago:*

573; *Cleveland:* 235; *North Carolina:* 681), *Scotland* (*Edinburgh:* 629), *U.K.* (*London:* 882a), *Greece* (*Lavrion*: 332), and *New Zealand* (*Dunedin:* 721; *Christchurch:* 247), in which neuropsychological and/or behavioural deficits were documented in children. The results are also partly congruent with findings in *Australia* (*Sydney:* 503) and *Germany* (*Duisburg:* 875; *Stolburg:* 876; *Nordenham:* 872).

However, there are some studies from the *U.K.* (*London:* 739; *Southampton:* 616; *Birmingham:* 330) and *Italy* (829), the result of which did not fit into this general picture.

In a metaanalysis of eight European cross-sectional studies covering B-Pbs in the range 0.2-2.9 µmol/l, there were weak negative association bewteen B-Pb on the one hand, and psychometric intelligence and visual-motor integration on the other, but the explained variance was low (about 1%; ref. 873).

Of particular interest is a cross-sectional study from Denmark, in which there was a negative association between tooth lead and IQ in first grade children from Århus (301,468, 475,567,568). Children with dentin lead levels <5 (average 3) µg/g were compared to those with ≥19 (average 27) µg/g. The average B-Pb in the study group (a few years after the collection of the teeth) was only 0.25 µmol/l (0.18 and 0.27 µmol/l, respectively, in the two groups). In a Swedish study, there was no convincing association between various minor neuropsychiatric disorders and the tooth lead levels of the children (275).

It should be stressed, that there are several methodological problems (e.g. inadequate marker of exposure, insensitive measures of performance, bias of selection, reverse causality, and inadequate handling of confounding by under- and/or over-controlling) in this type of studies (306,473,475,543, 731). Further, the total variance of the intelligence that is explained by lead exposure is small, a few per cent.

The reversibilty of the CNS effects is not adequately known. In preliminary data from one study, it was claimed to be partly still present in children five years of age (77, 802,804).

There was an association between lead exposure and *hearing impairment* in a U.S. study (688). Further, changes in *electroencephalogram* (EEG, including evoked potentials) have been recorded (603,651,707).

The effects in infants and children may, in principle, be due to exposure *in utero*, during breast feeding, or later. Exposure through *milk* may be considered to be a reproductive effect. As said above (Section 3.4.3.), lead is excreted in breast milk. In Swedish women without particular exposure, the level in milk was about 0.01 µmol/l; the lead level in human milk was lower than that in milk formulas (437). In one study, the average level in milk was about 9% that in the mother's blood (524; Figure 9).

This is compatible with levels reported in three other subjects (664,706,778; Figure 9). There is a considerable varation; but it is not known whether this is due to analytical problems, to a variation from day to day, or an inter-individual difference permanently over time. In one of these, the infant of a lead worker, who was studied in some detail, the milk displayed levels up to 0.3 µmol/l, and the lead intake was 3.7 µg/kg/day (664). In spite of that, the B-Pb in the infant decreased

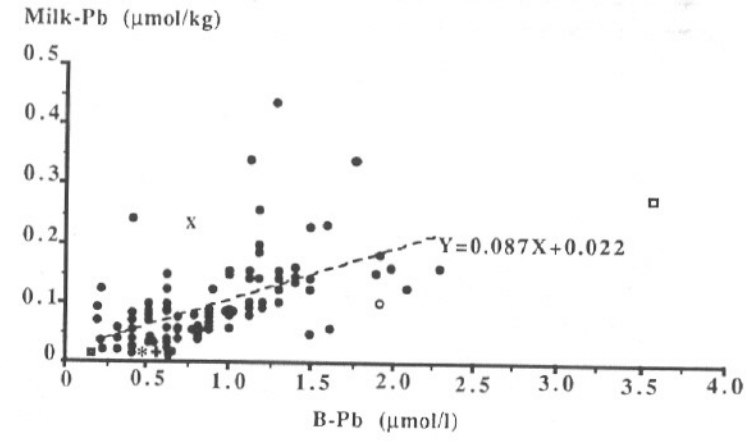

Figure 9. Relationship between lead levels in blood (B-Pb) and milk (Milk-Pb). Closed circles (and the regression line) denote 97 subjects from Moore et al (524), open circle denotes one subject from Rye et al (664; average for the first 3 weeks after delivery), a star the average of 28 subjects from Kovar et al (422), a plus the average of 39 subjects from Rockway et al (652), a open square one subject from Thompson et al (778), an "X" average of 114 subjects from Ong et al (583), a closed square the average of 27 subjects from Schramel et al (680), and a triangle one subject from Sensirivaratna et al (706).

during lactation (from 3.4 at delivery to 1.0 µmol/l at 9 months). In one other woman, who had suffered acute lead encephalopathy as a child, and who had present symptoms indicating lead toxicity and a B-Pb of 3.6 µmol/l, the level in milk was 0.3 µmol/l (778). Her breast-fed infant had a B-Pb of 2.6 µmol/l. One 2-month old infant with suspected lead encephalopathy had a B-Pb of 5.4 µmol/l (706). Her mother had a B-Pb of 1.6 µmol/l, and her milk contained 0.3 µmol/l.

Further, toxicity has been reported to have occurred in an infant, who was breast fed by an exposed woman (426). However, the latter data are too vague to allow firm conclusions on this point.

In a study of childhood cancer, there was no association with parental lead exposure (575). However, in another study, paternal exposure to lead was associated with childhood leukemia (117); however, the number of tests was so large, that the possibilty of an association by chance must be considered, and the finding needs verification.

10. Need for further research

In spite of the fact, that scientific studies on the toxicology of lead have been performed for more than a century, many problems are still unsolved. Here will only be given a few examples.

There is insufficient information on the mechanism behind the toxic effects of lead.

B-Pb is extensively used for monitoring of exposure. Not enough is known about the binding of lead in blood cells and plasma, including inter-individual variations.

Alternative means of monitoring of exposure have not been sufficiently penetrated, e.g. levels in plasma and urine, as indices of mainly short-term absorption, and skeletal lead concentrations as an index of long-term uptake. The relationship between skeletal lead levels and effects should be penetrated.

Also, the effects of the exposure on the kidneys must be further analysed, as well as the effects on male and female reproduction, and on the CNS of infants.

11. Discussion and evaluation

11.1. Limitations of the available information on dose-response

Occupational exposure to inorganic lead occurs mainly through inhalation. However, absorption from the gastro-intestinal tract is also of importance, as some of the particles deposited in the respiratory tract are cleared and swallowed, whereafter some absorption occurs. Also, many lead workers are exposed through contaminated smoking tobacco, snuff or foods. Cutaneous absorption is generally unimportant, but may probably occur, to a limited extent, for lead soaps.

There is only limited information on the relationship between air levels and toxic effects of lead. But there is a wealth of information on the association between biological indices of exposure and effects. Biological monitoring of the lead exposure has several advantages over air monitoring. It compensates for variations in ventilation, particle size, and solubility of the particular lead species, it takes into account different routes of uptake (which is important in the case of lead), and it reflects non-occupational exposure (which may be of considerable importance for lead).

In most of the studies on different toxic effects of lead, B-Pb is used as an biological exposure index. However, it should be stressed that even the employment of B-Pb in dose-response evaluations implies several serious problems.

First, the relationship between lead uptake and B-Pb is non-linear, the relative increase of B-Pb decreases with increasing exposure. This is probably the reason why some effects (e.g. on the heme metabolism) display non-linear relationships with B-Pb, patterns which have sometimes, mistakenly, been interpreted as indicating a threshold. Further, B-Pb is not only affected by the recent uptake of lead, but also by the endogenous exposure from the skeleton, which may be considerable (see Section 11.6.).

Second, there is a substantial inter-individual variation in the kinetics of lead. This should mean, that different subjects attain varying B-Pbs at the same rate of uptake.

Third, there seems to be a great inter-individual variation in the effects suffered by different individuals at the same B-Pb; some subjects have been reported to sustain extremely high B-Pb levels without adverse effects, in others, toxic effects have been associated with quite low B-Pbs. This might, *i.a.*, be due to inter-individual variations in the pattern of binding of lead in the blood cells, a possibility that has not been adequately clarified, though there are some indications.

Other media for biological monitoring of exposure has been employed more seldomly. P-Pb or S-Pb is probably a more accurate estimate of exposure, and of the metabolically active body lead pool, but the combination of extremely low levels with problems of contamination and analysis, precludes the use of those media. U-Pb and chelatable lead may may have the same advantages, but have been used in only a limited number of studies.

Thus, due to the wealth on information on B-Pb, and the lack of other information, any estimate of the dose-response must mainly be based upon B-Pbs, but with careful observation of its inherent problems. This is the procedure to followed here. Then, the critical B-Pbs will be translated into exposures, in terms of uptakes and air levels.

Exposure to lead may affect many organs and functions in the body. Thus, in man effects on the reproduction, cardiovascular system, heme synthesis, blood cell formation, central and peripheral nervous system, kidneys, gastrointestinal tract and immunosystem have been reported. Also, there are some indications of genotoxic effects, and, in animal experiments, carcinogenic properties.

Besides the limitations of B-Pb, there are several other problems associated with the interpretation of available information on the relationship between dose and effects/response. One is frequent lack of information on earlier lead exposure. B-Pb at a certain time reflects mainly recent exposure, and only to a limited extent earlier exposure. This is a particular problem when the effects may be due to a chronic exposure. Recently, skeletal lead levels have been used as an index of long-term exposure, but the information is still very limited.

Most studies on dose-effect/response are cross-sectional. This implies that there may have been a selection. Thus, subjects who developed adverse effects may have left more often than those who did not, which may have caused an under-estimate of risk. On the contrary, there may have been a primary association between malfunction and exposure, which may cause an opposite bias, an over-estimate of the risk.

Also, it is generally not the clinically manifest effects that are of main interest, but subclinical disturbances of function, assumed to be early signs of effect. However, such effects may involve several problems. Sometimes they are subjective and unspecific. In other cases, the health impact of the subclinical effects is not clear.

For only a few effects, do we have well-defined dose-response curves. Unfortunately, in most cases, there is no basis for establishment of reliable relationships; it is difficult to state accurately at what exposures effects appear. This is a particular problem in the case of lead, as the exposures in the occupational

setting (and the general environment in many areas of the world) are close to the effects levels.

In the following, first two particular problems will be discussed separately, reproductive disturbances and effects on the blood pressure. The reason is, that these effects involve special problems of interpretation, especially in relation to occupational exposure. Then other toxic effects will be discussed.

11.2. Reproductive effects

Of great importance are the potential consequences of lead exposure for the *embryo/fetus*. Thus, exposure of the female during pregnancy, causes lead accumulation in the placenta. Also, it may cause an secondary exposure, *in utero* or during lactation, of the offspring. Fertile women (and, though to a less degree, males, see below) may thus be considered a surrogate risk group for the embryo/fetus and the infant.

Lead is embryotoxic/fetotoxic in experimental animals. The information in man is incomplete, but indicates severeral types of effects. Historically, the reproductive effects of lead in man attracted much interest from physicians and public health authorities at the turn of this century. This more or less lead to the exclusion of women from the workforce in lead-using industries. This is probably one reason why there are few data on reproductive effects in occupationally exposed women.

Available information does not firmly support a teratogenic effect (malformations) in man. However, several studies have shown effects on the fetus, including reduction of gestational age, birth weight, and disturbances of heme synthesis. Further, retardation of neurobehavioural development, and growth, as well as electrophysiological and hearing changes, have been reported in infants and children. Slight effects on the heme metabolism and mental and motor development have repeatedly been claimed to be associated with exposure corresponding to low B-Pbs, prenatally and/or early in life. There are many methodological problems (reversed causality and confounding) associated with such studies, but the observations in several recent prospective studies of pregnant women, exposed in through the general environment, and of their infants, cannot be disregarded. They indicate that effects may occur even at B-Pbs in the pregnant woman and infant of only 0.5-0.75 µmol/l. However, it must be stressed, that, in most studies, the fraction of the total variance, which was explained by lead was marginal.

In accordance with the situation in adults (see below), the health consequences of the heme synthesis disturbances in the fetus are not known. However, such biochemical phenomena may be the background of the lead-associated CNS-effects seen in infants.

The *breast-fed infant* may be exposed to significant amounts of lead. The intake of breast milk may be as high as about 150 g kg body weight^{-1}day^{-1} (349). The provisional tolerable weekly intake of lead for infants is 25 µg kg^{-1} (244), corresponding to 3.6 µg kg^{-1} day^{-1}. This would correspond to a level in breast milk of 24 µg kg^{-1} (0.12 µmol kg^{-1}). On the basis of available data, this corresponds to an average B-Pb of approximately 1.2 µmol/l. It is probable, that in some infants, the exposure may be even higher at this maternal B-Pb, due to inter-individual variation of the levels in the milk at a certain B-Pb in the woman. It could be

mentioned here, that an adult Swede, without occupational exposure, ingests about 0.5 µg kg^{-1} day^{-1}.

To this should be added, that it may be assumed that the gastrointestinal absorption of lead in the lactating woman probably is enhanced, that there probably is a mobilisation of lead from the skeleton during lactation (see below), that the absorption in infants is higher than in adults, and that the lead absorption may be enhanced when the lead is contained in milk. Further, the penetration of lead into the CNS probably is more effective in infants than in adults. There is thus reason for cautiousness. One single mentioning of case of lead toxicity in a breast fead infant has occurred in literature, but the information on this case is so scarce, that it cannot be evaluated.

It is not known for sure to what extent the reported effects in infants/children are due to prenatal exposure, to exposure *via* breast milk, and/or to later exposure. Also, the reversibility of the effects is not known. However, it should be stressed, that even if the effects should be technically reversible at a later age, they may already have disturbed the psychosocial development of the child during early childhood, which may have later consequences. Even minor effects must therefore be regarded as potentially harmful.

Lead has caused disturbances of the hypothalamic-pituitary-testis endocrine axis, testis damage, and sperm defects in studies of *male* animals. The studies in man are few, and not fully conclusive. However, based upon available information, it seems reasonable to assume, that B-Pbs of about 2-3 µmol/l, or higher, are associated with both endocrine dysfunction and sperm changes.

In addition to the effect through germ cells, placenta, and breast milk, *secondary exposure* may occur in children, of both male and female workers, as a result of contamination of the infant/child´s environment, but this will not be discussed further here.

11.3. Cardiovascular effects

Lead causes an increase of *blood pressure* in experimental animals. The exposure-response relationship is unusual: the relative effect is probably more pronounced with low doses than with high ones.

Also, several studies of samples of the general population, indicate that a similar effect may occur in man, and already within the B-Pb range of the general population in some countries. It seems (as in animals), that the slope of the B-Pb/blood pressure curve is steepest at low B-Pbs, levelling off at higher ones. In the B-Pb range of the general population, there was an increase of systolic and diastolic blood pressure by 1-2 mm Hg for each doubling of B-Pb. This is a rather small effect, from an individual risk point of view. However, from a population health point of view, it might be important, as an effect on the blood pressure may have impacts on the cardiovascular system, mainly cerebrovascular disease and coronary heart disease.

It has been proposed that lead is the background of the association in the general population between soft drinking water and coronary heart disease. However, it seems, that lead is not a *major* contributor to risk of cardiovascular disease in the general polulation. Each mm Hg is associated with an increase of ischemic heart disease by about 1% (617). An association between lead exposure in the general

population and risk of cardiovascular disease has not been empirically demonstrated.

However, it should be stressed, that the available information does not allow firm conclusions on whether the association between B-Pb and blood pressure in man is causal; there may be methodological problems (reversed causality and confounding). Even less is known about the actual public health impact, if any.

Several studies indicate a blood pressure effect in heavily exposed lead workers. It is possible that these blood-pressure effects may be associated with kidney damage (see below, Section 11.4), and that this affect is different from the effect at lower exposures, which may mainly be due to effects on vascular reactivity.

Increased risks of cerebrovascular (perhaps also cardiovascular) disease have been reported in some epidemiological studies of lead workers. Probably as a result of the effect on blood pressure, in those cases, the exposure has been intensive.

Lead also seems to have a cardiotoxic effect, but only at high exposures, corresponding to 5 µmol/l, or higher.

11.4. Other effects

Gastrointestinal effects occur at high exposures, mainly at B-Pbs of 3.0 µmol/l, or higher.

Lead exposure may induce *kidney* damage, with interstitial nephritis, often combined with gout. The information on dose-response is incomplete. However, it is clear, that such severe effects occur mainly a long time after high exposures.

However, there is evidence, that slight effects on the tubular epithel, with enzymuria occurs at considerably lower exposures, probably already at about 1.5-2.0 µmol/l. The health significance of slight enzymuria is not known; there is some information indicating reversibility after end of exposure. However, considering the severe kidney effects that lead exposed subjects may suffer, the subclinical changes will here be considered adverse.

Lead also affects vitamin D and calcium metabolism. Such effects might be mediated through effects on the kidney. In children, such disturbances have been documented in the B-Pb range 0.75-1 µmol/l. However, adults seem to be less sensitive.

Lead also affects the *nervous system*. Very severe toxicity with clinical encephalopathia may occur in some persons at B-Pbs as low as about 4 µmol/l. There is evidence of slight effects on the CNS at exposures corresponding to B-Pbs of 2.5 µmol/l. Limited data may indicate CNS effects already at 1.5 µmol/l. Infants are probably more sensitive than adults. The health impact of such slight CNS effects is not fully clear; however, it seems reasonable to consider them adverse.

Severe lead exposure causes peripheral neuropathy with axonopathy. Limited information indicates that slight peripheral nerve dysfunction (reduced nerve conduction velocities at neurophysiological examination, but no signs or symptoms) may occur in adult subjects with B-Pbs about 1.5 µmol/l. It is not known whether the reduced conduction velocities are really subclinical signs of the clinical neuropathy; it might be that they signify a more harmless disturbance of the ion transport over the cell membrane of the nerve cell. Also, there are some indications of reversibility. However, in light of the severe neuropathy, that may

affect lead exposed subjects, the conduction velocity disturbances will here be considered adverse. Effects on the autonomic nervous system have been recorded at the same B-Pbs.

Heavy lead exposure may cause *anemia*. Such is usually associated with B-Pbs of 3.0 µmol/l, or more, and is caused by hemolysis in combination with inhibition of several enzymes in the heme and nucleic acid metabolism.

However, there is slight enzyme inhibition in the bone marrow/red cells at much lower B-Pbs. Probably effects on the enzymes ALAD and P5N in red cells are proportional to B-Pb, right down to the B-Pbs in subjects without particular lead exposure. However, it is not known whether such slight effects have health consequences.

Neither is it known whether corresponding inhibition of heme synthesis occur in other tissues at similar low exposures. However, considering the central position of heme in the energy metabolism, including the CNS, and in handling of organic xenobiotics by the tissues, the effects on heme synthesis may well be important. However, for the time present, there is not sufficient eveidence for classifying such effects as defenitely adverse. They will thus not considered as determinants of critical exposures.

There is only limited information on *immunotoxic* effects og lead. Possibly, there are various effects on humoural and cellular immunity in groups of lead workers with B-Pbs of about 2.0 µmol/l, or higher. The health implications of some of these effects is not clear, but an increased sensitivity to infections has been reported in one study.

As to *genotoxic effects*, chromosome aberrations in peripheral lymphocytes have been reported in workers exposed at levels corresponding to average B-Pbs of about 2 µmol/l, or higher. However, the available information is conflicting. Further, the health significance of such findings is not known. They have been suspected to reflect a possible risk of reproductive risks in terms of inborn chromosome aberrations and of cancer. However, there are no other indications of such effects in man, although some chemical forms of lead are animals carcinogens.

In summary, the available data indicate slight adverse effects on the CNS and PNS, as well as on kidney tubuli, at exposures corresponding to B-Pb as low as 1.5-2.0 µmol/l (expressed as an average in groups of exposed subjects). The available data does not allow a closer definition of the risk (response). As said above, effects on the fetus, as well as on the cardiovascular system may occur at even lower exposures.

11.5. Critical exposures

On the basis of the discussion above, a B-Pb of 1.5 µmol/l may be a critical level for adverse effects of exposure to inorganic lead in the adult human. The next step is to translate this into an approximate uptake of lead into the body and into air lead level.

There is a considerable amount of data on the association between exposure to lead and B-Pb. Generally, in industry, there has been a poor correlation between air lead measurements and B-Pb. This may have several explanations: (1) The particle size of the aerosol and the solubility of the lead species. (2) Area sampling instead

of sampling in the breathing zone has been employed. (3) There may have been an "occupational" exposure through food and tobacco. (4) The "background" lead exposure may vary. (5) There is an inter-individual variation in lead metabolism. (6) The time of employment (skeletal accumulation) is important.

Thus, it is not possible to use these data for a translation of B-Pb into an air lead level. Instead, estimates of the relationship, based mainly upon other sources will be used (Figure 6, p.24). According to this, a B-Pb of 1.5 µmol/l corresponds to an average uptake of roughly 100 µg day^{-1} (with a considerable inter-individual variation). This corresponds to 700 µg $week^{-1}$.

There is no reason to assume that the environmental and the occupational exposure will not add up toxicologically. Thus, when translating the B-Pb into exposure in the occupational setting, first the background B-Pb must be considered. In the Nordic countries, the B-Pbs in the general population is low, in average about 0.4 µmol/l in males. This level is somewhat lower in females and somewhat higher in smoking males than in nonsmoking ones.

The background B-Pb of 0.4 µmol/l is mainly due to absorption from foods, to some extent also from drinking water, air, and tobacco. The uptake is about 5 µg day^{-1} (about 30 µg $week^{-1}$). This is compatible with the relationship between uptake and B-Pb assumed above (Figure 6, p.24).

This low background uptake leaves the major part of the 100 µg day^{-1} to reach a B-Pb of 1.5 µmol/l as a margin for occupational exposure.

Further, in many other areas of the world, where the background B-Pb is higher, the margin for occupational exposure is correspondingly lower, if the same critical B-Pb is applied.

Let us now assume, that all the occupational exposure occurs through inhalation. The next step is to make assumption about the absorption. For small particles (mean mass equivalent diameter ≤1 µm; e.g. lead fume), roughly 40% are deposited in the alveolar region of the lung and is completely absorbed. Let us assume that the air lead has this particle size. In many occupational settings, the average particle size is larger, with a lower alveolar deposition, and a lower absorption.

Out of the rest of the particles, some are deposited in other parts of the respiratory tract, swallowed and partly absorbed there. Let us assume that all of the inhaled lead reaches the gastrointestinal tract. This is certainly an overestimate, as some particles are exhaled. Let us further assume that the absorption in the gastrointestinal tract is 15%.

The total uptake of 700 µg $week^{-1}$ leading to a B-Pb of 1.5 µmol/l, leaves an uptake of 670 µg $week^{-1}$ for "occupational" exposure. This corresponds to inhaled amount of roughly 1,650 µg $week^{-1}$. A worker with moderately heavy industrial work, during work inhales about 10 m^3 day^{-1}, i.e. 50 m^3 per working week. 1,650 µg in 50 m^3 corresponds to a level of 33 µg m^{-3} (0.03 mg m^{-3}).

The B-Pb and the air level thus arrived at, do probably not protect the fetus in an exposed pregnant woman. If it is assumed that the critical B-Pb in the pregnant woman, as regards toxic effects in the fetus, is in the range 0.5-0.75 µmol/l, it is obvious, that this allows only a limited occupational exposure on top of the background B-Pb of 0.3 µmol/l (the average level in females without occupational exposure). The level 0.75 µmol/l corresponds to an uptake of roughly 50 µg day^{-1}, which means an "occupational" uptake of about 320 µg $week^{-1}$, corresponding to

an inhaled amount of about 790 µg $week^{-1}$, and an air concentration of about 16 µg m^{-3} (0.02 mg m^{-3}).

Correspondingly, a calculation of the exposure in the lactating woman, giving rise to the provisional tolerable weekly intake in the breastfed infant may be roughly calculated. As said above, this intake corresponds to a B-Pb in the woman of about 1.2 µmol/l, which is reached at an average uptake of about 80 µg day^{-1}, which means an "occupational" uptake of about 530 µg $week^{-1}$, corresponding to an inhaled amount of about 1,380 µg $week^{-1}$, and an air concentration of about 28 µg m^{-3} (0.03 mg m^{-3}).

In women, the inhaled amount of air is usually lower than in males (less heavy work), and the two estimates of air levels are thus somewhat low.

Of course, these estimates has a considerable degree of uncertainty; probably it is an underestimate of the inhalation exposure at work needed to reach the specified B-Pbs. On the other hand, they do not allow for any occupational exposure through food, drink, and tobacco. Further, these calculations do not take into account inter-individual variations in lead metabolism; individual workers may well be more sensitive. Further, the skeletal lead content may affect the margins (see below).

Also, they do not preclude marginal effects on the blood pressure.

11.6. Skeletal accumulation

Lead accumulates in the skeleton. Bone contains several pools with varying kinetics. The trabecular bone probably accumulates for a few years after start of exposure, and then levels off. The compact bone may accumulate for decades.

This accumulation is important from several points of view. Lead is released from the skeleton, which causes an endogenous exposure. This may be considerable in an old lead worker, and goes on for decades after end of exposure. Thus, the margin for external exposure decreases with increasing endogenous lead mobilization.

It should be stressed, that the calculations on critical exposures do not systematically take into account the degree of endogenous exposure from the skeleton. However, as the association between uptake and B-Pb employed relates to subjects with a chronic exposure, the estimates on air levels should be reasonably valid for an average lead worker, with a moderate skeletal lead burden and a correspondingly moderate endogenous lead exposure. In the newly employed worker, the margin for occupational exposure is probably higher, in the old worker lower.

Further, the lead amount in the skeleton constitutes a potential risk, if it is rapidly mobilized. It has been proposed that this may occur as the result of tumours or other osteolytic processes, but firm evidence for such events is lacking.

There is thus reason to limit the accumulation of lead in the skeleton. A particularly important problem is skeletal lead accumulation in fertile women, as this may constitute a risk for the offspring. A woman may accumulate lead in the skeleton for decades before becoming pregnant. Even if the external exposure is reduced immediately, when pregnancy is diagnosed, the endogenous exposure will continue during the full pregancy, thus exposing the embryo and fetus. Further, the mobilization will probably increase during lactation, causing an exposure of the

infant through the breast milk. Thus, in fertile women, even a limited skeletal pool may constitute a risk.

11.7. Particularly sensitive groups

As discussed above, *fetuses* and *infants* are probably the most sensitive parts of the population. However, this will not be further discussed here.

Women are, at least in some regards, more susceptible to lead exposure than males. There seems to be sex differences in the *metabolism* of lead; reflected in higher U-Pb in women than in males at the same B-Pb. Further, *iron deficiency*, which is more prevalent among women than among males, will increase the absorption of lead from the gastrointestinal tract (from the food and water, or of lead that is inhaled, deposited, cleared, and swallowed). Further, iron deficiency is particularly common during *pregnancy*, calcium deficiency during pregnancy and *lactation*.

Further, the disturbance of heme synthesis is, at the same B-Pb, more pronounced in females than in males. This is in accordance with other findings of sex differences at exposure to toxic agents (120). The even more important risks for the offspring has been extensively discussed above.

There are some indications, that subjects with inborn errors of heme metabolism (certain types of *porphyrias)* are particular sensitive to lead exposure, which also causes a disturbance of the heme metabolism. It has also been claimed that hemoglobin disorder may predispose for some effects.

Moreover, generally, it may be assumed, that subjects with *certain other diseases*, affecting the same organs as those disturbed by lead, may be particular sensitive to lead exposure. Such conditions are anemias, hypertension, kidney disease, disease in the nervous system, and - possibly - some immunodeficiences.

12. Summary

Staffan Skerfving. 104. Inorganic lead.Nordic Expert Group for Documentation of Occupational Exposure Limits. Arbete och Hälsa 1993:1, pp 125-238.

Survey of litterature on inorganic lead, to be used as background for dicussion of occupational exposure limits. The metabolism and effects of inorganic lead are summarized, with special reference to biological monitoring of exposure and risk of toxicity. From a practical point of view, a two-compartment model sufficiently well describes the metabolism. There is a rapid compartment (reflecting soft tissues), with a half-time of about one month, and a slow one (reflecting the bone lead pool), with a half-time of approximately one decade. There are considerable inter-individual variations in lead metabolism.

The whole-blood lead level is the most valuable tool for biological monitoring. The blood lead level is affected by recent absorption. The relationship between exposure and blood lead concentration is curvilinear, with a decreasing impact of rising exposure. In addition, the blood lead level is affected by endogenous lead release, mainly from the large skeletal lead pool, which, in subjects with a history of excessive exposure, may be considerable. In vivo determination of lead in the skeleton by X-ray fluorescence offers several possibilities. As the turnover of lead in bone is slow, the level is a time-integrated measure over years of the lead absorption. The average blood lead level in exposed only to "background" lead exposure varies considerably between different areas; in the Nordic countries the level in males is in average 0.4 µmol/l.

The nervous system and the kidney seems to be the critical organs. Animal experiments indicate that there is no linear relationship between blood lead concentrations and levels in the nervous system. Sensitive adult subjects display potentially adverse effects on the central and peripheral nervous system and kidney tubuli at exposures corresponding to an average blood lead level in a group of exposed subjects of about 1.5-2.0 µmol/l. There are reproductive effects. Probably, sperm is affected at blood lead levels of 2 µmol/l. Further, it is likely, that fetuses suffer non-specific effects on the central nervous system at even lower exposures, perhaps already at exposures corresponding to B-Pbs of 0.5-0.75 µmol/l in the pregnant woman. There may also be a considerable lead exposure of the breast-fed infant. Further, there are some indications of slight effects on the blood pressure at similarly low exposures.

The blood lead levels are roughly translated into air lead levels in the occupational setting. An average level of 1.5 µmol/l would, in subjects with a low background exposure, corresponds to about 0.03 mg/m^3, 0.75 µmol/l to about 0.02 mg/m^3. These levels may be underestimated; on the other hand, they do not take into account "occupational" exposure through foods, drinks, and tobacco.

In English. 907 references.

Keywords: air, blood, blood pressure, bone, breast milk, cancer, exposure, fetus, hematological, inorganic, kidney, lead, level, limit, occupational, nervous system, skeleton, urine.

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Appendix I.

Current practices for biological monitoring of exposure and risks

The current practice as regards biological monitoring of lead exposure varies widely between different countries. In general, nowadays, the monitoring is mainly focused upon the blood lead levels, and the frequency of sampling is governed by the intensity of the lead exposure. Sometimes the erythrocyte porphyrin level and/or urinary levels of lead, ALA and/or porphyrin are employed. Also, mobilization tests are used, but mainly for clinical diagnosis of lead toxicity.

Occupational exposure

In the following some examples of strategies for biological monitoring of occupational lead exposure will be described.

WHO (843) recommends a health-based maximum blood lead level of 1.9 µmol/l) in adult male workers and for female workers in the nonfertile age. Further, it is recommended, that in female workers in the fertile age, the blood lead level should not be significantly higher than in the general population. Urinary ALA, should not increase above the the laboratory's upper "normal" level (e. g. mean plus two standard deviations) for a general adult population with blood-lead level not exceeding 1.0 µmol/l). For protoporphyrins, a 50% increase could be accepted.

The *European Community* (EEC) in 1982 released its directive on the protection of workers lead (236). This notes, that an employee must not continue at his work, or any other work involving an equal or greater risk of exposure to lead, if B-Pbs are in excess of 70 µg/100 ml. There are no special rules for pregnant women.

In *Sweden*, any subject to be employed in lead-exposing work should be examined by a physician (768). The examination includes an occupational (including information on relevant exposures) and medical history. Blood pressure,

blood hemoglobin level, protein concentration in urine, and blood lead level is determined. If the examination reveals that the presumptive lead worker will run an increased risk by the lead exposure, he shall not be exposed. A full medical examination should be repeated in lead workers every third year.

Further, after onset of exposure, the blood lead level shall be determined after one month. Thereafter, the blood lead level is analysed each third month. If the level at three successive samplings is below 2.0 µmol/l, the following sampling may be performed each six months. If the levels are below 1.0 µmol/l, further examination is not needed.

If the blood lead level is above 2.0 µmol/l, the employer shall investigate the cause of the absorption, and measures to decrease the exposure shall be taken. A worker who displays a blood lead level of more than 3.0 µmol/l may not be employed in lead-exposing work until he has been examined medically and the blood lead level has decreased under 2.0 µmol/l. Temporary extemption from this rule has been made for workers with a particularily long and heavy exposure history, whose skeletal lead burden is such, that they will only reach that blood lead level after a very long exposure-free period. The same applies to a worker who has displayed levels in the range 2.5-3.0 µmol/l at three consective samplings.

Female workers under the age of 50 shall be informed about the risks for the fetus at a pregnancy and shall inform the employer immediately if she becomes pregnant. She may then not be employed in work causing lead exposure during the pregnancy and lactation. Females who must abolish their lead work because of pregnancy, and who may not be transferred to another job, has the right of economic support (havandeskapspenning) from the first day of diagnosed pregnancy (210).

In *Finland* (Rihimäki, personal communication), workforces in which any worker has a B-Pb of 1.9 µmol/l, or more, must be carefully monitored for potential health effects. A worker dsiplaying a B-Pb of 2.4 µmol/l, or more, cannot be employed for assignments involving lead exposure.

In *Denmark* and *Norway*, the transfer level is 60 µg/100 ml, with no special regulation for women (867).

In the *U.K.*, female workers were abolished from the white lead factories in 1878 (241). The transfer B-Pb is 70 µg/100 ml in males and 40 µg/100 ml in females of reproductive capacity (800). Further, a woman is required to notify her employer if she becomes pregnant, and is then suspended from work which exposes her to lead.

In *Germany*, the transfer level is 70 µg/100 ml for males, 30 µg/100 ml for females below 45 years (200). It is noted that effects on the offspring cannot be excluded at the allowed air level, 0.1 mg/m^3. A short-term level of 1 mg/m^3 is allowed for a maximum of 30 min.

In France, workers with B-Pb above 1.9 µmol/l shall be medically surveilled, those above 2.9 will be removed from exposure (515).

In the *U.S.A.*, transfer is required for both male and female workers at a B-Pb of 2.4 µmol/l as an average over last three readings or last six months (810), with return to work at 1.9 µmol/l. A maximum B-Pb of 1.4 µmol/l is *recommended* in both males and females who wish to bear children. Similar levels have been recommended by the American Conference of Governmental Industrial Hygienists

(6), which also gives an exposure limit for U-Pb of 80 µmol/mol creatinine, and threshold limit values (TLVs) of 0.15 mg/m^3 for inorganic dust and fumes of lead and lead arsenate, 0.05 mg/m^3 for lead chromate, which is classified as carcinogenic.

In *Australia*, the worker is removed from exposure at a B-Pb of 70 µg/100 ml until work has been recommended by a physician (867). Further, there is a recommendation, that pregnant women should not be employed in work which exposes them to risk of lead absorption. Also, "maternal B-Pb" should be maintained below 40 µg/100 ml.

Environmental exposure

EEC (1977), in a biological quality guide, stated that in representative groups of the populatation the B-Pb should be ≤1.7 µmol/l in 98% of the subjects examined, ≤1.4 µmol/l in 90%, and ≤0.96 µmol/l in 50%.

The *Dutch* government set a lower limit for young children: 98% ≤1.4 µmol/l, 90% ≤1.2 µmol/l, and 50% ≤0.96 µmol/l.

In the *U.S.A.*, the Center for Disease Control 1985 recommended that children, who have blood-lead levels of 3.5 µmol/l) or more (2.4 µmol/l if the erythrocyte protoporphyrin level exceeds 250 µg/l whole blood, or more), shall be treated with chelating agents. Children who have blood-lead levels above 2.4 µmol/l or more (1.2 µmol/l if the protoporphyrine level exceeds 110 µg/l whole blood) shall be further evaluated with a mobilization test. In children having blood-lead levels exceeding 1.2 µmol/l), and protoporphyrine levels exceeding 35 µg/l, effort shall be made to remove sources of lead exposure from the child's environment. All children with blood-lead levels exceeding 1.2 µmol/l shall be followed. Recently, lowered the level necessitating intervention to 0.5 µmol/l (805).

Appendix II.

Permitted or recommended maximum levels of inorganic lead

Country	ppm	mg/m^3	Comments	Year	Ref.
Denmark	-	0.1	dust & fumes	1988	1
Finland	-	0.1		1988	2
Iceland	-	0.1	dust (total)	1989	3
	-	0.05	respirable dust		
The Netherlands	-	0.15		1989	4
Norway	-	0.05	dust & fumes	1989	5
Sweden	-	0.1	dust (total)	1990	6
	-	0.05	respirable dust		
USA (ACGIH)	-	0.15	dust & fumes	1990-91	7
(NIOSH)	-	<0.1		1989	8

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Selenium

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Contents

1. Physical and chemical data

Selenium is an element, and belongs to group VI in the periodic table. Closely related elements are sulfur and tellurium, which have outer electron shells with the same structure. Elemental selenium is regarded as having relatively low biological activity, but selenium occurs in numerous compounds, many of which are biologically very active and extremely toxic. Selenium is one of the essential trace elements, and is an integral component of several of the body's proteins. Particular attention has been given to the role of selenium in the enzyme glutathione (GSH) peroxidase. The recommended daily intake of selenium is 0.05 to 0.07 mg.

If selenium is heated it forms selenium dioxide (SeO_2), which at room temperature is a white, crystalline powder. The oxide is soluble in water, forming selenious acid (H_2SeO_3). Its salt is called selenite, and commonly occurs as sodium selenite. Selenium trioxide also occurs: its acid is called selenic acid and its salt selenate. Another important compound is hydrogen selenide, which is volatile and forms under a variety of conditions.

According to the literature, the most commonly used organic selenium compound is selenomethionine. The amino acid selenocysteine plays a central role in the body (e.g. in the enzyme GSH peroxidase).

Several different ways of reporting doses and concentrations of selenium compounds are used in the literature. In this document they have usually been converted to amounts of Se in order to simplify comparisons.

Some chemical and physical data

Atomic weight:	78.96
Atomic number:	34
Valences:	-2, 0, +2, +4, +6

Conversion factors for hydrogen selenide

1 ppm = 3 mg/m^3; 1 mg/m^3 = 0.33 ppm

2. Occurrence, use

2.1. Occurrence

Selenium is a by-product of copper production. World production in 1982 was 1340 tons. Commercially produced compounds include selenium dioxide, sodium selenite, sodium selenate and selenium oxychloride. Some selenium compounds are also produced for research and for use in medicine and veterinary medicine (37).

Selenium compounds occur naturally in foods, and are added to some commercial fertilizers. Selenium compounds are also sold over the counter as dietary supplements. Selenious acid occurs in a few consumer products, such as gun blueing.

Selenium is used in the electrical industry (in rectifiers, photoelectric cells etc.), in the glass industry (as a decolorizer or color additive), and in the rubber industry (as a vulcanizer). Selenium compounds have been used medically in dandruff

remedies and contrast dyes, and some compounds have also been proposed for therapeutic use (37).

2.2. Air concentrations in the work environment

In a Swedish study, the air in an aluminum foundry was analyzed just after the foundry had received a shipment of scrap aluminum that contained 3 to 5% Se. On one shift the air concentration of hydrogen selenide reached 0.03 mg/m^3, but on the other shifts air concentrations were considerably lower. For Se and inorganic compounds, average values for a workshift were sometimes as high as 0.1 mg/m^3 but were usually 30 to 40% lower (43).

In a study from 1947, in a factory where 5 of 25 workers were complaining of various health problems there was a noticeable odor of hydrogen selenide: air analyses indicated that the level was below 0.2 ppm (0.66 mg/m^3). The odor occasionally became unendurable, indicating an air concentration of 5 mg/m^3 (9).

2.3. Methods for analysis of air concentrations

Few attempts to measure air concentrations in work environments have been reported. In one of the exceptions, the analysis method is not given (43). In the other, an old-fashioned colorimetric method was used (9).

There are several methods described for measurement of selenium in food and biological samples (37).

3. Kinetics

3.1. Uptake

Human uptake of selenium has been studied only with regard to oral intake of various selenium compounds. Uptake of the inorganic compounds sodium selenite and sodium selenate was compared in 13 female students who drank a solution containing 1 mg Se in either form; it was found that the selenate was absorbed more efficiently than the selenite (62 $\pm$ 14%, compared to 94 $\pm$ 4%) (84). In another study, in which a somewhat lower dose of selenite (200 µg ^{74}Se) was given to three women and three men, uptake was calculated to be 84 $\pm$ 1% (66). This was remarked to be somewhat higher than the results of two earlier studies, which reported uptakes of 44 to 77%, but in good agreement with a "two-period study" which reported uptakes of 76.0 $\pm$ 9.0% and 68.0 $\pm$ 6.0%. The ^{74}Se was found in blood plasma after only half an hour, indicating that selenite was rapidly absorbed from the digestive tract (66). The organic compound selenomethionine is also efficiently absorbed in the digestive tract: uptake of 75 to 97% has been registered in studies with human subjects (see e.g. Reference 37).

Uptake of selenium depends to some extent on the body's selenium status. In a study published in 1989 (50), in which two groups of eight men received either a low-selenium diet (18 $\pm$ 1 µg/day) for 29 days or a high-selenium diet (119 µg/day) for 9 days and thereafter were given 145 µg Se in the form of ^{74}Se-labeled selenite,

it was found that over the next two weeks the group that had been on the low-selenium diet retained more of the labeled selenium (74.8 $\pm$ 3.1% of absorbed dose) than the other group (67.6 $\pm$ 3.8% of absorbed dose).

Other dietary factors may also affect selenium uptake, either directly or by altering the selenium to a less soluble form. One such factor that has been studied is ascorbic acid, particularly its effect on uptake of selenite. Ascorbic acid rapidly reduces selenite to elemental selenium, which is generally regarded as biologically inert because of its presumed poor uptake in the digestive tract. A dose of 1 g ascorbic acid given simultaneously with 1 mg Se as selenite reduced Se uptake from 57 $\pm$ 13% to virtually 0% (70). In the same study, however, it was found that simultaneous intake of orange juice (equivalent to about 60 mg ascorbic acid) increased selenium uptake (from 51 $\pm$ 2.5% to 71 $\pm$ 14%). The results of another study, in which two groups of four men were given either a diet low in ascorbic acid (20 mg/d) for 45 days, or a diet high in ascorbic acid (2 x 0.5 g/d) for 25 days, also indicate that under some circumstances ascorbic acid can increase the biological availability of selenite (51).

In general, animal studies indicate that most water-soluble selenium compounds are efficiently absorbed in the digestive tract. Uptake is localized primarily to the small intestine, and no absorption seems to occur in the stomach. Transport of selenomethionine and selenate is energy-dependent, whereas it has been suggested that selenite is transported primarily by diffusion (6, 86). In vitro studies, however, have indicated that an active uptake mechanism may be involved in uptake of selenite as well (4). (Surveys of animal studies with selenium are found in References 37 and 40.)

There have been only a few studies on uptake of selenium via lungs or skin. These are reviewed in two survey articles (37, 40). When uptake of selenious acid (H_2SeO_3) and elemental selenium was compared in inhalation studies with rats and dogs, it was found that elemental selenium was absorbed more slowly. Rats absorbed 94% of the deposited dose of selenious acid within 4 hours, compared to 57% for elemental selenium. The dogs absorbed 94.7% of the initial body burden (IBB) of selenious acid (40 $\pm$ 17 µg Se/kg body weight, as H_2SeO_3) within 2 hours, compared to 74% for elemental selenium (IBB = 22 $\pm$ 9 µg Se/kg body weight). Skin uptake of H_2SeO_3 was also reported in the study with rats (37, 40).

In another of the above cited studies, it is reported that 10% of a solution of sodium selenite (0.1 mol/l) applied to the skin of rats was absorbed within one hour. There is usually no skin uptake of elemental selenium or selenium sulfide, but "garlic breath" and elevated excretion of selenium in urine are mentioned in a case report of a patient with an ulcerated scalp who had been using a shampoo containing selenium sulfide (37, 40).

3.2. Distribution

Little is known about how selenium is transported in the blood, but the role of plasma proteins has been discussed. Three different selenium-containing proteins have been identified in human blood plasma: selenoprotein P, glutathione peroxidase, and albumin (15). Selenoprotein P and glutathione peroxidase contain selenium in the form of selenocysteine, whereas albumin contains

selenomethionine. The presence of selenomethionine in albumin is of questionable significance, since incorporation of this amino acid into proteins is usually regarded as a non-specific process dependent on the relative amounts of methionine and selenomethionine in the diet. It has been suggested that selenoprotein P is one of the transport proteins for selenium (55), but other functions for this protein have also been proposed (10). Albumin has also been proposed as a transport protein for selenium in the form of selenite (72).

It was observed in animal studies that trace amounts of selenite were rapidly absorbed by red blood cells and re-distributed to plasma proteins, and then taken up by the liver (for reference see Reference 37). Gel filtration analysis of blood plasma from sheep that had been given intravenous doses of radioactively-labeled selenite revealed that the labeled selenium was bound to all protein fractions. This bond was found to be sensitive to treatment with mercaptoethanol when the blood sample was taken 20 minutes after the injection, and also if sheep blood was incubated with selenite in vitro for half an hour at 37 °C. However, if the blood sample was taken 10 hours after the injection and then analyzed in the same way, it was found that the selenium was bound primarily to a fraction with high molecular weight and that the bond was resistant to mercaptoethanol (14).

When human subjects were given a dose of labeled selenite it was distributed primarily to the liver, followed by kidneys and then lungs. The smallest amounts were traced in muscles and articular tissue. When total selenium content was measured in internal organs the highest concentration was found in kidneys, followed in order by liver, spleen, pancreas, testes, heart, intestines, lungs and brain. In similar measurements on autopsy material from 106 persons, kidney tissue was found to contain two to three times as much selenium as liver. Unlike other selenium compounds, selenomethionine tends to accumulate in the pancreas rather than in the liver. (For references and surveys see References 37, 40.)

There are somewhat conflicting reports on whether the selenium compound itself affects the distribution of selenium. A WHO document cites a study in which it was found that distribution was the same whether the selenium was administered as selenite or selenomethionine, orally or intravenously, and concludes that the form and the administration method seem to have little effect on the distribution of selenium. Other reports, however, indicate that the form of the selenium can have an effect on distribution. It is known, for example, that selenomethionine accumulates in the pancreas (37). It was also found that a subcutaneous dose of the selenium metabolite trimethylselenonium ion resulted in a selenium concentration in the heart half an hour after administration, an effect that was not observed with other selenium compounds (24). Several studies, with both humans (2, 49) and animals (8, 71), have also shown that retention of organic selenium in the form of selenomethionine is higher than retention of inorganic selenium as selenite or selenate. This may be because selenomethionine is incorporated into proteins as a replacement for methionine.

The distribution of selenium in the tissues of experimental animals is to a great extent determined by the animal's selenium status. In a study in which rats were fed on a low-selenium diet and then given a dose of radioactively-labeled selenite, most of the selenium was traced in the reproductive organs, brain and thymus (37). In a recently reported study, it was found that selenium-depleted animals retained 20 to

50 times more selenium from a tracer dose of selenite seven weeks after administration, when they were compared with selenium adequate animals (7). Most of this was in the brain, reproductive organs and various endocrine organs. The two groups in this study also showed different distribution patterns for the labeled selenium in specific selenoproteins.

The age of the exposed animals has also been shown to affect the uptake and distribution of selenium. Young animals (14 days old) given subcutaneous doses of 30 μmol/kg (2.37 mg/kg) radioactively labeled selenite were compared to adults (90 days old) given doses of 15 μmol/kg (1.185 mg/kg). The young animals were found to have about 10 times as much ^{75}Se in blood, liver, kidneys and heart during the entire study period (1 to 7 days). They had the highest concentrations in liver, while the adults had the highest concentrations in kidneys (64).

Both inorganic and organic forms of selenium have been reported to pass the placental barrier in both experimental animals and man. In a study with hamsters, it was found that during the 24-hour period after a single dose of selenomethionine the selenium content in embryonal tissue increased, whereas concentrations in maternal tissue dropped. When selenate was given instead, the selenium concentration in embryonic tissue reached a plateau (experimental data and survey in Reference 89). It has also been reported that selenium compounds are transferred to nursing babies in mother's milk (see for example References 46, 49), and selenium concentrations in serum from nursing babies and their mothers are correlated to each other.

3.3. Biotransformation

Inorganic selenium in the form of selenate or selenite is reduced to selenide in glutathione-dependent reactions. The amino acids selenocysteine and selenomethionine are also broken down to selenide. Selenomethionine can be transaminated to selenocysteine in the same way as methionine can be transaminated to cysteine. Another possibility is that a similar enzyme, such as L-methionine-γ-lyase, catalyzes a reaction that leads to the formation of methane selenol. Selenocysteine is broken down with the help of a selenocysteine-specific enzyme, selenocysteine lyase, which liberates selenide. The formation of selenide is believed to have a key role in the synthesis of specific selenoproteins. Any selenium surplus is methylated to the excretable metabolites dimethylselenide and trimethylselenonium ion. (See for example References 11, 80.)

Dimethylselenide, which is excreted in exhaled air, and trimethylselenonium ion, which is excreted in urine, are generally regarded as detoxification metabolites. The methylation reactions are dependent on S-adenosylmethionine, and methylation of dimethylselenide to trimethylselenonium ion is catalyzed by a cytosolic enzyme, S-adenosyl-L-methionine:thioether S-methyltransferase (thioether methyltransferase). The kinetics of this enzyme are assumed to partially account for the fact that dimethylselenide formation is observed only with relatively high toxic doses of selenium, whereas the excretion of trimethylselenonium ion reaches a maximum at "moderately" toxic doses (56). The formation of dimethylselenide is not catalyzed by this enzyme, but by another S-adenosyl-methionine-dependent microsomal enzyme, thiol-S-methyltransferase (36). It is interesting to note that the microsomal

methyltransferase, but not the cytosolic enzyme, is inhibited by arsenic, since it is known that arsenic affects selenium metabolism in vivo as well (37).

Metal ions (primarily heavy metals) can also inhibit the formation of dimethylselenide. Here, however, the mechanism is believed to be the formation of relatively insoluble metal-selenide complexes (see for example References 37, 62). Other factors can also affect selenium metabolism. Methionine has been found to affect the metabolism of selenium, particularly of selenomethionine. It was found that with low dietary intake of methionine the anticarcinogenic effect of selenomethionine dropped and tissue levels increased. This effect was not observed when selenium was administered in the form of selenite (39). A proposed explanation for this was that selenomethionine replaced methionine in protein syntheses when methionine was a limiting factor. A non-specific incorporation into proteins other than selenoproteins was also observed in rats that received ten times the normal dose of selenite in food for three weeks (8).

There are also other factors that can alter the biotransformation of selenium. It has been reported, for instance, that administration of methylmercury yielded a dose-dependent increase in the exhalation of dimethylselenide and a simultaneous lowering of concentrations in the liver, kidneys and blood of female rats that had been given selenite (s.c.) in doses of 0.25 or 24 µmol/kg (0.019 or 1.90 mg/kg), without affecting excretion via feces or urine (81).

Pre-treating animals with selenite (1.2 µmol/100 g body weight) for three days before administration of labeled selenite in doses of 0.1 or 1.2 µmol (0.008 or 0.095 mg) /100 g body weight increased excretion of dimethylselenide and reduced retention of the labeled selenium. Similarly, it was found that a dose of non-radioactive selenite (1.2 µmol/100 g) given 24 hours after the last of three daily doses (1.2 µmol/100 g) of labeled selenite increased excretion of the labeled selenium as dimethylselenide (48).

The age of the exposed animals has also been shown to affect the metabolism of selenium. When young animals (14 days old) were given subcutaneous doses of 30 µmol/kg (2.37 mg/kg) labeled selenite and compared with adults (90 days old) given doses of 15 µmol/kg, it was found that the young animals had about ten times as much ^{75}Se in blood, liver, kidneys and heart during the entire experiment (1 to 7 days), and also that the pattern of metabolites excreted in urine was different from that of adults (64).

3.4. Elimination

The primary pathways for elimination of selenium are via urine (partly as trimethylselenonium ion) and exhaled air (as dimethylselenide, which has characteristic garlic-like odor). When excretion of the inorganic compounds sodium selenite and sodium selenate was compared in 13 female students who had drunk a solution containing 1 mg Se in each form, it was found that with selenate there was an initial rapid excretion two to four hours after intake --about three hours earlier than when the selenium was taken in the form of selenite --and that the excretion level was 5 to 6 times higher. Excretion in feces was lower for selenate than for selenite (84). In another study, in which a somewhat lower dose of selenite (200 µg

^{74}Se) was given to three women and three men, excretion in urine reached a peak two to four hours after administration (66).

Rats given selenite in drinking water (4 µg Se/ml) for 30 days absorbed the substance effectively; only about 10% of the selenium intake was recovered in feces, and an equilibrium excretion in urine (54 ± 2% of Se intake) was reached within a few days. Trimethylselenonium ion accounted for 35 to 40% of Se in urine, but for only 2% in a control group that received de-ionized water. There were also indications that elimination pathways other than urine or feces, probably excretion in exhaled air, are relevant at these dose levels (42).

In another experiment, rats were given a single oral dose of selenite (1.5, 120, 500, 1500 or 3000 µg Se/kg body weight) and the dose-response relationship was mapped for excretion of trimethylselenonium ion in urine. Analysis of 48-hour urine samples indicated that with doses up to 500 µg Se/kg about 30% of the dose had been excreted in urine, primarily in a form other than trimethylselenonium ion which coeluted with selenite in the chromatographic analysis. With higher doses the percentage excreted via urine decreased and trimethylselenonium ion became the principal metabolite in urine. For animals given 1500 or 3000 µg Se/kg, the fraction appearing as trimethylselenonium ion in urine was found to be the same while the percentage excreted via urine dropped from 25 ± 2% to 12 ± 2% (96).

Excretion in young animals has also been compared with that in adults. Metabolites found in urine from young animals (14 days old) given subcutaneous injections of 30 µmol/kg (2.37 mg/kg) radioactively labeled selenite corresponded with those in the urine of adult animals (90 days old) given doses of 15 µmol/kg, but the proportions were different: in the young animals the primary metabolites were glutathione-selenotrisulfide and another unidentified non-polar metabolite, while in the adults the primary metabolite was trimethylselenonium ion (64).

3.5. Biological exposure indicators

Estimates of the amount of selenium in the human body range from 3 to 15 mg. This wide range may be partially due to differences in analysis methods. It is possibly also due to the fact that the low value comes from New Zealand, which is known to be one of the selenium-poorest areas in the world, while the high value comes from the United States, one of the world's selenium-rich areas (40).

In a study from 1967 it was proposed that a urine selenium level of 0.1 mg/l should be the maximum allowable concentration for both industrially exposed workers and rural populations (29). In a Canadian study from 1989, it was reported that copper refinery workers excreted 0.083 ± 0.030 mmol Se/mol creatinine in urine; after ten weeks away from the job, excretion had dropped to 0.056 ± 0.017 mmol Se/mol creatinine (34).

In a Chinese study, daily selenium intake in food was correlated with Se levels in urine, hair, nails, breast milk and blood. Subjects had consumed both physiological and toxic amounts. It was concluded that the Se level in whole blood is a good indicator of Se intake within the normal range, but that with higher intakes whole blood levels are less accurate indicators than levels in hair, nails or urine (93).

A newly published American study reports strong correlations between Se concentrations in whole blood, serum, urine and nails. The subjects in this study lived in selenium-rich areas and had high selenium intakes in food, but no over-frequencies of selenosis symptoms were noted (47).

A close correlation between Se and Hg has been found in pituitary tissue from autopsies of dental workers (63).

A model for calculating equilibrium concentrations in various organs at given air concentrations or given intakes via food has been described (53).

4. General toxicology

Selenium deficiency has been studied in animal experiments. One effect is a reduction in the activity of the enzyme GSH peroxidase. Low activity of this enzyme has been correlated to increased sensitivity to oxidative damage such as that caused by various chemicals.

4.1. In vitro studies

Several mechanisms for the toxic effects of high selenium intake have been proposed. One hypothesis is that selenium's ability to replace sulfur can lead to toxic effects (79). Reactions with sulfur bonds in proteins or with sulfhydryl groups can also conceivably have an inhibitory effect on enzymes or structural proteins (26).

The tendency of certain selenium metabolites to form redox cycles has been noted in recent years. This can have acute cytotoxic effects (5).

4.2. Factors that affect toxicity

There are a number of known factors that can affect both the kinetics and dynamics, and thus also the toxicity, of selenium. It has been shown, for example, that ascorbic acid can strongly inhibit human uptake of selenite (84). Prior administration of selenium has been shown to increase the excretion of dimethylselenide in rats (48), and thus probably affects the toxicity of e.g. selenite. Both animal studies (65) and human studies (92) indicate that young are more resistant to Se intoxication than adults, and animal studies indicate that the reason may be differences in metabolism (64). Animal studies have also shown that protein intake and other dietary factors (37), as well as ambient temperature (87), can affect the toxicity of selenium, but here the mechanisms are not known. It is also known that heavy metals, for example, form bonds with selenium: this should result in "detoxification" of both substances (37). A number of other factors that affect biotransformation can be demonstrated in in vitro systems (5).

4.3. Acute poisoning

4.3.1. Oral intake

Many selenium compounds are extremely toxic. Cases of acute poisoning have been described for several of them. Earlier published cases usually involve oral intake of gun blueing or preparations for sheep (for a summary see Reference 37). Some of these cases have been fatal. One death was reported to have been caused by as little as about 10 to 20 mg Se/kg body weight in the form of selenious acid (67). In another incident, five persons ate selenium-enriched animal feed. Selenium intake was estimated to be 1 to 5 mg/kg body weight (in the form of selenite) and symptoms were nausea, vomiting, abdominal pain and tremor (77).

Selenium tablets, later found to contain about 27 mg Se (including 25 mg sodium selenite) per tablet, were sold as a diet supplement; 13 persons were reported to have developed symptoms of poisoning after taking one or more of them (32). All of them became nauseous and many vomited; other common symptoms were nail damage, hair loss, fatigue and irritability, and some victims reported abdominal cramps, diarrhea, paresthesia and "garlic odor" (21).

The LD_{50} for oral doses of selenate, selenite, selenomethionine, etc. is below 10 mg/kg body weight for several animal species. Other selenium compounds have lower acute toxicity; the LD_{50} for selenium sulfide, for example, is 138 mg/kg. The LD_{50} for elemental selenium is 6700 mg/kg. (For a more detailed summary see Reference 37).

4.3.2. Work-related skin uptake

There is a case report of a galvanizer poisoned by selenious acid. Most of the uptake was assumed to have occurred via skin. Over the space of two weeks, the patient developed severe dermatitis on arms and face. He also developed hepatitis, with necroses and adipose deposits (68).

4.3.3. Work-related uptake via inhalation

Thirty-seven workers were exposed to selenium oxide during a fire in a rectifier factory. Symptoms were bronchial spasms, tremor, nausea, vomiting, headache, fever and bronchitis. Some of them developed chemical pneumonia (90).

Metal workers (5 of 25) were reported poisoned by hydrogen selenide emitted by an acid etching fluid. The symptoms were vomiting, diarrhea, dizziness and a metallic taste in the mouth. The authors (9) estimate that air concentrations may have been 0.2 to 1.5 ppm. Also quoted is a 1937 study reporting that a concentration of 0.3 ppm hydrogen selenide resulted in loss of the ability to notice the smell (37).

Rapidly mixing 450 l selenic acid (?) with caustic soda resulted in a rapid rise of temperature and an explosive overflow of selenium-containing liquid in a factory locale. One person in the area received skin burns, and died 90 minutes later from lung edema and instable blood pressure. An odor of garlic was noted (73).

Laboratory technicians conducting animal experiments have developed sore throats and bronchitis after giving high doses of selenite to dogs. The problems were attributed to the dimethylselenide exhaled by the dogs (54). The condition has also been described in other contexts in which persons have been exposed to dimethylselenide, and is sometimes called "rose cold" (31).

4.4. Chronic poisoning

4.4.1. Oral intake

Detailed studies of the maximum non-toxic dose for man have been published in both China and the United States, where there are agricultural areas with extremely high selenium levels in the earth. In the Chinese studies (92, 93), it is reported that in small villages in an area of endemic selenosis (chronic selenium poisoning) the intake in food was on average 1.3 mg Se/day (93). It is also shown that an intake of 0.40 mg/day can be regarded as safe (92). The lowest intake associated with symptoms of selenosis was 0.91 mg/day. This intake results in an estimated blood content of 1.054 mg Se/liter (92). The diagnosis of selenosis was based on changes in hair and nails, but lower whole-blood levels of GSH and prolonged prothrombin time were among the other observed effects. No correlation between clinical symptoms and blood Se could be demonstrated, but a group of five persons with chronic symptoms had blood Se values ranging from 1.054 to 1.854 mg/liter. The diagnosed cases of selenosis were almost exclusively adults, and the prevalence increased with age --the average prevalence was 23%, but in the 51 to 70 age group it was 37%. No liver changes or cardiac effects were reported. Nor was there any report of teratogenicity (92) .

In an American study of a symptom-free population, selenium intake (via food) ranged from 0.068 to 0.72 mg/day (47). Se concentrations in blood ranged from 0.18 to 0.67 mg/kg and urine excretion ranged from 0.024 to 0.55 mg/liter. In this population there was a correlation between selenium intake and alanine aminotransferase (ALT) in serum, but the range of ALT values was within normal limits (47).

In an earlier study of inhabitants in selenium-rich areas in China, it was reported that 49% of those with an average intake of 5 mg Se/day in food had symptoms of selenosis (91). The usual symptoms were hair loss and nail damage, but neurological and gastrointestinal symptoms were also reported (91). Another study from China reports anemia in people living in selenium-rich areas (92).

4.4.2. Uptake from occupational exposure

Workers in a copper refinery (n = 29-31) were examined before, during and after a ten-week work break, and compared with controls (n = 150; hospital and office workers, etc.). The study was made in 1986. At the time of the first examination, selenium levels in the refinery were said to have been above the TLV (at that time 0.2 mg Se/m^3), but no monitoring measurements are reported. The tellurium level was also said to have been above the TLV. Excretion of Se in urine was 0.083 $\pm$ 0.03 mmol/mol creatinine (0.090 $\pm$ 0.048 mg/liter) during exposure, but 0.056 $\pm$ 0.017 mmol/mol creatinine (0.077 $\pm$ 0.034 mg/liter) after the break in exposure. Selenium exposure was not estimated, but these urine values are lower than those elsewhere associated with selenosis (91, 92). The refinery workers reported more nose and eye irritation, digestion problems, stomach pains and fatigue than controls. A socially embarrassing garlic odor was observed in 52% of the subjects during one examination. Subjects had low Hb levels before the break in exposure, and 32% were anemic. The average Hb values rose during the break. It was also found that Hb was inversely correlated to the Se level in urine (34).

In a case report from 1986, gastrointestinal problems, "garlic breath," caries, conjunctivitis and irregularities in nails were reported after exposure to hydrogen selenide gas in an electrical research laboratory. The exposure was accompanied by a suffocating feeling, and had occurred at least once a week for a year (1).

A study from 1947 (9) describes the clinical effects of adding selenious acid to etching ink. After a month, 5 of 25 workers were complaining of various increasing problems such as nausea, vomiting, a metallic taste, dizziness and fatigue. Other workers also reported problems when they were asked. There was an odor of hydrogen selenide at the workplace, and air analyses indicated that levels were below 0.2 ppm (0.66 mg/m^3). On a few occasions the odor became unbearable, indicating a level of 5 mg/m^3. Urine excretion was on average 0.06 mg Se/liter (9).

Local symptoms have also been reported with occupational exposure to airborne selenium. A pink discoloring of the eyelids together with an inflammation of conjunctiva (Pink eye) has been described with exposure to selenium oxide (28).

Jobs that result in reduced Se levels in blood have also been studied. In a study made in 1987, workers at a coal-fired power plant (n = 49) and a rubber factory (n = 50) had lower blood levels of Se than controls (n = 58: students, office workers, farmers) (95). A similar study by some of the same authors reports reduced Se levels and lower GSH peroxidase activity in red blood cells from oil refinery workers (30).

In a Japanese study from 1990, 47 subjectively healthy subjects working with "aromatic nitroamines" in a chemical industry were compared with 107 healthy controls who did not work in industry. The industrial workers had elevated methemoglobin levels and reduced Se levels in blood plasma and erythrocytes, and lower GSH peroxidase activity. Diet analysis indicated that the two groups had similar Se intakes (94).

5. Effects on organs

5.1. Effects on skin and mucous membranes

A galvanization worker occupationally exposed to selenious acid, mainly via skin, developed severe irritative dermatitis on face and arms in the space of two weeks. He also developed hepatitis, with fatty deposits and necroses (68).

Allergic contact dermatitis has been described in a laboratory assistant who prepared media for cell cultures.The dermatitis was initially localized to the skin between the fingers, but soon spread over the hands, face and neck. The patient also suffered two asthma attacks. She had a positive reaction to a patch test with selenite (74).

Dermatitis has also been described in four glass workers exposed to selenite. Allergic contact dermatitis was diagnosed in two of them. Both barium selenite and sodium selenite were used in patch tests. They also had conjunctivitis (69).

Exposure to selenium oxide has been reported to cause discoloration and swelling of the eyelids ("pink eye") (28). In several other studies (see above) irritation of eyes and nose are reported as part of a more general pathological picture.

5.2. Effects on respiratory organs

Effects on respiratory organs are mentioned in all case reports of acute poisoning attributed to occupational exposure. Occupational exposures to selenium oxide (90), selenic acid (?) (73) and dimethylselenide (54) have been reported to cause several types of respiratory symptoms, variously described as bronchitis, chemical pneumonia, lung edema or "rose cold." Hydrogen selenide has been reported to cause a feeling of suffocation (1).

"Rose cold" is a condition characterized by cough, sore throat, runny nose and bronchitis, and has been suggested to be a consequence of excreted dimethylselenide (16). Excretion of dimethylselenide is associated primarily with a chronic high intake of selenium (16), but symptoms resembling those of "rose cold" are not connected with selenosis in other studies such as that made in China (91).

Allergic contact dermatitis has been described in a laboratory assistant who prepared media for cell cultures. The patient also suffered two asthma attacks. She had a positive reaction to a patch test with selenite (74).

5.3. Effects on liver

A galvanizer who was exposed primarily via skin developed a severe irritative dermatitis on hands and arms within the space of two weeks. He also developed hepatitis, with fatty deposits and necroses (68). Another case report describes slight effects on the liver after intake of selenate (13). These two case reports seem to be the only descriptions of liver effects in humans. Effects on the liver are a more common part of the toxicological picture in experimental animals exposed to selenium (37).

Prolonged prothrombin times, and also a correlation between ALT values and selenium intake, have been found in studies of populations that live in selenium-rich areas and have chronic high selenium intake in food (47, 92). However, it was not shown that these resulted from effects on the liver.

5.4. Effects on kidneys

No reports were found.

5.5. Effects on the digestive tract

Effects on the digestive tract, in the form of nausea, vomiting, stomach pains, diarrhea etc., are among the most commonly described symptoms of selenium poisoning. They occur with acute poisoning by either oral intake or inhalation, as well as with chronic oral intake or occupational exposure (1, 21, 32, 91). A single oral dose as low as 25 mg sodium selenite has been reported to cause acute symptoms.

For chronic intake in food, 5 mg Se/day has been reported to cause gastrointestinal symptoms.

5.6. Effects on blood and blood-forming organs

Reduced GSH levels, increased prothrombin time and increased numbers of white blood cells have been reported in persons who live in selenium-rich areas (92). The first two effects were associated with a daily intake of 0.85 mg Se (92). Anemia has also been associated with occupational exposure to selenium (34): no exposure measurements are reported, but the average excretion in urine was 0.09 mg Se/liter (34). Anemia has also been induced in rats (92).

5.7. Effects on central nervous system

Neurological effects are described with both acute and chronic poisoning. Irritability, fatigue, dizziness and headache are among the symptoms that can be regarded as effects on the central nervous system. Irritability is described with intake of one or more tablets containing 27 mg Se each (32). Irritability has also been noted in experimental animals given high doses of selenium (37). Paralysis and blindness have been described in farm animals in selenium-rich areas (37).

5.8. Effects on peripheral nervous system

Neurological effects are described with both acute and chronic poisoning. Tremor and paresthesias have been described in cases of acute poisoning. Doses have been from 27 mg Se up to 1-5 mg/kg body weight (21, 32). Paresthesias and paralysis have been observed in cases of chronic poisoning from intake of 5 mg Se/day (91).

5.9. Effects on hair and nails

Changes in nails and/or hair are used in many studies as diagnostic criteria . Hair loss has been described with both acute and chronic poisoning, as have discolored, brittle or dry hair (21, 91). Changes in nails are noted in sub-acute and chronic cases. They range from slight damage, with furrows or with white spots at the base of the nail, to more severe lesions and sometimes nail loss (12, 91, 92). Changes in hair and nails have been described in conjunction with intake of 0.9 mg Se/day over prolonged periods (91, 92).

5.10. Effects on hormonal systems

A close correlation between Se and Hg concentrations was noted in pituitary tissue from autopsies of dental workers. In some cases the measurements were made long after exposure to Hg had ceased, which indicates that the levels reflect a stable deposition (63).

Inhibited growth is a common effect in long-term studies in which experimental animals are given selenium in relatively high doses. It has been shown, for example, that selenite in food (5 mg Se/kg food) results in weight loss after three weeks, and the effect is more pronounced than with e.g. selenomethionine (52). In

an attempt to explain the weight reduction, rats were given selenite in drinking water (15 mg/liter) and the effect on growth hormone and somatomedin C was studied. The treated rats had lower growth hormone secretion and lower somatomedin C levels in plasma (85). An incompletely published study reports that 0.25 mg Se (administered as organic selenium) affects somatomedin C levels in serum, but this was not confirmed in the American study cited in 5.3 above (47).

5.11. Effects on reproductive organs

In a 240-day study with rats, 16 ppm selenite in drinking water had degenerative effects on testes. Edema, oligospermia, reduced tubule size and enzyme changes were observed (59).

5.12. Effects on eyes

Selenite (0.02 to 0.03 mmol Se/kg body weight, s.c.) (1.6-2.4 mg/kg) causes cataracts in rats 10 to 14 days old. The method is used as a model for cataract studies, and a relatively detailed molecular explanation for the occurrence of the cataracts has been presented (76).

5.13. Effects on sense of smell

Hydrogen selenide has a suffocating odor, and a concentration of 1 mg/m^3 (0.3 ppm) is reported in a study from 1937 to rapidly deaden the sense of smell (17).

6. Immunotoxicity and allergies

Allergic contact dermatitis is described in a laboratory assistant who prepared media for cell cultures. The dermatitis was initially localized to the skin between the fingers, but soon spread over the hands, face and neck. The patient also had two asthma attacks. She had a positive reaction to a patch test with selenite (74).

Dermatitis has also been described in four glass workers exposed to selenite. Allergic contact eczema was diagnosed in two of them. Both barium selenite and sodium selenite were used in patch tests. Conjunctivitis was also observed (69).

The effect of physiological or sub-physiological doses of selenium on the immune system has been studied quite intensively in experimental animals and in vitro systems, but the possibility that selenium may have toxic effects on the immune system has attracted less interest. In a recently published study, it was reported that selenomethionine (2.2 mg Se/liter drinking water), but not selenite (3.5 mg Se/liter drinking water) caused a deterioration in tuberculin response (delayed type hypersensitivity reaction). Selenomethionine at this dosage also affected serum ALT (19).

In an earlier study with rats, 5 mg Se/kg food (as selenite) inhibited the delayed hypersensitivity reaction and antibody production. At lower doses the activity of "natural killer cells" was elevated (44).

7. Mutagenicity, genotoxicity

Several selenium compounds, including selenite, selenate, selenide and selenocysteine, as well as selenium sulfide (83), have been shown to be mutagenic and genotoxic in several different in vitro systems. Positive results were obtained in Ames' tests with Salmonella and in tests of sister chromatid exchange in V79 cells, DNA repair in human fibroblasts, and various similar tests. Positive results have also been obtained in in vivo tests, such as sister chromatid exchange and chromosomal aberrations in bone marrow cells from Chinese hamsters given intraperitoneal doses of 3, 4 or 6 mg Se/kg (i.e. doses near the LD_{50}). In general, it can be observed that biotransformation of selenium compounds seems to be an important factor in the occurrence of reactive metabolites or compounds that can damage DNA, and that because of selenium's toxicity the DNA damage and mutagenic effects are usually observed in a relatively narrow dose interval (for a survey see References 37 and 75). Recent publications can be said to confirm these observations, and for selenite positive results have now also been obtained in yeasts (3). In a study with rats, it was found that an intravenous injection of sodium selenite (Na_2SeO_3), in doses up to 6 mg/kg x 2 at 24-hour intervals, caused no significant increase of abnormal metaphases in lymphocytes, but that the same treatment with 5 mg/kg x 2 doses caused a significant increase of abnormal metaphases in bone marrow (60).

In a study published in 1988, it is suggested that the mutagenic and toxic effects of selenite in Salmonella typhimurium may be due to the production of active oxygen species (45). Selenium metabolites such as selenide and selenopersulfide have earlier been proposed as agents for the mutagenic effects of selenium compounds such as selenite, selenate, selenide and selenocysteine (88). In another study, in which human fibroblasts were used, it was concluded that the DNA damage observed in these cells was not the result of production of free oxygen radicals (78). Other effects, such as inhibition of DNA polymerase (25, 27) can also conceivably help to explain the genotoxic and mutagenic activity of selenium.

It should also be noted that there are several published reports indicating that selenium, at physiological concentrations, also has anti-mutagenic qualities (for a survey see Reference 75).

8. Carcinogenicity

8.1. Human studies

A number of studies exploring the possibility that selenite may have an anti-carcinogenic effect have been published (see summary in Reference 23). No study regarding carcinogenicity in man was found.

8.2. Animal studies

Because of selenium's similarity to arsenic, the possibility that it might be carcinogenic was an early focus of research, and there are some studies that yielded positive results (20, 37). Selenate and food containing selenium (from selenium-

rich areas) were correlated to a carcinogenic response. There are reasons to question these results, however, and several negative studies have been published (37). It has been shown in several studies that selenium (selenite etc.) in moderate doses counteracts the occurrence of cancer caused by known carcinogens (37).

One particular selenium compound, selenium sulfide, was shown in a controlled NTP study to produce hepatocellular cancer in both male and female rats (F344) and female mice (B6C3F1), and an over-frequency of lung cancer in female mice (58). Doses, given by gavage every day for 103 weeks, were 3 and 15 mg/kg/day for rats and 20 and 100 mg/kg/day for mice. There were 50 animals in each group, including controls. The over-frequencies of cancers were noted in the high-dose groups, and weight loss was also observed in these groups (58). Selenium sulfide is regarded as a distinct compound in an EPA assessment, which states that generalizations to other selenium compounds such as selenite or selenate can not be made (20).

In a parallel study, selenium sulfide was applied to the skin of ICR mice. No carcinogenic effect was noted (57).

The IARC has placed selenium and selenium compounds in Group 3: "not classifiable as to their carcinogenicity to humans" (38).

9. Reproduction toxicology

Deformed chickens, but no deformed children, were seen in a study of selenium-rich areas in China (92). No comparisons of selenium intake were reported, however. This observation is in agreement with previously published epidemiological data, which showed no correlation between intake of selenium in drinking water and anencephalus or mortality due to birth defects (18, 41).

In a 240-day study with rats, it was found that 16 ppm selenite in drinking water had degenerative effects on testes. Edema, oligospermia, reduction of tubule size and enzyme changes were observed (59).

In a teratogenicity study, selenite, selenate and L-selenomethionine were given to hamsters in a range of doses and by several exposure pathways. Doses varied from 0.011 to 0.110 mmol/kg body weight. Deformities, primarily encephalocele, were observed after oral or intravenous doses of selenate or selenite, but the higher doses also had toxic effects (e.g. weight loss) on the mothers. Selenomethionine had similar effects on the embryos when given in single oral doses, but not when administered by other methods. In general, the LD_{50} for the mothers was equal to or less than the ED_{50} for teratogenicity, and the authors conclude that any assessment of selenium's teratogenic effects was impossible due to concomitant general toxic effects (22).

In a teratogenicity study with long-tailed macaques (*Macaca fascicularis*), L-selenomethionine was given by gavage, in doses of 0.025, 0.150 and 0.300 mg Se/kg body weight/day, for 30 days. There were ten monkeys in each dose group. Animals in the two highest dose groups showed toxic effects such as anorexia, vomiting and a reduction in body weight compared with controls. There were also some deaths among the mothers. There were three deaths among young in the highest dose group and one case of growth retardation in the low-dose group. The

fetuses examined on day 100 of gestation showed no definite effect in any dose group. The authors conclude that the young were no more sensitive than their mothers to the effects of selenomethionine. They also recommend further study of distribution and placental transport in order to determine the embryotoxic risk to humans (82).

Earlier published studies of teratogenic effects on laboratory mammals have also been generally negative (33, 61).

Birds seem to be more sensitive than mammals to effects on reproduction, which may possibly be due to selenium accumulation in eggs. The above-mentioned observations of deformed chickens are supported by earlier studies, and in California (Kesterton) Se concentrations in food chains were found to be 4 to 8 mg Se/kg (as selenomethionine), and may account for reproduction declines in sea birds (35).

10. Dose-effect / dose-response relationships

10.1. Effects of short-term exposure

A single dose of 27 mg Se (mostly in the form of selenite) taken under fairly well controlled conditions caused nausea.

A daily intake of about 27 mg Se (mostly in the form of selenite, but with large amounts of vitamin C; Reference 12) for 11 days caused hair loss. Neurological effects were also noted after intake of a few 27-mg tablets. Nausea was the most common symptom, and a garlic odor was sometimes noted as well.

After an intake of 1 to 5 mg Se/kg body weight (as selenite), 5 of 5 subjects became nauseous, vomited and developed tremors.

A suicide has been attributed to a dose of about 1000 mg Se as selenite.

Massive, uncontrolled emissions due to industrial accidents have been associated with deaths and toxic effects, primarily on the respiratory passages.

10.2. Effects of long-term exposure

Occupational exposure that may have been above 0.2 mg Se/m^3, the Treshold Limit Value (TLV) recommended by the American Conference of Governmental Industrial Hygienists (ACGIH), resulted in an increase of selenium excretion from 0.077 to 0.090 mg Se/liter urine and caused "garlic breath" in 52% of exposed workers. It was also found that 32% of them were anemic. The tellurium level at the workplace was also reported to be above the TLV (34).

A daily intake of about 1 mg Se (in the form of selenite) for a year has caused nail damage in human subjects.

A daily intake of 0.4 mg Se in food from selenium-rich areas (and a daily excretion of 0.173 mg in urine) can be considered safe, at least under some circumstances. A daily intake of 0.85 to 0.91 mg Se in food from selenium-rich areas has been found to cause nail damage and hair loss, as well as blood changes that may indicate effects on the liver. Some unconfirmed data indicate that liver damage may occur with a lower chronic intake than that causing nail damage. About 25% of a population with an average daily consumption of 1.3 mg Se showed

symptoms of selenosis. A garlic odor seems to be a more reliable indication of chronic selenium poisoning than of acute poisoning.

Nail damage, hair loss and neurological effects are observed in 49% of people with a daily intake of 5 mg Se in food grown in selenium-rich areas.

If there are any teratological effects on mammals, they can not be distinguished from the general toxic effects.

One particular selenium compound, selenium sulfide, is carcinogenic when given to rats and mice in large doses.

11. Research needs

Case reports indicate that hydrogen selenide can be emitted in some industries or laboratories in amounts large enough to cause health problems. More exact exposure data would be of considerable value.

A well documented study reports that relatively small increases of selenium in urine, not related to anemia in other groups, are related to anemia and other symptoms in copper refinery workers. An interaction with tellurium is possible, and it should be possible to study this in experimental systems. Better exposure data and more light on the cause-effect relationship would be valuable.

Comparative studies of placental transport in humans and experimental animals should be valuable in assessing the risks of selenium exposure for human embryos.

Selenium sulfide is one of the most potent carcinogens tested in the National Toxicology Program, and has been shown to be genotoxic. A closer examination of its genotoxic and carcinogenic mechanism would be valuable.

12. Discussion and assessment

Intake of selenium as a naturally occurring component in food seems to be the most obvious risk factor for people in some areas of the world. In this case, dose-effect and dose-response relationships are relatively clear. Accidents due to intake of dietary supplements are also reported, and dose-effect and dose-response relationships can be given here also.

Selenious acid appears to be a risk factor in industrial environments, especially in accidents. Uptake via skin and lungs can have toxic effects. Uptake of hydrogen selenide via inhalation is a risk factor under more normal circumstances, but the obnoxious odor may have an initial protective function (deadening of the sense of smell has been described). Dose-effect and dose-response relationships are poorly described, mostly because of vague reports of air concentrations.

With short-term exposures, the critical effect is gastrointestinal problems. With long-term exposure via food, nail damage is the critical effect. Some selenium compounds cause allergic skin reactions. Selenium sulfide has been shown to give cancer to rats and mice if given in high doses.

13. Summary

Per Garberg and Johan Högberg. Selenium 103. The Nordic Expert Group for Documentation of Occupational Exposure Limits. Arbete och Hälsa 1993:239-265.

A critical survey of the literature on selenium has been made for use as a scientific basis for the establishment of occupational exposure limits. Selenious acid can be considered an occupational risk factor, especially in connection with industrial accidents. Uptake via skin and lungs can have toxic effects. Inhalation exposure to hydrogen selenide is a risk factor under more normal conditions. Dose-effect and dose-response relationships are not well described, mainly due to lack of data on exposure levels. Dose-effect and dose-response relationships are fairly well described for intake of selenium in selenium-rich foods, however. Gastrointestinal symptoms are considered the critical effect for short-term exposure, and nail malformations the critical effect of long-term exposure via food. Some selenium compounds cause allergic skin reactions. Selenium sulfide in high doses gives cancer to mice and rats.

In English, 96 references

Key words: Selenium, exposure, uptake, distribution, biotransformation, excretion, toxicity, occupational exposure limits.

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Appendix 1

Permitted or recommended maxima for concentrations of selenium and inorganic selenium compounds in workplace air .

Country	mg/m^3	ppm	Remarks	Year	Reference
Denmark	0.1	-		1988	1
Finland	0.1	-	8-hour	1987	2
	0.3	-	15 minute		
Iceland	0.1	-		1989	3
The Netherlands	0.2	-		1989	4
Norway	0.1	-		1989	5
Sweden	0.1	-		1990	6
USA (ACGIH)	0.2	-		1990-91	7
(NIOSH)	0.2	-		1990-91	8

Permitted or recommended maxima for concentrations of selenium hexafluoride in workplace air.

Country	mg/m^3	ppm	Remarks	Year	Reference
Denmark	0.4	0.05		1988	1
Finland	0.4	0.05	8-hour	1987	2
	1.2	0.15	15 minute		
Iceland	0.4	0.005		1989	3
The Netherlands	0.4	0.05		1989	4
Norway	0.4	0.05		1989	5
Sweden	-	-		1990	6
USA (ACGIH)	0.16	0.05		1990-91	7
(NIOSH)	0.4	0.05		1990-91	8

Permitted or recommended maxima for concentrations of hydrogen selenide in workplace air.

Country	mg/m^3	ppm	Remarks	Year	Reference
Denmark	0.05	0.01		1988	1
Finland	0.03	0.01	15 minutes	1987	2
Iceland	0.05	0.01		1989	3
The Netherlands	0.2	0.05		1989	4
Norway	0.05	0.01		1989	5
Sweden	0.03	0.01		1990	6
USA (ACGIH)	0.16	0.05		1990-91	7
(NIOSH)	0.2	-		1990-91	8

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Summary

Beije B, Lundberg P (eds). Criteria documents from the Nordic Expert Group 1992. Arbete och Hälsa 1993:1, pp 1-271.

The Nordic Expert Group is a standing committee with the task of producing criteria documents on health effects of occupationally used chemicals. The documents are meant to be used by the regulatory authorities in the five Nordic countries as a scientific basis for the setting of national occupational exposure limits.

The volume consists of English translations of the criteria documents which have been published in a Scandinavian language during 1992.

Key words: Aluminium, Cadmium, Criteria document, Inorganic Acid Aerosols, Inorganic Lead, Nordic Expert Group, Occupational Exposure Limit, Selenium.

Sammanfattning

Beije B, Lundberg P (eds). Kriteriedokument från Nordiska Expertgruppen 1992. Arbete och Hälsa 1993:1, pp 1-271.

Den Nordiska Expertgruppen är en arbetsgrupp med uppgift att producera kriteriedokument om hälsoeffekter av kemiska ämnen i arbetsmiljön. Dokumenten skall användas av tillsynsmyndigheterna i de fem nordiska länderna som ett vetenskapligt underlag vid fastställande av hygieniska gränsvärden.

Volymen omfattar en engelsk översättning av de kriteriedokument som har publicerats på ett skandinaviskt språk under 1992.

På engelska.

Nyckelord: Aluminium, hygieniska gränsvärden, kadmium, kriteriedokument, nordiska expertgruppen, oorganiskt bly, oorganiska syraaerosoler, selen.

Appendix

Documents published in English by the Nordic Expert Group:

Acetonitrile	Arbete och Hälsa 1989:37, pp 149-174
Creosote	Arbete och Hälsa 1988:33, pp 7-51
Diacetone alcohol	Arbete och Hälsa 1989:37, pp 59-78
Dimethylethylamine	Arbete och Hälsa 1991:50, pp 7-24
Dimethylsulfoxide	Arbete och Hälsa 1991:50, pp 155-192
Hydroquinone	Arbete och Hälsa 1989:37, pp 79-114
Inorganic arsenic	Arbete och Hälsa 1991:50, pp 193-234
Isophorone	Arbete och Hälsa 1991:50, pp 25-37
Methyl bromide	Arbete och Hälsa 1987:40, pp 7-44
Methylene chloride	Arbete och Hälsa 1987:40, pp 74-120
Methyl formate	Arbete och Hälsa 1989:37, pp 175-202
Methyl isobutyl ketone	Arbete och Hälsa 1988:33, pp 53-76
Microorganisms	Arbete och Hälsa 1991:50, pp 39-69
n-Decane and n-Undecane	Arbete och Hälsa 1987:40, pp 45-73
Nitrilotriacetic acid (NTA) and its salts	Arbete och Hälsa 1989:37, pp 115-148
Nitroalkanes	Arbete och Hälsa 1988:33, pp 115-163
N-Nitroso compounds and cancer	Arbete och Hälsa 1991:2, pp 67-128
Organic acid anhydrides	Arbete och Hälsa 1991:2, pp 129-188
Paper dust	Arbete och Hälsa 1989:37, pp 203-246
Thiurams and dimethyldithio-carbamates	Arbete och Hälsa 1991:2, pp 7-66
Trichloroethene	Arbete och Hälsa 1991:50, pp 71-153
Styrene	Arbete och Hälsa 1991:2, pp 189-279
Toluene	Arbete och Hälsa 1989:37, pp 7-58
Vinyl acetate	Arbete och Hälsa 1988:33, pp 77-113
Welding gases and fumes	Arbete och Hälsa 1991:2, pp 281-315

Documents published by the Nordic Expert Group (NEG) in collaboration with the Dutch Expert Committee for Occupational Standards (DEC/DECOS) or the National Institute for Occupational Safety and Health (NIOSH):

7/8-Carbon chain aliphatic monoketones (DEC & NEG)	Arbete och Hälsa 1990:2, pp 1-44
Ethyl acetate (NEG & DEC)	Arbete och Hälsa 1990:35, pp 1-36
Ethyl ether (NEG & NIOSH)	Arbete och Hälsa 1992:30, pp 1-41
Methyl chloride (NEG-DECOS)	Arbete och Hälsa 1992:27, pp 1-23
Methyl methacrylate (DEC & NEG)	Arbete och Hälsa 1991:36, pp 1-58
Propylene glycol ethers and their acetates (NEG & NIOSH)	Arbete och Hälsa 1990:32, pp 1-47

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