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1989

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PREFACE

The Nordic Council is a corporative international body for the governments in the five countries Denmark, Finland, Iceland, Norway and Sweden. Within the Nordic Council one committee, 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 producing 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 Insitute of Public Health, Iceland
Per Lundberg (Chairman)	National Insitute of Occupational Health, Sweden
Petter Kristensen	National Insitute of Occupational Health, Norway
Vesa Riihimäki	Institute of Occupational Health, Finland
Adolf Schaich Fries	National Insitute 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 of significance 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 1989. The names of the scientists who have written the separate documents are given in the list of contents, where also the dates of acceptance by the Expert Group are given.

Solna in November 1989

Brita Beije
Secretary

Per Lundberg
Chairman

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TOLUENE

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BACKGROUND

The yearly production of toluene amounts to around 7 million tons (60). Up to 90-95% of the production is used in petrol to increase the octane number (32). Between 4 and 16 weight % of petrol is toluene. Technical grade toluene contains less than 0.5% benzene.

About 20% of the rest (approximately 70,000 tons) is used in the chemical industry in production of e.g. toluene diisocyanate, phenol, benzene, benzyl- and benzoeylderivates, benzoic acid, nitrotoluenes (e.g. TNT), and vinyltoluene. If encapsulated systems are used for the syntheses, the risk of exposure to toluene may be limited in the chemical industry.

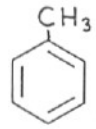
The remaining 80% of the rest of the toluene production (about 280,000 tons) is used as solvent and thinner in industries producing paint, printing ink, lacquers, glue and rubber. Furthermore, toluene is used to a great extent as cleansing solvent at processes where toluene based products are used, e.g. in printing plants. In the graphic industry it can be assumed that a high risk of exposure exists, as toluene is present in many of the products used, and as the chemical is also used for cleaning of machines etc.

In all occupations where paints, lacquers and glues based on organic solvents are used, a considerable risk of exposure to toluene also exists.

Toluene is found in the atmosphere in concentrations ranging from 2 microg/m^3 in rural areas to 2 mg/m^3 in urban areas (60).

PHYSICO-CHEMICAL DATA

Systematic name	Methylbenzene
Synonyms	Toluene, toluol, phenylmethane, methacide, methylbenzol
CAS number	108-88-3

Molecular formula	C_7H_8
Structural formula	
Molecular weight	92.13 g/mol
Properties	Colourless, flammable liquid with an unpleasant, sour to burned aromatic smell (53). The solubility in water is appr. 6.5 mmol/l at 20° C. Toluene is soluble in acetone and carbon disulphide, and miscible with most ethers, ketones, alcohols, esters, aliphatic and aromatic hydrocarbons. With many of the above mentioned solvents toluene creates azeotrophic mixtures. Furthermore toluene is an excellent solvent for a variety of products, e.g. bitumen, tar, paints, lacquers, fats, natural and artificial resins.
Boiling point at 101.3 kPa	110.6°C
Melting point at 101.3 kPa	-95°C
Vapour pressure at 25°C	3.73 kPa
Density at 20°C	0.876 g/ml
Vapour density (air=1)	3.20
Concentration of saturation (in air at 25°C)	142,000 mg/m^3
Explosive limits (% volume in air)	1.17-7.10
Log partition coefficient octanol/water	2.69
Flash point (closed cup)	4.4°C
Odour threshold	1.5-3.2 mg/m^3 (52) 17.5-262.5 mg/m^3 (106) 11$\pm$6 mg/m^3 (4)
Conversion factors at 25°C	1 mg/m^3 = 0.267 ppm 1 ppm = 3.75 mg/m^3

TOXICOLOGY

1. METABOLIC MODEL

1.1. Uptake

1.1.1. Skin

Liquid toluene is absorbed through the skin.

Maximum concentrations of toluene in blood (0.17 mg/l) were found after submerging a hand in toluene for half an hour (111).

The capability of toluene to penetrate the skin was investigated in isolated rat skin. At steady state a penetration of 8.5 nmol/cm^2min (0.78 mg/cm^2 min) was determined (130).

At skin exposure to toluene vapour (2250 mg/m^3 (600 ppm)), excluding respiratory uptake, steady state occurred after 30 minutes with a toluene concentration of 1.08 /umol/l (100 /ug/l) in venous blood. Based on average values for lung retention and lung excretion of toluene, it has been estimated that the percutaneous uptake of toluene amounts to approximately 1% of the respiratory uptake at the identical air concentration (104). A similar relation between lung and percutaneous uptake of toluene is given elsewhere (99).

1.1.2. Respiratory organs

The major uptake of toluene vapour is through the respiratory system. A number of investigations (23, 24, 95, 148) has shown that at rest a three hour exposure to toluene vapour will result in an uptake amounting to approximately 50% of the inhaled toluene.

The concentration of toluene in alveolar air and in arterial and venous blood rises quickly during the first 10-15 minutes of exposure (23, 149). After only 10 seconds of exposure toluene can be detected in blood from brachial arteries (149).

Physical work results in increased toluene uptake. Using a 50 W work load, exposure to 300 mg/m^3 toluene for 2 hours did not result in steady state of the blood concentration of toluene. The toluene uptake was 2.4 times higher than the uptake at rest. During the work, lung ventilation was increased 2.8 times. Concentrations of toluene in alveolar air and blood increased with increasing work loads (0-150 W in periods of 30 minutes) (23). The amount of toluene absorbed increased with greater amounts of body fat (25).

In dogs 3-4% of toluene was absorbed in the upper respiratory organs (35).

1.1.3. Alimentary system

Case reports from accidents and attempted suicides plus trials to treat leuchaemia with toluene (17) show that toluene can be absorbed via the alimentary system.

In rats, uptake of toluene via the alimentary system is slower than the respiratory uptake. Toluene concentration in blood reached maximum values two hours after an oral dose (102). About 76% was recovered as hippuric acid in the urine (66), and approximately 18% was excreted as toluene vapour through the respiratory system (117). Absorption appears to be nearly 100%.

In rabbits, orally dosed toluene also seems to be absorbed 100% (36, 117).

1.2. Distribution

The blood/air partition coefficient for toluene is 11.2-15.6 at 37°C (74, 109, 110, 115, 132).

The distribution of toluene in the body is among other factors dependent on the tissue/blood partition coefficients and the metabolism. In rabbits the following partition coefficients have been found: brain, heart, liver, and intestine: 2.3, muscle tissue: 1.6, adipose tissue: 74.3, bone, connective tissue, and lung tissue: 1.9 (112). In humans the adipose tissue/blood partition coefficient for toluene is determined to be 81-83 (112, 115).

In mice the distribution of toluene and its metabolites was investigated using whole body autoradiography after inhalation of side chain marked ^{14}C toluene (12, 13). In adipose tissue, bone marrow, spinal nerves, spinal cord, and in the white parts of the brain, high concentrations of radioactivity occurred. In blood, liver, and kidneys, radioactivity was also found. One hour after exposure nerve tissue showed no radioactivity. In adipose tissue nearly all radioactivity had disappeared four hours after exposure, and only traces of non-volatile radioactivity could be found in the liver. After 24 hours all radioactivity had disappeared from the body.

In rats, subcutaneous injection of toluene (100 or 500 mg/kg) resulted in maximum concentrations of blood toluene after 2 hours (10).

Toluene can pass the placenta. Two hours following exposure via inhalation to 1375 or 2700 mg/m^3 for 24 hours, fetal blood had a toluene concentration of 74% of that found in the dams blood. The amnion liquid contained a toluene concentration of 5% of the dams blood. Four and six hours after exposure, similar relative toluene concentrations were found (133).

1.3. Biotransformation

Biotransformation of toluene occurs mainly by oxidation in one of several possible positions. The endoplasmatic reticulum of liver parenchymal cells is the principal site of the oxidation (96). Of the biotransformed toluene, appr. 99% is oxidized via benzyl alcohol and benzaldehyde to benzoic acid.

The remaining 1% is oxidized in the aromatic ring, forming e.g. cresols (147).

In Figure 1 the different biooxidation products (phase 1 reactions) for toluene are shown.

Water solubility of the biooxidation products is achieved through linkage with suitable substances (phase 2 reaction). Benzoic acid is linked to either glycine or glucuronic acid forming either hippuric acid or benzoylglucuronide (96). Cresols and benzyl alcohol are linked to glucuronic acid or sulphate (96).

1.4. Elimination

1.4.1. Lungs

The toluene concentration in expired air decreases rapidly during the first 10 to 20 minutes after cease of exposure. Two to four hours later, very low toluene concentrations are found in expired air (23, 96). Of the toluene absorbed, 15-20% are exhaled during the first 2 hours (96).

The accumulated elimination of toluene via the lungs amounts to 4-8% and 7-14% after 2 and 20 hours, respectively (23).

The accumulated elimination (in per cent) of toluene via the lungs appears to increase with increasing amounts of toluene taken up (23).

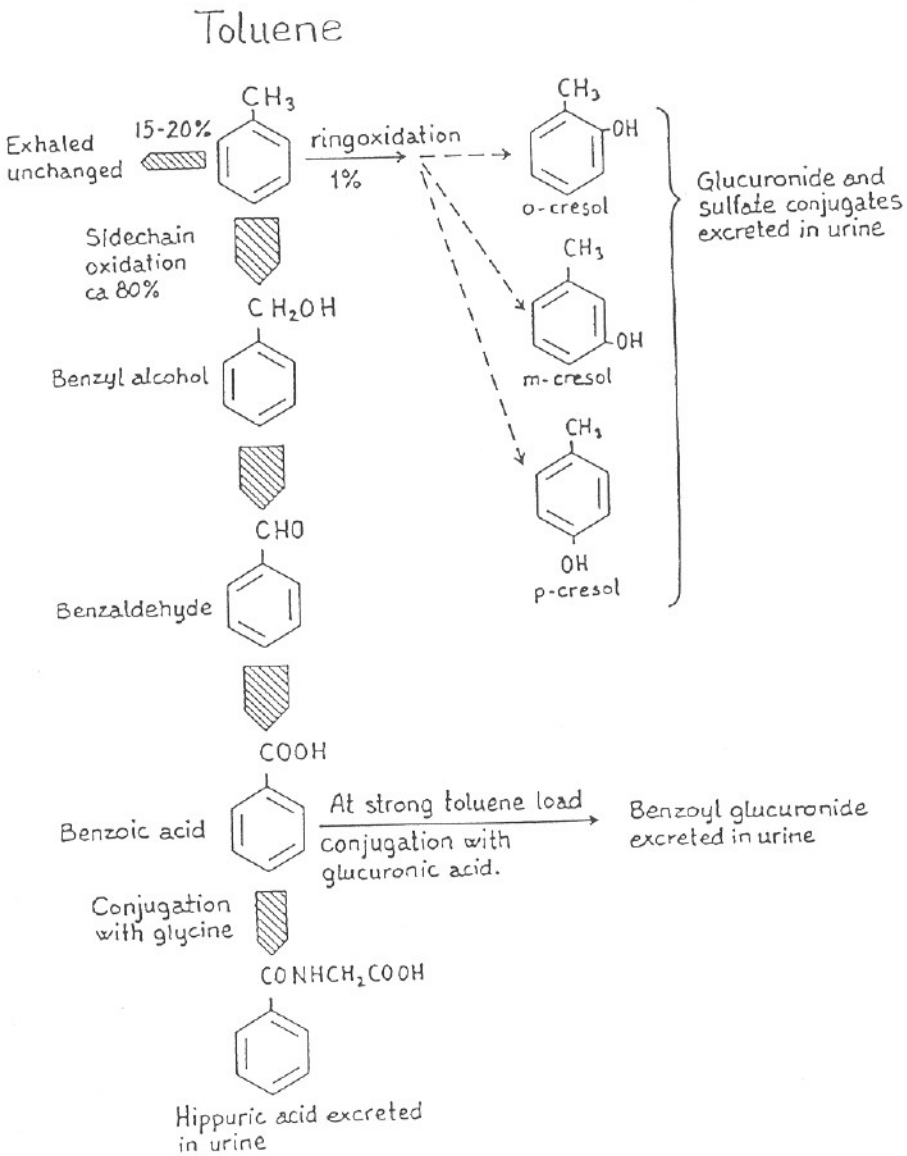


Figure 1. Metabolism and excretion of toluene in man.

1.4.2. Kidneys

The majority (80-90%) of absorbed toluene is biotransformed and excreted from the body via the kidneys. At an exposure level of 750 mg/m^3 (200 ppm) the excretion is mainly as hippuric acid. About 1% of the biotransformed toluene is excreted as glucuronides or sulphates of o-, m-, or p-cresol.

Figure 2 shows mean values, based on 20 volunteers, for blood toluene concentration and concentrations of toluene metabolites in urine before (t=0), and after (t=4, 8, 24, and 48 hours) a 4 hour inhalation of 750 mg/m^3 (200 ppm) toluene (146).

Approximately 0.06% of the toluene absorbed is excreted unchanged in the urine (145).

At heavy toluene exposures excretion of benzoyl glucuronides is possible if glycine becomes limiting for the excretion of hippuric acid.

A good correlation was found between toluene exposure and concentration of hippuric acid in post exposure urine (73).

1.4.3. Alimentary system

In rats less than 2% of the absorbed toluene is excreted via the bile to the intestine. The substances excreted are reabsorbed in the intestine. Thus very small amounts are excreted in faeces (1).

1.5. Biological halftimes

Two hours' inhalation of 375 mg/m^3 (100 ppm) and determination of the time relations for toluene in blood and expired air after exposure gave a three phasic halflife curve. Biological halftimes of 2 minutes, appr. 30 minutes, and appr. 3.5

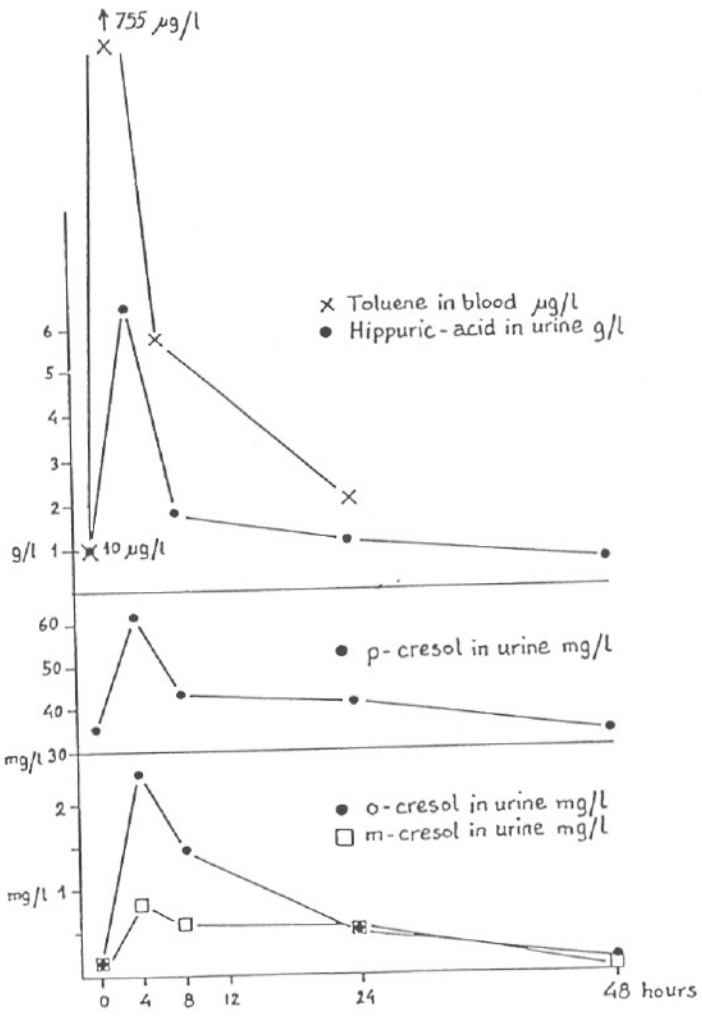


Figure 2. Concentrations of toluene in blood and of toluene metabolites in urine as a result of 4 hours exposure to 750 mg toluene/m^3 (t= 0 to 4). Data from (146).

hours, respectively, were calculated (96, 112). Halftimes of 22 minutes and 175 minutes for the two last phases have been determined (107). In a study of workplace accidents with coma as a result of exposure to high toluene concentrations, a fourth phase with a 20 hour halftime was found. This phase is taken to represent toluene elimination from adipose tissue (20).

The slow elimination of toluene from adipose tissue suggests that daily toluene exposure results in some accumulation of the chemical in adipose tissue.

1.6. Factors affecting the metabolic model

Ethanol, 0.8 g, in orange juice given orally half an hour before and followed by 6 doses (0.15 g ethanol/kg and hour) during exposure to 375 mg/m^3 (100 ppm) toluene for 7 hours was found to reduce toluene metabolism by 50% as measured by the urinary excretion of hippuric acid and o-cresol. The toluene concentration in alveolar air was increased during and up to 45 minutes after exposure. Propranolol and cimetidine had no such effect (34).

Ethanol, 1.5 ml vodka/kg, consumed after three hours' exposure to 300 mg/m^3 (80 ppm) toluene, resulted after a further three-hour exposure in increased blood toluene levels as compared to blood toluene levels in the same persons after toluene exposure without alcohol intake. Among males occupationally exposed to toluene, the lowest blood toluene levels were found among individuals who consumed alcohol regularly (138).

A comparison of toluene excretion from blood via the lungs in unexposed persons and in spray-painters with previous toluene exposure showed no difference. The toluene excretion was independent of age, body weight, and alcohol consumption. Smokers showed a tendency to faster excretion of blood toluene via the lungs (140).

After work shift, concentrations of metabolites in urine were compared among four groups of men. The first group (65 persons) was occupationally exposed to benzene, the second group (35 persons) was exposed to toluene, and the third group (55 persons) was exposed to both benzene and toluene, the unexposed control group consisted of 35 persons. Hippuric acid concentration and, to a lesser extent, the concentration of o-cresol were decreased in the group exposed to benzene and toluene as compared to the group with toluene exposure (59).

Rats given ethanol corresponding to 30% of daily calorie intake for three weeks showed increased metabolism of inhaled toluene. One day after the last ethanol dosing, normal values for toluene metabolism were found (113).

In rats on low protein diet (9 g% protein as opposed to the normal 18 g%) a reduced excretion of hippuric acid was observed (51).

2. TOXICOLOGICAL MECHANISMS

The toxicological mechanism of toluene is not known. The most important effect of acute exposure appears to be influence on membranes.

3. EFFECTS ON ORGANS

A number of investigations on organ effects of toluene carried out up to about 1975 were performed with toluene containing considerable amounts of benzene. Many of those studies have been accounted for previously (96), therefore the present contribution has seeked only to include studies in which the toluene used contained only small amounts of benzene (less than 0.1%). Many of the effects previously ascribed to toluene have not been found using the more purified grades of toluene.

Table 1. Acute toxicity data for toluene

	Species	Route	Value	References
LD50	Rat	Oral	7.5 g/kg	(118)
LD50	Rat	Oral	5.9 g/kg	(135)
LD50	Rat	Oral	5.5 g/kg	(64)
LD50	Rabbit	Dermal	12.2 g/kg	(118)
LD50	Rat	Intraperitoneal	1.6 g/kg	(40,58,77)
LD50	Mouse	Intraperitoneal	2.15 g/kg	(67)
LC50	Rat	Inhalation, 6.5 h	45,750 mg/m^3	(22)
LC50	Mouse	Inhalation, 7 h	19,950 mg/m^3	(121)
LC50	Mouse	Inhalation, 6 h	26,033 mg/m^3	(14)

3.1. Skin and mucous membranes

Toluene has a degreasing effect on the skin and can therefore cause development of toxic contact dermatitis (18, 48).

Epicutaneous occlusive application of toluene (1 ml on 3.1 cm^2 skin of guinea pigs) was found to result in pyknosis of epidermal nuclei after 15 minutes. After one hour of exposure, separation of basal membrane and epithelial cells was observed. Karyolysis was observed following 4 and 16 hours of exposure (69).

Six hours' exposure to 375 mg/m^3 (100 ppm) resulted in some complaints of irritation in the eyes and on the mucous membranes of the airways (5).

In rats, dose related effects on eyes were not observed following exposures up to 1125 mg/m^3 (300 ppm) toluene for 2 years (6 h/day, 5 days/week) (49).

3.2. Respiratory organs

Nasal mucus flow and lung function in students were not affected as a result of 6 hours' inhalation of 37.5 mg/m^3 (10 ppm), 150 mg/m^3 (40 ppm), and 375 mg/m^3 (100 ppm) toluene (5).

RD-50 is a measure of irritation of the airways. It is the air concentration of a chemical that reduces the frequency of respiration to half. For mice, RD-50 values of 12,590 mg/m^3 (87), 12,650 mg/m^3 (3373 ppm) (29), and 19,875 mg/m^3 (5300 ppm) (93) have been determined.

In mice, inhalation of toluene in the concentration range from 1875 mg/m^3 (500 ppm) down to 9 mg/m^3 (2.5 ppm) for three hours resulted in increased death of pneumonia caused by streptococci. Groups of mice not exposed to toluene served as controls. Control mice and mice having inhaled toluene were together exposed to a streptococcus aerosol. Nine different concentrations of toluene were used. At 3.7 mg/m^3 (1 ppm) no difference in mortality was observed (7).

3.3. Liver

No increase in levels of the enzymes serum aspartate aminotransferase and alanine aminotransferase was found, in 59 men with occupational exposure to toluene (recorded level 375 mg/m^3) for more than one year (1-5 years, 22 men; 6-10 years, 18 men; more than 10 years, 19 men) when compared to an equal sized unexposed control group (139).

Inhalation of 2000 mg/m^3 or 3000 mg/m^3 toluene, either for 24 hours or 8 hours per day in a week did not result in histological liver changes in mice, rats, and rabbits. The levels of the enzymes esterase, acid and alkaline phosphatase and succinate dehydrogenase were unchanged, while cytochrome P-450 and cytochrome b_5 concentrations were increased in the toluene exposed groups (136).

In rats, intraperitoneal injection of 1/16 (0.1 g/kg) or 1/32 (0.05 g/kg) of LD-50 did not affect activity of sorbitol dehydrogenase and aspartate aminotransferase (77).

In rats inhaling 1000 mg/m^3, 1500 mg/m^3, 3000 mg/m^3, 3500 mg/m^3 or 6000 mg/m^3 toluene 8 hours/day for up to 6 months, reversible dose dependent liver changes were observed. The changes were increases in relative weight of the liver, succinate dehydrogenase activity, and concentration of cytochrome P-450 and b_5, and a decrease in glycogen content.

3.4. Kidneys

Inhalation of 382 mg/m^3 toluene for 6.5 hours in an exposure chamber resulted in unchanged excretion of albumin and beta-2-microglobulin for 43 printers as compared to 43 age-matched unexposed controls (94).

Compared to a control group no signs of renal damage in 118 painters were found. The painters had a mean of 9 years' occupational exposure to toluene and xylenes. At the time of investigation the exposure was appr. 94 mg/m^3 (25 ppm) as determined from metabolites in urine (42).

In 42 printers with an occupational toluene exposure averaging 300 mg/m^3 (range 100-900 mg/m^3) compared with 48 unexposed controls, no changes in glomerular filtration rate, renal concentrating ability, beta-2-microglobulin excretion, and excretion of erythrocytes and leucocytes were found (9).

Sniffing of toluene resulted in reversible kidney damage (97), haematuria (83), reversible type 1 renal tubular acidosis (11, 38, 68, 86, 98, 103, 120, 123, 142, 144) and hypokalemia (63, 123). In some cases sniffing resulted in irreversible damage of the kidneys (105).

A workplace accident with massive toluene exposure for 18 hours resulted in renal failure with oligouria probably caused by dehydration and myoglobinuria (103).

3.5. Blood and blood-forming organs

In a study including 38 female workers doing shoeglueing and a control group of 16 women from the same plant, but not exposed to organic solvents, the values of blood density, haemoglobin content, haematocrit and number of leucocytes were not different. However, the Mommsen toxic granula in the periferal neutrophile granulocytes developed faster in the group exposed to toluene. Mean values of hippuric acid in urine were 3.26 mg/ml in the exposed group and 0.35 mg/ml in the control group (84).

3.6. Digestive tract

Information on the effect of toluene on the digestive tract has not been found.

3.7. Heart and blood vessels

In 325 printers, a slight increase in systolic blood pressure showed correlation with toluene exposure, as judged by an exposure index, (89).

3.8. Central nervous system

The results achieved in a number of performance tests were not influenced by six hours' inhalation of toluene in concentrations up to 375 mg/m^3 (100 ppm). At 375 mg/m^3 (100 ppm) headache, dizziness, and feeling of intoxication were more often reported by the study subjects (16 students) than at the lower concentrations (0 mg/m^3, 37.5 mg/m^3 (10 ppm), 150 mg/m^3 (40 ppm)) (5).

For 12 volunteers inhaling 300 mg/m^3 toluene for 4.5 hours, the results in 4 performance tests carried out after 2 and 3.5 hours of exposure were not significantly different from the results obtained from the same persons during exposure to

clean air. Subjective complaints of headache and irritation were more frequent at toluene exposure, during which a small decrease in the pulse at rest was observed (62).

In eleven performance tests 34 printers with 3 to 32 years' exposure to toluene showed only significantly different (worse) results in simple reaction time, when compared to an equal-sized, age-matched, unexposed control group (61).

Following exposure to 375 mg/m^3 (100 ppm) toluene for 6.5 hours, 43 printers with 9 to 25 years' occupational toluene exposure did not show significantly different results in 10 performance tests compared to an equal-sized control group matched for sex, age, education and smoking habits. The exposure was found to decrease manual dexterity, colour discrimination, and accuracy in visual perception in printers as well as in control persons (21).

Significantly reduced results in the British National adult reading test were seen for 59 men who had been exposed to toluene (375 mg/m^3 to 1875 mg/m^3 (100-500 ppm) for an average of 9.4 years) in comparison to a similar number of unexposed workers from the same plant. Matching regarding age, race and length of employment was carried out (26).

Table 2 shows results found by neurological examination of 24 patients with a mean age of 23 $\pm$ 4.4 years and 6.3 $\pm$ 3.9 years of toluene sniffing. Based on the results of the neurological examination the patients were divided into an affected group (four or more abnormal neurological findings) and a non-affected group (less than four abnormal findings in the neurological examination). In four psychological tests abnormal results were found for the affected group. For the non-affected group abnormal score was not found. CT-scanning results revealed significant brain atrophy in the affected group (41).

Table 2. Neurological observations in 24 chronic toluene sniffers

Observation	Number of persons	%
Tremor	11	45
Ataxia	11	45
Memory impairment	5	20
Decreased sense of smell	2	8
Optic atrophy	2	8
Hearing impairment	2	8
Spasticity and hyperreflexia	2	8
Peripheral neuropathy	2	8
Pathological reflexes	2	8

Inhalation of toluene resulted in development of cerebellar, pyramidal and cognitive dysfunction. In a case of short term occupational exposure the effects were reversible. Reversibility was not observed in a patient with 10 years of toluene sniffing (15).

In a number of case reports different effects of toluene sniffing (19, 30, 65, 75, 80, 108, 131, 141, 143) and of workplace exposure to toluene (70, 79) have been described. These reports essentially describe the observations given in Table 2.

A one hour inhalation of toluene (472-588 mg/m^3 (126-157 ppm)) was found to affect nystagmus reflexes (visual suppression) in 15 volunteers (56).

In macaka monkeys exposed to 0, 375, 750, 1875, 3750, 7500, 11250, or 16875 mg/m^3 (0, 100, 200, 500, 1000, 2000, 3000 or 4500 ppm) toluene for 50 minutes, increased response time and decreased precision at 7500 mg/m^3 and higher concentrations were observed (125). During the last 18 minutes of exposure to toluene concentrations from 375 mg/m^3 to 11250 mg/m^3 concentration of carbon dioxide in expired air was significantly increased (125).

Inhalation of toluene during 1, 2 or 4 hours has been found to affect the behaviour of rats. In the study (88), the concentration (EC50), which affects 50% of the animals at a given time of exposure was calculated for 16 behavioural patterns. EC50 values in the range 2400 mg/m^3 (640 ppm) to 5025 mg/m^3 (1340 ppm) were determined. In general, the values were higher for 1 hour inhalation than for 4 hours inhalation.

In rats given 1.5 or 1.7 g toluene/kg subcutaneously for 7 days, a significant hearing loss at the frequencies 8, 12, 16, and 20 kHz was found 34 days after dosing. At 4 kHz no hearing loss was observed (100). In rats, the same research group previously has shown that inhalation of toluene (3750 mg/m^3 (1000 ppm), 14 hours/day for 14 days) can result in hearing loss (101).

Inhalation of 5625 mg/m^3 (1500 ppm) toluene for 50 minutes affected nystagmus reflex in rats (71). In rats with a blood toluene concentration of 0.9 mmol/l or higher, the nystagmus reflex was increased (126).

Concentration-effect curves for behavioural toxicity of toluene in mice were determined. At 1125 mg/m^3 (300 ppm) and 1875 mg/m^3 (500 ppm) no change in activity was seen. At 3750 mg/m^3 (1000 ppm) activity was increased. At a concentration of 9000 mg/m^3 (2400 ppm) activity was reduced and at 16,875 mg/m^3 (4500 ppm) activity ceased (50).

Dose-related increases in hypothalamic catecholamine levels and serum-prolactin concentrations were seen after exposure of male rats to 0 mg/m^3, 300 mg/m^3 (80 ppm), 1875 mg/m^3 (500 ppm), 5625 mg/m^3 (1500 ppm), and 11250 (3000 ppm) toluene 6 hours per day for three days (6).

In male rats inhaling toluene 6 hours per day for three days, a reduced dopamine level in the forebrain was observed at 300 mg/m^3 (80 ppm). However, at the higher concentrations (1875

mg/m^3 (500 ppm), 5625 mg/m^3 (1500 ppm), and 11250 mg/m^3 (3000 ppm)) dopamine levels did not differ from those of the controls (44).

In male rats inhaling 1500 mg/m^3 (400 ppm) toluene for 30 days the concentration of norepinephrine in ventral cortex and the concentration of dopamine in olfactory cortex were increased. Reduced concentrations of norepinehprine in olfactory cortex and hypothalamus and of dopamine in striatum were recorded. At 750 mg/m^3 (200 ppm) no significant changes relative to an unexposed control group were observed (57). However, the experimental groups comprised 5 animals only.

3.9. Peripheral nervous system

No evidence suggesting that pure toluene can cause damage to the peripheral nervous system has been found (129). Previous reports on peripheral nervous system damage in occupationally exposed persons can probably be explained by exposures to toluene mixed with e.g. ethanol and/or n-hexane. Sniffing of solvent mixtures is a likely explanation of the two cases of peripheral neuropathy in table 2.

3.10. Reproductive organs

Increasing toluene exposures have been shown to correlate with increasing levels of plasma-follicle stimulating hormone in printers (89).

Increased frequency of menstrual disorders (50% as opposed to 19% in the control group of 16 women) was recorded in a group of 38 women glueing shoes. They were exposed to appr. 375 mg/m^3 (100 ppm) toluene and small amounts of light gasoline (84).

Menstrual disorders were recorded with increased frequency (41% of 141) among women exposed to toluene in the electronics industry. The toluene originated from varnishes and exposure was for 4 to 20 years at a level of 25-450 mg/m^3 (7-120 ppm). Toluene concentrations between 250 and 300 mg/m^3 (67-80 ppm) were found in 75% of the determinations (122).

Toluene did not increase the number of abnormal spermatozoa in mice (127).

3.11. Fetus

Birth of children with fetal solvent (alcohol) syndrome has been related to toluene sniffing of their mothers (54, 120, 128).

Toluene has been investigated for effects on the fetus in several animal experiments (Table 3) and is considered toxic to the fetus according to the Danish criteria (76).

4. ALLERGY

No description was found of allergic effects on the skin or the airways caused by toluene exposure.

5. GENOTOXIC EFFECTS

5.1. Mutations in model systems

Toluene did not show activity in the thymidine screening system (TSS) (3) the Ames test, the Salmonella strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538, neither without nor with metabolic activation (S9-mix) (16, 27, 39, 92, 119).

Toluene (1875 mg/m^3 (500 ppm) and 3750 mg/m^3 (1000 ppm)) did not induce recessive lethal mutations in Drosophila melanogaster males (33).

Table 3. Animal studies on the embryotoxic and fetotoxic effects of toluene

Species	Dosage	Results	Ref.
Rats, CFY	1500 mg/m^3 (400 ppm) inhalation 24 h/day, day 9-14 of gestation	Extra ribs fused sternebrae	(55)
	1500 mg/m^3 (400 ppm) inhalation, 24 h/day, day 1-8 of gestation	Reduced fetal weight in half of the fetuses, delayed ossification	(55)
	1000 mg/m^3 (276 ppm) inhalation, 8 h/day, day 1-8 of gestation	Delayed ossification	(55)
	1000 mg/m^3 inhalation 24 h/day, day 7-24 of gestation	Delayed ossification	(124)
Mice, CFLP	500 mg/m^3 (133 ppm) inhalation, 24 h/day day 6-13 of gestation	Reduced fetal weight	(55)
Mice, ICR	3750 mg/m^3 (1000 ppm) inhalation 6 h/day, day 2-17 of gestation	Slight increase in no. of resorptions, extra ribs	(116)
	375 mg/m^3 (100 ppm) inhalation 6 h/day, day 2-17 of gestation	Slight increase in no. of resorptions	(116)
Mice, CD-1	0.3, 0.5, and 1.0 ml/kg body weight by gavage each day on days 6-15 of gestation	Increased fetal death at all dose levels. Reduced fetal weight at 0.5 and 1.0 ml/kg. At 1.0 ml/kg increased frequency of cleft palate	(91)
Mice, CD-1	1498 mg/m^3 (400 ppm) inhalation, 7 h/day, day 7-16 of gestation	Change in fetal rib profile	(28)
	749 mg/m^3 (200 ppm) inhalation, 7 h/day, day 7-16 of gestation	Increase in dilated renal pelves	(28)

5.2. Chromosome damage

In a group of 35 printers with from 3 to 33 years' toluene exposure, no increase in frequency of chromosome breaks and sister chromatid exchanges in lymphocytes was observed when compared to 15 employees at a research institution. The two groups had the same mean age (90).

Increased frequency of chromatid gaps and aberrations was observed in lymphocytes of 27 rotogravure workers for up to 2 years after toluene exposure had stopped. Sister chromatid exchanges were slightly affected by toluene exposure, however the effect could not be observed post toluene exposure. The control group were 26 non-exposed workers from the same plant (114).

Increased numbers of abnormal cells and chromosome breaks were found in 14 workers exposed to toluene in a rotoprinting factory as compared to a control group of 42 persons (43).

Chromatid gaps and breaks were increased in bone marrow cells from rats following injection of 1 g toluene/kg and day for twelve days (78).

In rats inhaling 1125 mg/m^3 (300 ppm) toluene 6 h/day, 5 days/week for 15 weeks no increase of chromosome aberrations was seen in bone marrow cells. Sister chromatid exchanges were increased in weeks 11 and 13 but not in week 15 of the exposure. Sister chromatid exchanges were determined in weeks 11, 13, and 15, only (33).

Toluene was not found to induce chromosome aberrations in cells of the bone marrow nor dominant lethal mutations in SHR-mice given doses up to 0.2 times LD50 (37).

Toluene given orally (1720 mg/kg twice) did not increase the frequency of micronuclei in bone marrow cells, number of damaged cells, chromosome breaks and exchanges in mice (45).

In mice, two doses of either 0 mg, 105 mg (0.12 ml), 220 mg (0.25 ml), 324 mg (0.37 ml), or 438 mg (0.50 ml) toluene/kg body weight given intraperitoneally 24 hours apart, resulted in an increased number of micronuclei in polychromatic erythrocytes at the three highest doses (85).

6. CARCINOGENIC EFFECTS

Studies elucidating a carcinogenic effect of toluene in humans have not been found.

No increase of tumour frequency in male and female F344 rats was seen in a 24-month inhalation study using four dose levels (maximum 1125 mg/m^3 (300 ppm)) (49).

Significant increases of hemolymphoreticular neoplasias and malignant tumours were seen in Sprague-Dawley rats given 500 mg toluene (98.43% pure, benzene content not stated) per kilo body weight by gavage once daily, 4-5 days/week for 104 weeks followed by observation until natural death (Table 4). It is concluded that toluene, at high concentrations, causes an increase in the total number of malignant tumours (81, 82).

Table 4. Frequency of hemolymphoreticular neoplasias and malignant tumours in rats given 500 mg toluene/kg by gavage 4-5 days/week for 104 weeks. Data from (82):

	Toluene	Control
Number of animals at start	80	100
Thymomas	3(3,9%)	0
Other hemolymphoreticular neoplasias	7(9.1%)	4(4.2%)
Malignant tumours	55	23
No. animals with malignant tumours	39	21

7. INDICATORS OF EXPOSURE

7.1. Air concentrations

Toluene in the air can be determined by sampling in charcoal tubes followed by gas chromatography. Based on a 15 minutes air sample, the detection level for toluene by gas chromatography is 1/10 of the Danish exposure limit (190 mg/m^3) with a sample error of $\pm$ 10% (8).

Toluene was the chemical most frequently identified in workplace air by the Danish Labour Inspection in the years 1983-86 (72). In 97% of the cases toluene concentrations were below the exposure limit.

When toluene is found in workplace air, it is often found together with other chemicals. Of 141 samples with toluene, the most frequent other chemicals were: xylenes (60%), butylacetates (55%), acetone (50%), butanols (50%), ethanol (40%), and 2-propanol (40%). Some of the effects described in the previous document (96) may have resulted from exposure to toluene and n-hexane or benzene. These two chemicals have been found with toluene in 3% and 2%, respectively of the samples.

7.2. Biological indicators

A number of biological measures can be used to evaluate toluene exposure.

1) toluene in blood
2) toluene in exhaled air
3) hippuric acid in blood
4) hippuric acid in urine
5) benzoic acid in urine
6) o-cresol in urine
7) m-cresol in urine

In USA, ACGIH (2) suggests the following biological measures for toluene exposure: hippuric acid in urine, toluene in venous blood, and toluene in exhaled air. In West Germany, DFG (31) suggests toluene in whole blood as a measure of exposure to toluene.

An evaluation of the usefulness of the above-mentioned methods 1-6 in estimating toluene exposure (73) concludes that different biological measures are necessary depending on the time at which sampling occurs relative to the time of exposure. Furthermore, the necessity of studies elucidating the influence on toluene metabolism and toxicity of other factors is stated. The use of m-cresol in urine as a measure of toluene exposure has not been studied in relation to the other biological measures.

Just after sniffing, concentrations of 9.8-29.3 mg toluene/litre blood have been found in toluene sniffers. These concentrations are in the range of those found in seven deaths caused by inhalation of toluene (47).

8. EXPOSURE, EFFECT, AND RESPONSE RELATIONSHIPS

8.1. Effects of short-term exposure

In Table 5 effects of short-term toluene exposure are given.

8.2. Effects of long-term exposure

Long-term high concentration toluene exposure (sniffing) has caused irreversible damage to the central nervous system (see 3.8.). Some case reports of fetal solvent syndrome attributed to toluene sniffing during pregnancy are known (see 3.11.).

Table 5. Effects of short-term human exposure

Concentration	Exposure	Effects	References
3000 mg/m^3 (800 ppm)	1 x 8 h	Reduced coordination ability and increased reaction time after few hours	(137)
2250 mg/m^3 (600 ppm)	1 x 8 h	From 3000 to 750 mg/m^3 a concentration effect relationship	(137)
1500 mg/m^3 (400 ppm)	1 x 8 h	From 3000 to 750 mg/m^3 a concentration effect relationship	(137)
1125 mg/m^3 (300 ppm)	1 x 8 h	From 3000 to 750 mg/m^3 a concentration effect relationship	(137)
750 mg/m^3 (200 ppm)	1 x 8 h	Slightly reduced coordination ability and slightly increased reaction time at the end of exposure	(137)
375 mg/m^3 (100 ppm)	1 x 8 h	No effect observed	(137)
187 mg/m^3 (50 ppm)	1 x 8 h	No effect observed	(137)
2700 mg/m^3 (714 ppm)	4 x 20 min	Increase in simple and choice reaction time	(46)
1875 mg/m^3 (500 ppm)	4 x 20 min	Increase in simple and choice reaction time	(46)
1125 mg/m^3 (300 ppm)	4 x 20 min	Increase in simple reaction time	(46)
375 mg/m^3 (100 ppm)	4 x 20 min	No effect observed	(46)
300 mg/m^3 (80 ppm)	1 x 4.5 h	Headache and irritation	(62)
375 mg/m^3 (100 ppm)	1 x 6 h	Headache, dizziness, feeling of intoxication. Irritation of eyes and nose	(5)
150 mg/m^3 (40 ppm)	1 x 6 h	No effect observed	(5)
37.5 mg/m^3 (10 ppm)	1 x 6 h	No effect observed	(5)

In male printers with long-term toluene exposure, a dose dependent increase in plasma concentrations of follicle stimulating hormone has been observed. Increased frequency of menstrual disorders has been reported for women in the electronics and shoe industries (see 3.10).

For up to two years after toluene exposure, increased frequencies of chromatid gaps and aberrations were observed in printers. In another study this effect could not be shown (see 5.2.).

9. RESEARCH NEEDS

Further studies on the effect of toluene on reproduction and the fetus are desirable. In such studies effects of catecholamine and sexhormone balance should be included.

The ability of toluene to affect defence mechanisms of the airways should be studied further.

The carcinogenic and genotoxic effects of toluene are only partially elucidated, therefore studies clarifying the role of toluene with respect to these effects are desirable.

As toluene is rarely found alone in workplace air, the effects of mixed exposures need to be better clarified. National differences in these mixed exposures may exist for which reason more detailed proposals for such studies cannot be given.

10. DISCUSSION AND EVALUATION

A number of toxic effects previously ascribed to toluene exposure are probably caused by mixed exposure to toluene and e.g. benzene, or n-hexane.

In humans the first symptoms have been recorded at 375 mg toluene/m^3. The symptoms are headache, dizziness, intoxication and irritation of mucous membranes.

Animal evidence shows increased susceptibility to airborne infection at toluene concentrations down to 9 mg/m^3 (2.5 ppm).

Two long-term studies on the carcinogenicity of toluene are recorded. In the inhalation study (49) using 1125 mg/m^3 as highest concentration no increase in tumour frequency was found. The other study reported an increase of tumour frequency. In this study doses of 500 mg toluene/kg were given by gavage. As both concentration and method of dosing in the latter study is unphysiological, the relevance of the observations to workplace exposures can be questioned.

Some information on the effects of toluene on reproduction is found. These are changes in sex-hormone concentration, menstrual disorders, and case-reports of fetal solvent syndrome caused by mothers sniffing toluene during pregnancy. In animal experiments, fetotoxic effects are recorded. All the information seems to indicate that toluene, even at concentrations close to exposure limit values may have an effect on reproduction. This effect may be reduced fertility among toluene exposed persons.

Long-term toluene sniffing can result in irreversible damage to the central nervous system. In occupational toluene exposure the critical effect seems to be influence on the central nervous system, as recent experimental studies report subjective symptoms such as dizziness and headache at toluene concentrations around 375 mg/m^3. At 150 mg/m^3 these symptoms seem to disappear (59). Repeated toluene exposure may lead to some accumulation in adipose tissue.

11. SUMMARY

J.E. Jelnes: Toluene. Nordic Expert Group for documentation on occupational exposure limts.

Based on recent literature about toxic effects of toluene, it is concluded that the acute effects on the nervous system should be considered when exposure limit values are determined. Also it should be taken into account that toluene rarely occurs alone, and that it possibly has an effect on reproduction and on the defence mechanism against infection of mucous membranes.

In English, 149 references.

Key words: Toluene, exposure limit values, CNS effects, accumulation, reproduction, mixed exposures.

A Danish version is available in Arbete och Hälsa 1989:3.

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Appendix I. Occupational exposure limits for airborne toluene

Country	mg/m^3	ppm	Year	Note	Ref.
BRD	380	100	1988		5
Denmark	190	50	1988	S	2
Finland	375	100	1987	S	11
	565	150		15 min	
France	375	100	1987		12
	550	150		15 min	
Iceland	375	100	1978	S	9
The Netherlands	375	100	1986	S	7
Norway	280	75	1984		1
	185	50		P	
The Soviet Union	50		1978	g	6
Great Britain	375	100	1988	S	4
	560	150			
Sweden	200	50	1988	NGV, S	3
	400	100		KTV	
USA (ACGIH)	375	100	1988-89		10
	560	150		STEL	
(OSHA)		200	1973		8
		300		T	
(NIOSH)		100	1982		8
		200		T	

P = for new plants
g = gas
S = skin
KTV = short-term value
T = ceiling limit
STEL = short-term exposure limit
NGV = nivågränsvärde (8 h value)

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DIACETONE ALCOHOL

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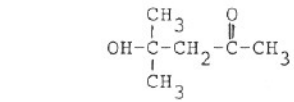
1. PHYSICAL AND CHEMICAL DATA

Chemical name:	4-hydroxy-4-methyl-2-pentanone
CAS No.:	123-42-2
Synonyms:	Diacetone alcohol, Pyrantone, Dimethyl acetonyl carbinol
Formula:	$(CH_3)_2C(OH)CH_2COCH_3$
Structure:	
Molecular weight:	116.16
Boiling point (101.3 kPa):	169°C
Melting point:	-44°C
Vapor pressure (20°C):	100 kPa
Density (d 25/4):	0.93
Combustion point:	8-13°C (commercial grade)
	66°C (reagent grade)

1 ppm = 4.75 mg/m^3; 1 mg/m^3 = 0.21 ppm

Diacetone alcohol at room temperature is a colorless liquid with a sweetish odor that many people consider pleasant. The reported odor threshold is 1.33 mg/m^3 (0.28 ppm) (1, 11, 20, 22). All exposed subjects reported that they could recognize the odor at a concentration of 8.08 mg/m^3 (1.7 ppm) (11). Saturated air at 20°C contains 0.13% diacetone alcohol. The explosion point is between 1.8 and 6.9% (15).

Diacetone alcohol mixes with water, alcohols, esters and aromatic and halogenated hydrocarbons.

2. OCCURRENCE, USES

2.1. Uses

Diacetone alcohol is produced from acetone and hydroxide of either calcium or barium. It is used as a solvent for nitrocellulose, cellulose acetate, celluloid, waxes, greases and oils. Diacetone alcohol is also used in some antifreezes and hydraulic fluids, and in some pharmaceutical preparations. Exposure also occurs in the petrochemical industry.

2.2. Air concentrations in the working environment

Monitoring measurements taken in a screen printing plant showed a time-weighted average of 66.5 $\pm$ 29.5 mg/m^3 (14 $\pm$ 6.2 ppm) in the breathing zone around the printing presses (23). At other monitored work areas in the plant the average concentrations ranged from 8.55 to 59.4 mg/m^3 (1.8 to 12.5 ppm).

2.3. Methods for analysis of air concentrations

Diacetone alcohol in air is collected in a carbon rod filter. A suitable rate of flow is 0.01 to 0.2 liters/minute, with a total volume of 1 to 10 liters. After desorption with a 5% solution of 2-propanone in carbon disulfide, the sample is analyzed by gas chromatography and flame ionization. The method is considered suitable for air concentrations in the range 15 to 150 mg/m^3 (17).

3. KINETICS

3.1. Uptake

There are no quantitative date regarding uptake of diacetone alcohol in either man or animals. However, it has been shown experimentally that the substance can be taken up via both the respiratory passages and the digestive tract (14, 19).

3.2. Distribution

No information is available.

3.3. Biotransformation

Diacetone alcohol is one of two biotransformation products that were identified in serum of guinea pigs after intraperitoneal administration of methyl isobutyl ketone (7). Diacetone alcohol can be conjugated with glucuronic acid or sulfuric acid and then be excreted, or it can be incorporated in the intermediary metabolism and then eliminated as carbon dioxide (10).

In vitro studies with isolated rat liver microsomes have shown that diacetone alcohol binds to cytochrome P-450 and stimulates NADPH oxidation in a way typical for cytochrome P-450 substrate (12). The concentration of microsomal enzymes is not affected.

3.4. Elimination

There are no quantitative data on elimination of diacetone alcohol.

After intraperitoneal administration of methyl isobutyl ketone to guinea pigs (450 mg/kg), the half time of diacetone alcohol in serum was determined to be 16 hours (7).

3.5. Biological exposure indicators

No information is available.

4. GENERAL TOXICOLOGY

The following LD_{50} values are reported:

mouse	intraperitoneal	933 mg/kg	(18)
mouse	peroral	3,950 mg/kg	(18)
rat	peroral	4,000 mg/kg	(26, 28)
rabbit	skin	13,500 mg/kg	(18)

Rats given about 10 mg/kg diacetone alcohol in drinking water daily for 30 days developed no observable pathological effects (26).

Acute toxicity tests have also been made with aquatic organisms, using dilutions of diacetone alcohol. A 96-hour LC_{50} of 420 mg/liter was obtained for both freshwater fish (Lepomis macrochirus) and saltwater fish (Menidia beryllina) (6). Substances with a value lower than 500 mg/l are classified "hazardous" by the EPA in the US. In another study (2), an LC_{50} of >5,000 mg/l was given for goldfish (Carassius auratus). A cell multiplication inhibition test gave a threshold toxicity value of 825 mg/l for bacteria (Pseudomonas putida), 3,000 mg/l for green algae (Scenedesmus quadricauda), and 1,400 mg/l for protozoa (Enfosiphon sulcatum) (3).

5. EFFECTS ON ORGANS

5.1. Effects on skin and mucous membranes

Twelve volunteers were exposed to diacetone alcohol for 15 minutes; most of them complained about irritation of eyes, nose and throat at a concentration of 475 mg/m^3 (100 ppm) (25). Most of them considered both the smell and the taste sensation unpleasant at this concentration, but judged that they could nevertheless tolerate working in it for 8 hours. In a summary published later (22), a concentration of 240 mg/m^3 was reported as irritating, but the source of the information was not given.

Inhalation of 10,000 mg/m^3 (2,100 ppm) diacetone alcohol causes irritation to the mucous membranes of mice, rabbits and cats (19).

5.2. Effects on the respiratory organs

There are no data on humans.

For effects on respiration frequency in experimental animals, refer to section 5.8., Effects on the central nervous system.

5.3. Effects on the liver

There are no data on humans.

Twenty rats were given about 2,000 mg/kg (2 cc/kg) diacetone alcohol by gavage. They were then killed in pairs at intervals ranging from 1 hour to 60 days after administration. After 6 hours increased lymphocyte activity and vacuolization were observed in the liver. The maximum effect was

seen after 24 hours, along with extensive "cloudy swelling" of the liver cells. After 7 days the cells began to regain their normal shape, and after 35 days there was no visible sign of damage (14).

5.4. Effects on the kidneys

There is a case report of a man who became ill about 40 days after painting a floor with 30 liters of paint containing diacetone alcohol and ethanol as solvents. The paint job had taken 3 days. (The man was not a professional painter.) A kidney biopsy showed a subacute glomerulonephritis. The man gradually recovered over the following year (24).

Four groups of 12 male and 12 female rats were exposed by inhalation to diacetone alcohol in concentrations of 0, 232, 1,035 and 4,494 mg/m^3. Exposures lasted 6 hours/day, 5 days/week for 6 weeks. Rats in the highest dose group had eosinophilic drops in the proximal tubuli of their kidneys. The only other effect noted was a slight increase in weight of liver and kidneys. The study is incompletely reported (21).

Kidney effects were noted in rats that received 40 mg/kg diacetone alcohol in drinking water daily for 30 days (15).

Kidney damage was seen in rabbits that inhaled 10,000 mg/m^3 (2,100 ppm) (17). An oral dose of about 2,000 mg (2 cc) given to rabbits 12 times a day caused kidney damage. The damage was indicated by the presence of albumin and sugar in the urine (19). (Three-quarters of the animals died after this treatment.)

5.5. Effects on the digestive tract

No information is available.

5.6 . Effects on the heart and blood vessels

There is no information regarding man.

Rabbits that received about 1,000 mg/kg (1 cc/kg) diacetone alcohol intravenously showed a drop in blood pressure. This was considered a result of reduced heart function rather than vasodilation, and was not affected by dissection of the vagus nerve (27).

5.7. Effects on blood and blood-forming organs

There is no information regarding man.

In rats given about 2,000 mg/kg (2 cc/kg) diacetone alcohol by gavage, effects on red blood cells were indicated by reduction of hemoglobin content to about 75% of normal. The values had returned to normal after 6 days (14).

5.8. Effects on the central nervous system

There is no information regarding man.

Epileptic spasms were induced in rats by giving electric impulses to the brain. The reported threshold for development of spasms was 8 milliamperes. This threshold was increased by 55% if the animal had previously received 1,200 mg/kg diacetone alcohol, and diacetone alcohol was therefore considered effective against epilepsy (8). Diacetone alcohol also had an anti-convulsive effect when the spasms were induced by thujone (4-methyl-1-(1-methylethyl)bicyclo-[3.1.0]-hexane-3-one) (13).

Diacetone alcohol given intravenously to rabbits caused depressed respiration at concentrations of about 400 mg/kg

(0.4 cc/kg) or more. The animals became unconscious at concentrations exceeding about 1,000 mg/kg, and died immediately at about 3,000 mg/kg (3 cc/kg) (27). When the substance was given by intramuscular injection or gavage, higher concentrations were needed to cause loss of consciousness and death. The cause of death was reported to be respiratory arrest.

Repeated subcutaneous injections of about 80 mg/kg (about 0.08 cc/kg) had a narcotic effect on rats (19). Diacetone alcohol (the effective component in the grass Stipa vaseyei) has reduced motoric activity in rats and mice. The dose (method of administration not reported) was about 400 mg/kg (0.1 to 0.2 ml/250 g) for rats, and about 4,000 mg/kg (0.1 to 0.2 ml/25g) for mice (9).

5.9. Effects on the peripheral nervous system

No information is available.

5.10. Effects on other organs

A factory producing rubber raincoats employed 75 people, 19 of whom complained of eye irritation within two months after the introduction of a solvent mixture consisting of butanol, diacetone alcohol and denatured ethanol. Characteristic changes in the cornea, in the form of a large number of clear vacuoles – primarily in the central part – were noted in 17 of these 19. The authors (5) consider that it was either the butanol or the mixture as such that caused the damage. Experimental attempts to cause the same kind of damage in mice, guinea pigs, rabbits and dogs have given negative results.

6. IMMUNOTOXICITY, ALLERGY

No information is available.

7. MUTAGENICITY, GENOTOXICITY

In a mutagenicity study with an E.coli strain, diacetone alcohol reduced the number of mutants caused by the mutagenic substance [6]-gingerol (16). Diacetone alcohol was considered to have a weak clastogenic effect in experiments with rat liver cells in vitro (4). Mutagenicity tests with bacteria and yeasts, however, have given negative results.

8. CARCINOGENICITY

No information is available.

9. REPRODUCTION TOXICOLOGY

No information is available.

10. EXPOSURE-EFFECT AND EXPOSURE-RESPONSE RELATIONSHIPS

There are in general no data from which to estimate a dose-effect or dose-response relationship. This is particularly the case for long-term exposure and exposure via inhalation. Data from single exposures are presented in Table 1.

Table 1. Dose-effect relationships for single doses of diacetone alcohol.

Dose mg/kg	Species	Administration	Effect (Reference)
5000	rabbit	p.o.	Loss of consciousness within 6 min. Death within 60 h. (27)
4000	rabbit	i.m.	Loss of consciousness within 10 min. Death within 48 h. (27)
4000	rabbit	p.o.	Loss of consciousness after 46 min. Normal after 48 h. (27)
4000	rat	p.o.	LD_{50} (26)
3950	mouse	p.o.	LD_{50} (18)
3000	rabbit	i.v.	Immediate death (27)
3000	rabbit	i.m.	Loss of consciousness after 37 min. Death after 60 h. (27)
2400	rabbit	p.o.	Respiration reduced to 1/3. Normal within 24 h. (27)
2000	rat	p.o.	Reversible changes in liver and hemoglobin content. (14)
2000	rabbit	i.v.	Immediate loss of consciousness. Normal after 24 h. (27)
2000	rabbit	i.m.	Respiration rate halved. Normal after 48 h. (27)
1150	rabbit	i.v.	Immediate loss of consciousness. Normal after 7 h. (27)
1000	rabbit	i.v.	Immediate loss of consciousness. Drop in blood pressure. Normal after 30 min. (27)
933	mouse	i.p.	LD_{50} (18)
800	rabbit	i.v.	Slight sedation. Normal after 15 min. (27)
400	rabbit	i.v.	Reduced respiratory rate. Normal after 11 min. (27)

p.o. = peroral i.m. = intramuscular
i.p. = intraperitoneal i.v. = intravenous

11. RESEARCH NEEDS

There are almost no studies of the effects of either long-term or occupational exposure to diacetone alcohol. Toxicokinetic studies and studies of the biotransformation of diacetone alcohol are needed in order to judge the toxic potential of the substance. Epidemiological studies and mutagenicity studies are also desirable. It might be difficult, however, to find a cohort that has been exposed only to diacetone alcohol.

12. DISCUSSION AND EVALUATION

Available information on the toxic effects of diacetone alcohol is scarce. The information that exists applies mostly to acute toxicity and to exposure pathways other than inhalation. The critical effect for determining an occupational exposure limit, based on available data, is irritation of eyes and mucous membranes. This is reported to occur at concentrations of 240 mg/m^3 or more.

The acute toxicity of diacetone alcohol has been estimated to be almost twice that of acetone. With long-term exposures, the two substances may well have similar effects. Since diacetone alcohol is a biotransformation product of methyl isobutyl ketone, it can also be suspected to have toxic effects like those demonstrated for methyl isobutyl ketone.

13. SUMMARY

P. Lundberg. Diacetone Alcohol. Nordic Expert Group for Documentation of Occupational Exposure Limits.

A survey of the literature is presented as scientific basis for establishment of occupational exposure limits.

Data on the toxic effects of diacetone alcohol are scarce, and refer primarily to acute toxicity. The substance has greater acute toxicity than acetone. The critical effect is irritation of eyes and mucous membranes, which is reported at air concentrations of 240 mg/m^3 or higher.

Higher single doses of diacetone alcohol have effects on liver and kidneys, and also result in lowered blood pressure, reduced respiration rate and narcosis.

It is possible that long-term exposure has an effect on the nervous system.

Originally written in Swedish, 28 references.

Key words: Diacetone alcohol, Exposure limit, Irritation, Narcosis.

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APPENDIX. Occupational exposure limits for airborne diacetone alcohol.

Country	mg/m^3	ppm	year	note	ref
FRG	240	50	1988		6
Denmark	240	50	1988		3
Finland	240	50	1987	8 h	10
	360	75		15 min	
France	240	50	1988		11
Iceland	240	50	1978		8
Netherlands	240	50	1989		7
Norway	240	50	1984		1
Soviet Union	100		1976		11
Sweden	-	-	1988		5
UK	240	50	1988		4
	360	75		STEL	
USA (ACGIH)	240	50	1988-89		9
(OSHA)	240	50	1989		2

STEL = short-term exposure limit

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HYDROQUINONE

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Appendix 1. List of recommended or allowed maximum concentrations of hydroquinone in air.

1. PHYSICAL AND CHEMICAL DATA

CAS No.: 123-31-9

Synonyms: 1,4-benzenediol; 1,4-dihydroxybenzene; 4-hydroxyphenol; alpha-hydroquinone; benzohydroquinone; dihydroxybenzene

Formula: $C_6H_4(OH)_2$

Structure:

Molecular weight: 110.11

Melting point: 170 – 171°C

Boiling point: 285 – 287°C (97 kPa)

Vapor pressure: 2.4×10^{-3} Pa (20°C)

Odor threshold: 0.4 mg/m^3 (0.09 ppm) (71)

Conversion factors: 1 ppm = 4.55 mg/m^3; 1 mg/m^3 = 0.22 ppm

Hydroquinone at room temperature consists of hexagonal crystals, colorless to white in color. Hydroquinone is soluble in water (7.3 g/100 g water) and also in alcohol and ether, but is only sparingly soluble in benzene and other nonpolar solvents. In water and in the presence of oxygen, hydroquinone undergoes a pH-dependent auto-oxidation: increased oxidation at increased pH (80). This auto-oxidation gives aqueous solutions of hydroquinone a brown color.

2. OCCURRENCE AND USE

2.1. Uses

Hydroquinone is used as an anti-oxidant, a reducing agent and a stabilizer in e.g. the rubber industry. It is also used in the film industry as a component in developing fluid. Hydroquinone is used to slow polymerization in methyl acrylate cements (e.g. bone cement). Hydroquinone is also used in

cosmetics and pharmaceutical preparations as a skin whitener, and as an ingredient in hair dyes.

A criteria document discussing hydroquinone has been published by NIOSH (68).

2.2. Methods for analysis of air concentrations

Hydroquinone aerosols in air are sampled with a cellulose membrane filter and an adsorption tube containing XAD-2, and analyzed by high-pressure liquid chromatography (69). A flow speed of 1.5 liters/minute and a filter 37 mm in diameter (pore size 0.8 µm) are recommended. The sample is then extracted with 1% acetic acid and analyzed by high-pressure liquid chromatography with UV dector at 290 nm.

3. KINETICS

3.1. Uptake

Hydroquinone can be absorbed via the digestive tract and the skin.

Skin and mucous membranes: Hydroquinone applied to the foreheads of experimental subjects was rapidly absorbed through the skin. A 100 µl dose of 2% ^{14}C-labeled hydroquinone dissolved in 71% ethanol was applied to a surface of 16 cm^2. The average absorption of hydroquinone was estimated from 5-day urine data to be 57% (11).

Hydroquinone can also be absorbed through hairless rat skin in vivo and through both human and rat skin in vitro. A solution of 4% hydroquinone in oil was applied to skin in vitro (40 mg/cm^2). After 24 hours 1.68% of the dose had been absorbed by rat skin and 0.28% by human skin (59).

Respiratory organs: Occupational exposure to hydroquinone can occur by inhalation. There are no quantitative data on uptake via the respiratory organs.

Digestive tract: Hydroquinone is absorbed by the digestive tract. It was shown, for example, that rats given oral doses of 200 mg/kg ^{14}C-labeled hydroquinone excreted 91.9% of the radioactivity in urine within 2 to 4 days (26).

3.2. Distribution

In rats given oral doses of ^{14}C-labeled hydroquinone (200 mg/kg) the activity was distributed to all tissues, with higher concentrations in liver and kidneys (26).

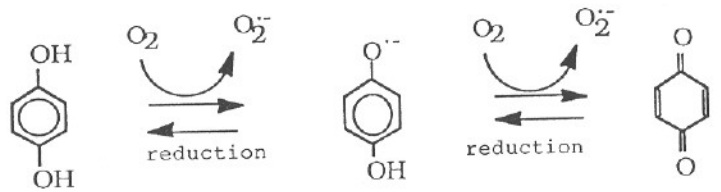
Rats given intravenous injections of ^{14}C-labeled hydroquinone had radioactivity in bone marrow, but not in liver or thymus, 24 hours later. The activity that was covalent-bound increased with time in all examined organs, with greatest increase in bone marrow (43).

Whole-body autoradiography of rats after intravenous injection of ^{14}C-labeled hydroquinone (1.3 and 14 mg/kg) showed a dose-related accumulation measured as radioactivity in bone marrow and lymphatic tissues (42).

3.3. Biotransformation

At physiological pH (7.4), hydroquinone spontaneously oxidizes to semiquinone and then to benzoquinone. Both substances can be enzymatically reduced back to hydroquinone, thus forming a redox cycling system (Fig. 1). Superoxide anions and hydrogen peroxide are formed during this process (43, 87). Hydroquinone is detoxified in the liver and excreted as various conjugates, primarily in urine (95). Metabolites recovered in urine (see 3.4) indicate that hydroquinone is probably metabolized by several alternative pathways.

Since hydroquinone is a metabolite of benzene, portions of its biotransformation are described in the literature on benzene. The Swedish criteria group has recently published a criteria document on benzene (44).



hydroquinone benzosemiquinone benzoquinone

Figure 1. The redox cycle of hydroquinone.

3.4. Excretion

Respiratory organs: Rats given 200 mg/kg ^{14}C-labeled hydroquinone per os excreted about 0.4% of the dose in exhaled air (26).

Kidneys: When 100 µl ^{14}C-labeled hydroquinone was applied to a 16-cm^2 patch on the foreheads of volunteers, 57% of the dose was excreted in urine during the next five days with highest elimination during the first 12 hours (11).

Twenty-four hours after a single dose of hydroquinone (3 mg/kg), both sulfate-bound hydroquinone and hydroquinone bound to glucuronate were found in urine; no unmetabolized hydroquinone was found, however (68).

Rats given oral doses of 200 mg/kg ^{14}C-labeled hydroquinone excreted 91.9% of the radioactivity in urine within 2 to 4 days: 1.1 to 8.6% of the dose was excreted as hydroquinone, 25 to 42% as monosulfate, and 56 to 66% as monoglucuronide (26).

Rabbits were given doses of 100 and 200 mg/kg hydroquinone; within the next 24 hours 30% was excreted as sulfates, 43% bound in monoglucuronides, and 0.0065% as free hydroquinone (37). A dose of 0.09 g/kg hydroquinone increased the rabbits' excretion of organic sulfates but had no effect on excretion of glucuronic acid conjugate (25).

Cats given 20 mg/kg hydroquinone intravenously excreted in urine 10% of the dose unmetabolized, 87% as conjugated sulfate and about 3% bound to glucuronide (60).

Digestive tract: Rats given oral doses of 200 mg/kg ^{14}C-labeled hydroquinone excreted 3.8% of radioactivity in feces (26).

4. GENERAL TOXICOLOGY

4.1. General toxicology

When hydroquinone (12 g) was ingested with intent to commit suicide, the acute symptoms (a general feeling of illness) disappeared within 24 hours. Blood analysis showed hypoglycemia and hypercholesterolemia. After 30 days only the cholesterol content of the blood was somewhat elevated (83).

The acute toxicity of hydroquinone has been studied in LD_{50} tests. With peroral administration, the LD_{50} was 780 mg/kg for rats (4), 200 mg/kg for dogs (104, 56), 80 mg/kg for cats (24) and 200 mg/kg for rabbits (24).

4.2. Toxicological mechanisms, in vitro studies

As mentioned earlier, hydroquinone at physiological pH undergoes redox cycling and forms free radicals, with simultaneous formation of conjugates (43, 87). The oxygen radicals formed during the redox cycle can lead to DNA damage, lipid peroxidation and enzyme inactivation (89).

Both the conjugation reactions and the formation of free radicals seem to be important to the cytotoxicity of hydroquinone. This is discussed in several articles (43, 87, 86, 91).

In a study using rat liver microsomes, it was shown that benzene forms both p-benzo-semiquinone and p-benzoquinone via hydroquinone, and these are bound to macromolecules (98).

Hydroquinone has also been shown to form covalent bonds to microsomal proteins in vitro (99).

Hydroquinone or its metabolites ($1 \times 10^{-5} - 1.5 \times 10^{-4}$M) have been shown to form covalent bonds with structural proteins in cells in vitro, and are assumed via this mechanism to disturb microtubuli functions and lead to abnormalities in the cytoskeleton and disturbances in cell division (48, 49).

Hydroquinone (3 to 100µM) has been shown to inhibit the liberation of hydrogen peroxide from lung macrophages in vitro. This is considered to decrease their ability to attack microorganisms (57).

4.3. Factors that affect toxicity

The toxicity of hydroquinone in LD_{50} tests was doubled or tripled if animals had first fasted for 18 hours (13).

Acute toxicity in vivo was reduced by pre-treatment with an inducer of the microsomal monooxygenase system (3-trifluoromethyl-alpha-ethylbenzhydrol). The authors believe this effect is due to stimulated biotransformation (95).

5. ORGAN EFFECTS

5.1. Skin and mucous membranes

There are case descriptions of leucodermia or vitiligo (skin depigmentation) caused by hydroquinone in developing fluid. A 54-year-old man who serviced equipment in photo booths developed vitiligo on hands and wrists. He was exposed to a 7% hydroquinone solution when he cleaned the machines and changed the developing fluid. Contaminated rubber gloves are believed to have functioned as an occlusive cover (52). Another reported case of depigmentation concerns a 30-year-old man who dipped his hand regularly into film developing fluid that contained 0.06% hydroquinone. After 8 months he developed vitiligo on the hand (33). A further case of vitiligo associated with handling photographic chemicals containing hydroquinone has been described (27).

Skin whitening preparations containing hydroquinone have caused reddening and stinging of the skin (7, 92, 54). In these cases the concentration of hydroquinone was over 3%. Damage from long-term use of skin whiteners containing over 5% hydroquinone is worse if the skin has simultaneously been exposed to sunlight (30). There are no reports of irritation by skin whiteners containing less than 2% hydroquinone (6, 92).

The U.S. Food and Drug Administration (FDA) considers a 1.5 to 2% concentration of hydroquinone to be safe and effective for skin bleaching (5).

In one study 33 workers exposed to hydroquinone and its derivatives were compared with 55 matched controls. Both groups worked in the same factory, which produced methionine and vitamins. The exposed workers showed a statistically significant higher incidence of eczema (16, 17).

In vitro studies showed that pigmented skin cells from mice were more sensitive to damage from hydroquinone than unpigmented skin cells (46).

In histochemical studies, 2 to 5% hydroquinone was observed to reduce the formation of melanosomes, change the melanosome structure and cause degradation of melanosomes. This was observed for both skin application and subcutaneous injection (51).

The effects of hydroquinone on pigmented and unpigmented cell lines have been compared in vitro. The study showed that hydroquinone caused a 30-fold reduction in DNA synthesis (thymine incorporation) and an 85-fold reduction in RNA synthesis (uridine incorporation) in pigmented cells. The depigmenting effect of hydroquinone is probably due to its selective effect on melanocyte metabolism rather than its effect on melanin synthesis (77).

5.2. Effects on the eyes

In several studies, persons who worked with production of hydroquinone have been observed to have reversible dark brown pigmentations in the cornea and conjunctiva (2, 3, 63). The authors consider that vapors from the hydroquinone oxidation product benzoquinone were most probably the main cause of the eye damage, though a direct effect of hydroquinone was also possible. The brown color is probably the end product of the oxidation of hydroquinone to quinone and the polymerization of the quinone (94).

A positive correlation between degree of eye damage and length of exposure was reported. Heavy pigmentation of the cornea and conjunctiva required at least 5 years of exposure to hydroquinone vapors (94).

A 40-year-old surgical nurse repeatedly developed corneal ulcers after mixing bone cement. The cause was believed to be the combination of vapors from the methyl methacrylate and hydroquinone in the cement (70).

A 2% solution of hydroquinone caused mild conjunctivitis in 3 of 6 experimental animals on day 1 of exposure. The inflammation had disappeared by the following day (19).

5.3. Effects on the respiratory organs

In one study, 33 workers exposed to hydroquinone and its derivatives were compared to 55 matched controls. Both groups worked in the same factory. The incidence of coughing was higher and lung function values were lower in the exposed group. The exposure to hydroquinone also increased the serum immunoglobulin fraction G. A positive correlation between immunoglobulin E and respiratory volume (FEV_1, PEF) was also shown: the results were statistically significant. The study reports no exposure data (16, 17).

5.4. Effects on the liver

There are no reports of liver effects after occupational exposure to hydroquinone.

Rats fed hydroquinone (5 mg/kg/day) for 10 days showed inhibited catalase activity in the liver (103).

5.5. Effects on the kidneys

No studies mentioning effects on the kidneys were found.

5.6. Blood and blood-forming organs

Workers exposed to hydroquinone during its manufacture were compared to unexposed workers in the same factory. The blood values of the exposed workers (hemoglobin, hematocrit, erythrocyte and leucocyte counts) were no different from those of the unexposed workers (94).

Subcutaneous injections of hydroquinone (20 to 100 mg/kg) given to mice daily for six days induced polychromatic erythrocytes in all dose groups. The number of micronuclei increased with the dose to a maximal value at 6 x 80 mg/kg. At low doses there was also an increase of cell density in bone marrow, but this dropped when doses exceeded 6 x 50 mg/kg. The number of granulopoietic stem cells varied with cell density (97).

In a study of hydroquinone's effect on the function of immature B lymphocytes, four C57BL6 mice were given 100 mg/kg hydroquinone (i.p. or i.v.) twice a day for 3 days. Cell density in bone marrow was reduced. The frequency of mature B lymphyocytes formed from spleen and bone marrow cells in vitro was also reduced (102).

Hydroquinone in concentrations of 10^{-5} to 10^{-4}M inhibits the ability of stromal cells to promote formation of granulocyte and monocyte colonies grown in vitro (36).

B lymphocytes from the bone marrow of mice were exposed to hydroquinone (10^{-7} to 10^{-5} M) in vitro. Brief exposure (1 hour) inhibited the maturation of B cells after 48 hours in culture. Both B-cell reduced bone marrow cells and unreduced cells showed the same effect (53).

Hydroquinone ($1 - 2 \times 10^{-5}$M) has been shown to have a dose-dependent inhibiting effect on RNA synthesis in mouse spleen

lymphocytes in vitro. These concentrations had no effect on viability (78).

Hydroquinone (0.5 to 3 mM for 2.5 hours) caused a reduction of glutathione but only a weak increase of methemoglobin in human erythrocytes (61).

It has also been reported that hydroquinone can lead to formation of Heinz bodies in experimental animals (23).

Treatment with hydroquinone (5 mg/kg/day for 10 days) inhibited catalase activity in blood and spleen of rats (103).

5.7. Effects on the peripheral and central nervous system

No information was found in the literature.

6. ALLERGIES, IMMUNOTOXICITY

Of 536 patients examined at a skin clinic in Brazil, about 9% showed a positive reaction in a contact allergy test using a 5% hydroquinone solution (64). From Nigeria, 1.5% of 223 women tested were reported to have had a positive reaction to a patch test using hydroquinone (72).

In one study 33 exposed workers were compared with 55 matched controls. Both groups came from the same factory and worked in the production of methionine and vitamins. The exposure was to hydroquinone and its derivatives. The incidences of eczema and coughing were higher and lung function values were lower for the exposed group. Exposure to hydroquinone also increased serum inmmunoglobulin fractions G and E. The results were statistically significant. A positive correlation between immunoglobulin E and lung function values (FEV_1, FEF) was also shown (16, 17).

Hydroquinone proved to be weakly sensitizing to guinea pigs when given in intracutaneous injections (0.1 to 0.001%; injection volume 0.1 ml) (81). Several studies have been made using the guinea pig maximization (GPM) test: about 50% of the animals were sensitized by hydroquinone (40, 100).

Hydroquinone given intravenously or intraperitoneally to mice has been shown to have an immunosuppressive effect (102). Hydroquinone treatment in vivo has also inhibited both T and B lymphocyte response to mitogen stimulation in vitro. Hydroquinone also affects cell density in bone marrow and spleen in vivo (50).

Hydroquinone (50µM) has been shown to inhibit the induction of interferon gamma in spleen cells isolated from mice (15).

7. MUTAGENICITY, GENOTOXICITY

Hydroquinone was mutagenic in Salmonella strain TA 1535A without metabolic activation (22), but was not mutagenic, either with or without metabolic activation, in Salmonella strains TA 1537, TA 1538, TA 98 or TA 100 (29, 32, 39, 82, 105).

Hydroquinone was negative in a mutation test with Micrococcus pyogenes strain FDA 209 (21).

Hydroquinone was mutagenic in an Escherichia coli DNA polymerase test (DNA repair test) (8). Hydroquinone was also mutagenic to Saccharomyces cerevisiae, and caused mitotic recombination (22).

In a DNA synthesis test with HeLa cells, 1.0×10^{-4}M hydroquinone without metabolic activation, and 3×10^{-5}M hydroquinone with metabolic activation, gave a positive result (73).

Hydroquinone given to mice per os (100 mg/kg) had no effect on DNA synthesis in testicles (88).

Abnormal ("three-group") metaphases were found in bone marrow and intestinal cells of hamsters after intraperitoneal injections of hydroquinone (0.15 to 0.20 mg/g) (75), and in intestinal cells of mice after subcutaneous or intraperitoneal injections (0.15 to 0.175 mg/g) (74).

Abnormal metaphases were also observed in vitro in chicken fibroblasts exposed to hydroquinone (10^{-7} to 10^{-6} mM); and in liver, bone marrow and corneal cells of rats after intraperitoneal injection of hydroquinone (0.15 to 0.20 mg/g). Abnormal metaphases were also noted in cornea after treatment with one drop of 5% hydroquinone (85).

No recessive lethal mutations were induced in F2 or F3 generations of Drosophila melanogaster by 50 or 100 mM hydroquinone (39). There has also been a study of dominant lethal mutations in rats exposed to atoxic doses (doses not reported); none could be shown (55).

Hydroquinone (1.6×10^{-6} to 2.0×10^{-4}M) increased the frequency of sister chromatid exchange in human lymphocytes in vitro (65). In another study, 1 mM of hydroquinone, both with and without metabolic activation, induced SCE in human lymphocytes in vitro (66).

In micronucleus tests on mice, hydroquinone (200 mg/kg) was weakly clastogenic (35, 39). An oral dose of 80 mg/kg also increased the number of micronuclei in bone marrow 18, 24 and 48 hours after administration. Intraperitoneal administration yielded an increase only after 18 hours (20).

The ability of hydroquinone to induce mitotic division (crossing over and errors in chromosome division) has been tested in Aspergillus nidulans. Exposure to 1 – 3 mM hydro-

quinone gave a tenfold increase in the frequency of mitotic division (41).

An in vitro study of hydroquinone's ability to cause DNA damage showed that 1 mM induced both single and double string breaks in DNA (58).

The effect of hydroquinone on DNA synthesis was measured in a mouse lymphoma cell line ([^{3}H] leucine incorporation). Thirty minutes of exposure to hydroquinone (1×10^{-5}) caused a 50% reduction of DNA synthesis (76).

8. CARCINOGENICITY

In a cohort of 478 workers in the photographic development industry there were 2 cases of brain tumor, compared to an expected 0.4. The difference was not statistically significant. The workers were also exposed to a large number of other substances. Measured hydroquinone concentrations were below 0.01 mg/m^3 (34).

In a study of induction of proliferative damage to the mucous membranes of the stomach, hamsters were given 0.5% hydroquinone in diet. Twenty weeks of exposure caused no changes (45).

The initiating ability of hydroquinone has also been tested. A 6.7% solution of hydroquinone in acetone (0.3 ml) was applied to the skin of mice for 3 weeks (total dose 20 mg). Croton oil in acetone was applied as a promotor (18 applications per week: 0.3 ml 0.5% solution). One mouse of 24 developed a tumor (84).

The tumor-promotive effect of hydroquinone was studied in a liver foci test. Rats initiated with diethyl nitrosamine (30 mg/kg) were given oral doses of 100 and 200 mg/kg hydroquinone daily for seven weeks. The lower dose group showed a significant increase of liver foci (93).

Mice (BALB/C) transplanted with malignant melanomas were given subcutaneous doses of 16 and 80 mg/kg daily for 9 days. The incidence of successful transplants was 91.7% in control animals, 55.6% in the lower dose group and 23.7% in the group that received 80 mg/kg. Hydroquinone also increased the survival of the animals (14).

The carcinogenicity of hydroquinone has been tested with an implantation method. A 10-mg pellet containing 20% hydroquinone was implanted in the bladders of mice. After 25 weeks there was a 12% incidence of tumors (carcinomas and papillomas) in 77 control animals and a 32% incidence (carcinomas) in 19 treated animals. The result was statistically significant (10).

The cocarcinogenic effect of hydroquinone has been tested on skin. Benzo(a)pyrene (5µg/appl) and hydroquinone (5 mg in acetone) were applied to 50 mice three times a week for 368 days. Hydroquinone was shown to have a weak inhibiting effect on the carcinogenicity of benzo(a)pyrene (101).

The International Agency for Research on Cancer (IARC) has stated that available data is not sufficient for assessment of the carcinogenicity of hydroquinone (47).

At the National Toxicology Program in the U.S., the carcinogenicity of hydroquinone is currently being tested in a two-year study (oral administration) (67). The preliminary results indicate an increased number of tubular adenomas in kidneys of female rats and an increase of leukemias in male rats. Female mice have shown an increase of hepatocellular neoplasias.

9. REPRODUCTION TOXICOLOGY

Female rats were exposed to 0.3% hydroquinone in diet for 10 days before fertilization. Fertility index, litter size, and mortality and viability indexes were recorded. No changes could be related to the hydroquinone exposure (1).

Hydroquinone (50 mg/kg/day for 14 days) lengthened the diestrus period in the reproductive cycle of female rats (79).

Subcutaneous injections of hydroquinone (100 mg/kg/day for 51 days) caused weight reduction in testicles, epididymis, seminal vesicles and adrenal glands of male rats. Histological studies indicated a disturbance in sperm production and reduced DNA content in sperm (90).

In another study, rats were exposed to a total dose of 0.5 g hydroquinone in food during pregnancy. The rats were sacrificed 22 days after mating. Of 126 controls, 40.8% had one or more resorptions and 10.6% of all implantations terminated in resorption; 100% of the treated rats showed resorptions, and in this group 26.8% of all implantations ended in resorption (96).

Hydroquinone (54 to 810 mg/kg) was applied to the skins of 20 pregnant rats from day 6 to day 19 of pregnancy; no difference between treated animals and controls was observed (19).

Hair coloring containing 0.2% hydroquinone has been tested for teratogenic effects: results were negative (12).

Hydroquinone (80 mg/kg) given orally to pregnant mice induced micronuclei in bone marrow cells and also in fetal liver cells. The transplacental effect on fetal liver cells was observed within 9 hours of hydroquinone administration (38).

10. CORRELATION BETWEEN EXPOSURE, EFFECT AND RESPONSE

The effects of hydroquinone on humans and in animal experiments are summarized in tables 1 and 2.

Table 1. Effects of hydroquinone on man.

Dose	Effects (reference)
12 g per os	General feeling of illness; hypoglycemia and hypercholesterolemia (62, 83).
7% solution dermal	Vitiligo on hands and wrists (52).
>3% solution dermal	Reddening and stinging of skin (54, 92, 7).
0.06% solution dermal	Vitiligo on hand (33).

10.1 Effects of short-term exposure

Oral intake of hydroquinone (12 g) in an attempt to commit suicide produced acute symptoms in the form of cramps, breathing problems and general malaise. Blood analysis showed hypoglycemia and hypercholesterolemia. The dose was not lethal (62, 83).

Hydroquinone given subcutaneously to mice induced polychromatic erythrocytes and micronuclei in dose groups receiving over 6 x 20 mg/kg. There was also an effect on cell density in bone marrow (97). A dose of 200 mg/kg was weakly clastogenic in micronuclei tests with mice (35, 39).

Hydroquinone was shown to have an immunosuppressive effect when given intraperitoneally or intravenously to mice (100 mg/kg, twice a day for 3 days) (102). The same treatments in

vivo also inhibited both T and B lymphocyte response to mitogen stimulation in vitro. It also affected cell density in bone marrow and spleen in vivo (50).

Table 2. Effects of hydroquinone on experimental animals

Dose	Effects (reference)
780 mg/kg per os	LD_{50} for rats (4).
200 mg/kg per os	LD_{50} for dogs and rabbits (104, 56, 24).
80 mg/kg per os	LD_{50} for cats (24).
100 mg/kg per os 2x/day for 3 days	Immunosuppressive effect; effects on bone marrow and spleen cell density in mice (50).
100 mg/kg/day subcutaneous 51 days	Weight reduction in testicles, epididymis, seminal vesicles and adrenal glands of male rats (90).
100 mg/kg/day per os	Increased number of cell foci in rat livers (93).
50 mg/kg/day per os 14 days	Lengthened diestrus period in reproductive cycle of female rats (79).
20 mg/kg/day per os 6 days	Induction of polychromatic erythrocytes and micronuclei in mice (97).
80 mg/kg per os	Induction of micronuclei in bone marrow cells of pregnant mice and in livers of fetuses (transplacental) (38).
10-mg pellet 20% hydroquinone	Implantation in bladders of mice increased tumor incidence (10).
0.1 to 0.001% solution intracutaneous	0.1 ml injected into the skin of guinea pigs for 10 days had a sensitizing effect (81).

Hydroquinone (50 mg/kg/day, 14 days) lengthened the diestrus period in the reproductive cycle of female rats (79).

In another study, rats were exposed during pregnancy to 0.5 g hydroquinone (total dose) in food. The rats were sacrificed 22 days after mating. Of 126 controls, 40.8% had one or more resorptions and 10.6% of all implantations terminated in resorption; 100% of treated rats had resorptions and 26.8% of all implantations in this group terminated in resorption (96).

Oral doses of hydroquinone given to pregnant mice (80 mg/kg) have been shown to induce micronuclei in bone marrow cells and also in the liver cells of the fetuses (38).

Intracutaneous injections of hydroquinone given to guinea pigs (0.1 to 0.001%; injection volume 0.1 ml daily for 10 days) had a weak sensitizing effect (81).

Experimental animals developed mild reversible conjunctivitis after exposure to 2% hydroquinone (19).

10.2. Effects of long-term exposure

In one study 33 exposed workers were compared with 55 matched controls. Both groups worked in the same factory, producing methionine and vitamins. Exposure was to hydroquinone and its derivatives. The incidences of eczema and coughs were higher and lung function values lower in exposed workers. Exposure to hydroquinone also increased the serum immunoglobulin fractions G and E. These results were statistically significant. A positive correlation between immunoglobulin E and lung function values (FEV_1, FEF) was also shown (16, 17).

There are case reports of leucodermia or vitiligo (skin depigmentation) caused by occupational exposure to hydroquinone in photographic developing fluid. A 54-year-old man

developed vitiligo on hands and wrists after servicing equipment in photo booths. He was exposed to a 7% hydroquinone solution when he cleaned the machines and changed the developing fluid. Contaminated gloves were thought to have functioned as an occlusive dressing (52). In another case report, a 30-year-old man had dipped his hand regularly into a developing solution containing 0.06% hydroquinone. After 8 months he developed vitiligo on the hand (33). There is also another case report describing vitiligo after handling photographic chemicals containing hydroquinone (27).

Human volunteers (19 men and women) were exposed to hydroquinone for several months. Two men ate 500 mg hydroquinone daily for 5 months, and 17 people (men and women) ate 300 mg/day for 3 to 5 months. Blood and urine analyses showed nothing abnormal (13).

Skin whiteners containing more than 3% hydroquinone have caused reddening and stinging, but no irritation has been reported for concentrations below 2% (7, 92, 54).

Subcutaneous injections of hydroquinone (100 mg/kg/day) given for 51 days caused weight reduction in testicles, epididymis, seminal vesicles and adrenal glands of male rats. Histological studies indicated disturbances in sperm production and reduced DNA content in sperm (90).

In a carcinogenicity test, a 10-mg cholesterol pellet containing 20% hydroquinone was implanted in the bladders of mice. After 25 weeks, 32% of 19 treated animals and 12% of 77 controls had developed tumors (10).

11. RESEARCH NEEDS

Toxicokinetic studies for inhalation exposure are lacking.

Effects on embryos and effects on reproduction have been inadequately studied. Data on genotoxic and carcinogenic effects and immunotoxicity are so scant that a risk estimate is impossible.

12. DISCUSSION AND EVALUATION

Occupational exposure to hydroquinone occurs primarily via respiratory organs and skin. There are data indicating that hydroquinone is rapidly absorbed by the skin.

Repeated exposure to low hydroquinone concentrations (below the irritation level) has caused vitiligo.

Hydroquinone has been shown to cause eye damage, and concentrations over 3% can irritate the skin.

There are some data indicating that hydroquinone has toxic effects on reproduction, but in both these studies doses were high. Hydroquinone has also been shown to cross the placental barrier and induce micronuclei in fetuses.

Effects on blood and blood-forming organs have been observed both in vivo and in vitro. Hydroquinone also has an immunosuppressive effect both in vivo and in vitro. In one epidemiological study, exposure to hydroquinone could be correlated to eczema, coughs and reduction of lung function.

Hydroquinone was reported to have genotoxic effects in a Salmonella test. Hydroquinone has also produced positive reactions in a DNA repair test, a test for mitotic recombination and a DNA synthesis test. Hydroquinone has induced sister chromatid exchanges in human lymphocytes and induced micronuclei in experimental animals. Skin contact with hydroquinone can cause sensitizing.

The data from animal experiments and epidemiological surveys are not sufficient basis for any conclusions regarding the carcinogenicity of hydroquinone. The 2-year cancer study now being conducted in the U.S. will provide a further basis for risk assessment.

The critical effect of exposure to hydroquinone seems to be its genotoxic effect. In assessing the risks of hydroquinone exposure, its possible harmful effects on the immune system, bone marrow, skin and mucous membranes should be considered.

13. SUMMARY

U Stenius: Hydroquinone. 84. Nordic Expert Group for Documentation of Occupational Exposure Limits.

The literature considered relevant to a discussion of occupational exposure limits for hydroquinone has been assembled and assessed. Hydroquinone is used industrially as a reducing agent, an antioxidant and a stabilizer, and also as a component in film developing fluids. Exposure can occur via both skin and respiratory organs.

In discussing an occupational exposure limit for hydroquinone, its genotoxic effects should be given attention. Its possible effects on the immune system, bone marrow, skin and mucous membranes should also be borne in mind.

A Swedish version is available in Arbete och Hälsa 1989:15.

105 references.

Key words: Hydroquinone, occupational exposure limit, genotoxicity.

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Appendix 1. Recommended or allowed maximum concentrations of hydroquinone in air.

Country	mg/m^3	Year	Comment	Reference
BRD	2	1988	irritating	5
Denmark	2	1988	upper limit	2
Finland	2	1987	skin	10
	4		15 minutes	
France	2	1988		11
Great Britain	2	1987		4
	4		10 minutes	
Iceland	2	1978		8
Netherlands	2	1989		6
Norway	0.5	1989		1
Sweden	0.5	1988		3
	1.5		short-term peak	
USA (ACGIH)	2	1988-89		9
" (NIOSH)	2	1983	15 minutes	7
" (OSHA)	2	1989	time-weighted average	12

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NITRILOTRIACETIC ACID (NTA) AND ITS SALTS

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1. PHYSICAL AND CHEMICAL PROPERTIES

Nitrilotriacetic acid (NTA) is an aminotricarboxylic acid, which was synthesized for the first time in 1862. NTA and its salts are chelators, which are able to bind for example calcium and magnesium ions in water soluble complexes. Both NTA and its sodium salts are colourless crystalline substances. Na_3NTA, which is the most common commercial form for "NTA"*, is manufactured from formaldehyde, hydrogen cyanide and sodium hydroxide.
The high water solubility of sodium salts of NTA explains why these are far more used than the acid itself. Technical Na_3NTA is a monohydrate of a purity of 98-99%. The most important impurities are inorganic salts (NaOH, Na_2CO_3 and iminodiacetic acid (11). Further, there may be formaldehyde residues in technical Na_3NTA, since formaldehyde is one of the starting materials for the manufacturing process (29).

The physical and chemical properties are shown in table 1 and 2.

Table 1. Phycical and chemical properties of NTA and Na_3NTA (11,50,67,4)

Chemical name:	Nitrilotriacetic acid (N,N-Bis(carboxymethyl)-glycine)	Sodium nitrilotriacetate,	monohydrate
Abbreviations:	NTA, H_3NTA	Na_3NTA	Na_3NTA,H_2O
CAS no.:	139-13-9	5064-31-3	18662-53-8
Empirical formula:	$C_6H_9NO_6$	$C_6H_6NO_6Na_3$	$C_6H_8NO_7Na_3$
Molecular formula:	$N(CH_2COOH)_3$	$Na_3[N(CH_2COO)_3]$	$Na_3[N(CH_2COO)_3],H_2O$
Molecular weight:	191.14	257.10	275.12
Melting point:	246°C	-	> 320°C
Dissociation constants (20°C)	pKA_1: 3.03 pKA_2: 3.07 pKA_3: 10.70		
Solubility in water (25°C):	1.5 g/l	500 g/l	

(* "NTA" means in this text a non-specified form of NTA.)

Table 2. Data concerning other NTA salts (67)

Abbreviation:	NaNTA	Na_2NTA	K_3NTA	CaNaNTA	FeNTA
CAS no.:	10042-84-9	15467-20-6	2399-85-1	60034-45-9	16448-54-7
Empirical formula:	$C_6H_8NO_6Na$	$C_6H_7NO_6Na_2$	$C_6H_6NO_6K_3$	$C_6H_6NO_6CaNa$	$C_6H_6NO_6Fe$
Molecular:	213.12	235.12	305.43	251.18	243.98

2. USE AND OCCURRENCE

2.1 Use

Sodium salts of NTA are often used as a softener in cleaning agents and a phosphate substitute in detergents. Further, "NTA" is used to prevent build up of mineral scale in the food industry, where steam will be in contact with food during processing. In the textile industry "NTA" is used to sequester trace metal that may disturb the dyeing of fabrics, and in the pulp and paper industry NTA is used to bind metal catalyzing the decomposition of bleaching agents (11,57). Smaller amounts of "NTA" is used in tanning of leather, photographic development, manufacturing of rubber and pharmaceuticals, in pesticides and for separation of rare earth metals (57,59). In 1970 the use of "NTA" in detergents stopped in USA, mainly because of a suspicion that "NTA" in the water environment is transformed into carcinogenic or teratogenic substances such as nitrosamines (27). This suspicion was later rejected, and since 1980 the importance of "NTA" has been growing in USA (65). (The fact that NTA in itself may imply a cancer risk is discussed in chapter 8).

For many years the compound has been extensively used in detergents in countries like Canada (in conc. < 2.2%), Finland, Sweden and Switzerland (9,26). Around 1980 the yearly production of "NTA" was about 30,000 tons in USA, and it was estimated that the production size would rise to perhaps 500,000 tons in connection with the expected increased usage of the chemical (65). In the Danish Registry of Chemical Products 55 products containing "NTA" in concentrations up to 52% are included. Most products are cleaning agents and degreasers for household, institutions and industry.

2.2 Air concentrations at workplaces

No information was available from Nordic countries, but in USA it was estimated in 1974 that 15,000 workers were exposed to "NTA" (65).

At production of NTA in USA typical air concentrations were around 6.5 mg NTA/m^3, and the occupational intake was estimated to be 8 mg NTA per 8 hours workday. Formulation of cleaning agents gave rise to air concentrations of around 1.4 mg NTA/m^3, and calculated intakes were typically <4.8 mg NTA/kg bw/d - in extreme cases 10 times higher (26).

2.3 Analytical methods

No information was available concerning analytical methods for air samples - not in the study referred to under section 2.2 either. However, it was stated that analyses of urine were done by GC/MS (gaschromatography/mass spectrophotometry) with a detection limit of 0.5 mg/l (26). Many different methods are developed for analysing water samples, such as polarographic, potentiometric, colorimetric, ion-chromatographic, and gas-chromatographic methods (11,44).

3. KINETICS

3.1 Absorption

Respiratory tract

No information.

Gastro-intestinal tract

The absorption depends on the pH of the stomach acid, since the undisssociated acid is better absorbed. At stomach pH (in rats) Na_3NTA mainly occurs as mono- and disodium salts (54). Oral administration of H_3NTA results in an absorption of about 12% of a dose of 10 mg in humans (16). The corresponding absorption of a more than hundred times higher Na_2NTA dose (in relation to body weight) was the same in monkeys, about 60% in dogs and about 90% in mice and rats (21,54).

Skin and mucous membranes

Less than 0.1% of a given dose of "NTA" was absorbed through the skin after skin application (11). Application of ^{14}C-labelled "NTA" (0.2% solution) on shaved rat skin showed a maximal 24-hours absorption of 0.25 µg/cm^2 (26).

3.2 Distribution

After oral intake of H_3NTA or Na_2NTA a maximal blood concentration is obtained in 1 to 2 hours in both animals and humans. Then the "NTA" concentration in the blood rapidly decreases to below the detection limit in about 12 hours (16,21,70,54).

One hour after administration of either 180 mg/kg orally or 45 mg/kg i.v. to mice the highest tissue concentrations of "NTA" are found in bladder, bone and kidneys; further in the uterus wall in pregnant animals (21,70). A few days later, when most of the NTA is excreted, the rest is mainly located in the bone (54).

3.3 Biotransformation

H_3NTA and its sodium salts are quite stable and are not undergoing any substantial except binding to divalent metals (see 4.1). The organic parts are mainly excreted unchanged, although a smaller part is degraded into CO_2 and water (16,54).

3.4 Elimination

"NTA" is excreted almost exclusively in the urine via the kidneys (table 3).

Lungs

After oral administration of ^{14}C-labelled H_3NTA or Na_2NTA <0.1-1% is exhaled as CO_2 in animals and humans (16,54).

Kidneys

Studies with 14_C-labelled H_3NTA have shown that 87% of the absorbed NTA from a 10 mg oral dose given to rats, are excreted in the urine during 24 hrs. (16). The total urinary excretion of "NTA" in experimental animals depends on the animal species. Rats and mice excrete >95% of an administrered oral dose in the urine during 1-3 days, while rabbits and monkeys only excrete 15-20% (21,54). The amount of "NTA" in the urine increases with the dose; in rats 27-32% of a dose at 0.1% Na_3NTA in the feed is recovered, while 32-40% is recovered at 2% Na_3NTA in the feed (7). The excretion of "NTA" is by glomerular filtration; it is neither active secretion nor resorption (11).

Gastro-intestinal tract

In mice and rats less than 1% of orally administrered H_3NTA or Na_2NTA is eliminated in the bile (21,54). After intravenous injection of Na_3NTA no trace of "NTA" was found in faeces (12). This indicates that when some authors (16,21,54) find a considerable radioactivity in faeces after oral dosage of labelled "NTA", this is due to unabsorbed "NTA".

Table 3. Elimination of orally administrated "NTA" (^{14}C-labelled)

Species	Dose mg/kg	% of orally dose urine	faeces	Measured after hours	Ref.
Humans	0.107-0.169	12±7	77±11	120	16
Mice	180	96±6	3.5±1.3	24	21
Rats	10	95	3	72	54
Dogs	50	69	5	72	54
Rabbits	50	23	33	72	54
Monkeys	50	14	65	72	54

Biological half-lives

The half-life of "NTA" in human blood from volunteers exposed to 10 mg Na_3NTA is about 6 hours, and the whole body half-life is less than 24 hrs. (16).

In mice the half-life in the blood is around 2 hours after administration of 180 mg Na_3NTA/kg bw. In the bone no radioactivity was detectable after 8 hours (21).

3.5 Biological indicators of exposure

No information is available - apart from a single, poorly documented case, where urinary measurements were used (26).

4. GENERAL TOXICOLOGY

4.1 Toxicological mechanisms

The basis for the toxicity of H_3NTA and its salts is likely to be the ability to chelate some essential divalent metal ions, including Ca^{2+}, Mg^{2+} and Zn^{2+}, in such a way that they are more soluble (5). Thus, trace elements may be transported from one place in the body to another. This means a greater biological availability which may cause toxicity in some tissues and trace element depletion in others. Several animal experiments have shown that exposure to doses of "NTA" which are toxic to the kidneys increases the excretion of zinc in the urine (10,61,17,30). The toxic effect on the kidney cortex is probably caused by an increased uptake of zinc in the proximal tubuli (11).

As regards damage to the transitional epithelium in the urinary bladder, in the proximal part of the urinary canal, and in the renal pelvis, this is supposed to be related to formation of crystals of CaNaNTA (12,1,6,7,10).

These effects may be reversible, if dosage is low and for a short time. Som scientists believe that renal damage is a precondition for development of tumors in the kidneys (see section 7.8). Therefore, it has been suggested to classify "NTA" as a promotor of cancer (12).

4.2 Factors affecting the toxicity

In general, it can be concluded that "NTA" may increase the bioavailability and thus intensify the toxicity of metals. This property has been used in animal model experiments studying metal accumulation.

Supplementation of zinc to animal feeds increases the renal damage by "NTA" in exposed animals, and a low zinc content in the feeds decreases the toxicity of Na_3NTA (10).

Administration of Na_3NTA by stomach tube to rats previously exposed to lead acetate (2 mg lead/ml drinking water), decreased the tissue concentrations of lead in the "NTA"-dosed animals (20). However, in another study with simultaneous administration of Na_3NTA and lead (200 µg/ml) in drinking water no change in lead deposition was observed (47).

An investigation aimed to explain whether Na_3NTA administration could increase excretion of cadmium in cases of intoxication, did not show any effect on elimination or distribution of cadmium. The animals were dosed by 1 mg Cd/kg bw (i.v.) and 48 hours later with 0.2 g "NTA"/kg bw (i.p.) each day for 5 days (18).

In another study in which pregnant rats were dosed with $CdCl_2$ (4 mg/kg bw) and Na_3NTA (20 mg/kg bw) no increased cadmium accumulation was observed in the liver of the fetus (63). Simultaneous administration of Na_3NTA and $CdCl_2$ did not increase the teratogenicity or toxicity of cadmium (64).

Aluminium administrered as AlNTA may result in liver- and kidney damage in rats (24). Further "NTA" and other chelators may be responsible for the effects on the central nervous system observed after simultaneous administration of aluminium salts (24).

FeNTA may cause lipid peroxidation and diabetes in rats (11,31).

Administration of FeNTA causes glucosuri and morphological changes in the liver of rats, changes which are parallel with idiopathic hemochromatosis in humans (13).

"NTA" increases the solubility of chromates and lead compounds, and thus their cytotoxicity and mutagenicity (19,55,46,22,66).

4.3 General effects

H_3NTA and most of its salts have a low acute toxicity. In table 4 some LD_{50} values are shown.

Table 4. Acute toxicity of NTA and salts

Compound	Species	Administration	LD_{50}(g/kg)	Ref.
H_3NTA	rat	peroral	5.34	11
	rat	peroral	1.470	67
	mouse	peroral	3.160	67
Na_2NTA (30%opl)	rat	peroral	1.46	57,67
Na_3NTA	rat	peroral	1.90	11
(20%opl)	rat	peroral	1.68	57
(40%opl)	rat	peroral	2.33	57
(50%opl)	rat	peroral	1.10	67
	mouse	peroral	0.681	67
(50%opl)	monkey	peroral	0.75	67
(80%opl)	dog	peroral	>5	57
K_3NTA (60%opl)	rat	peroral	1.22	57,67
CaNaNTA	rat	peroral	>20	11
CuNaNTA	rat	peroral	0.81	11
NiNaNTA	rat	peroral	>22.5	11
ZnNaNTA	rat	peroral	18.6	11

Loss of weight was observed in rats exposed to 2% (1000 mg/kg bw./d) Na_3NTA in the feed for 4 weeks (39). Increased mortality was seen in investigations in which 0.1% (150 mg/kg bw./d) Na_3NTA was administered in drinking water to rats for 2 years (19.7% versus 11.2% in controls) (32), and when 0.5% (250 mg/kg bw./d) Na_3NTA or its calcium chelate (CaNaNTA) was administered to rats for 2 years (61). Bodyweight and survival were not affected in mice dosed with 0.5% Na_2NTA (200 mg/kg bw./d) drinking water for 26 weeks (33). Similarly, 0.5% (250 mg/kg bw./d) Na_3NTA in the feed for 90 days had no effects in dogs (16).

5. EFFECTS ON ORGANS

5.1 Skin and mucous membranes

A neutralised 25% solution of H_3NTA, but not a 5% solution, caused skin irritation in rabbits (57). However, a solution of 20% Na_3NTA was not irritating or sensitive in a patch test with 66 human volunteers (60).

5.2 Respiratory tract

Well-described inhalation experiments are not available. Anderson et al. (1985) refer to an unpublished inhalation experiment with rats, guinea pigs and monkeys, in which inhalation of 342 mg "NTA"/m^3 air for 6 hours/day. 5 days/week for 4 weeks had no effect in rats and monkeys. Details of the experiments were not given, and the results of experiments with guinea pigs were not given either. Therefore, this study has not been discussed in chapter 10.

5.3 Liver

Female rats exposed to 0.5% (250 mg/kg bw./d) Na_3NTA and 0.5% (265 mg/kg bw./d) CaNaNTA in the feed for 12 months had a relatively increased liver weight (61). However, intraperitoneal injections of 200 mg Na_2NTA/kg bw./d for 54 days had no effect on the liver of rats (24). Contrary to this, i.p. administration of 1.5-2.0 mg AlNTA/kg bw./d for 54 days caused liver necrosis in rats (24).

5.4 Kidneys

"NTA" exerts its main toxic effect in the urinary tract, and urinary concentrations of NTA may be up to 200 x the concentrations in plasma (10). The effect on the urinary tract is on the tubular cells of the kidney cortex and on the transition epithelium in the renal pelvis, in the urether and in the urinary bladder (vesica). The effects appear clinically as crystaluri, hematuri, hydronephrosis, weight loss and an increased kidney/body weight ratio (60,39,6,1,52).

By microscopy are seen cytoplasmic vacuoles in the proximal tubuli cells in the kidney cortex. These vacuoles may increase in size and finally displace the cytoplasma, which results in a swollen appearance (52). The formation of vacuoles is reversible, but may in the long term result in serious changes of the kidney tubuli. On the basis of a 30 days experiment with rats, the observed tubuli changes were classified in 3 groups referring to the size of tubuli and appearance of cytoplasma in the tubuli cells:

1. basophile tubules
2. simple hyperplasia increased number of cells, unaltered tubulus diameter
3. nodular hyperplasia

Merski (51,52) observed that "NTA" dosing induced an increased number of hyperplastic tubules and in up to 90% of these tubules vacuoles were observed in the cells. This indicates a connection between the formation of vacuoles and hyperplasia, a connection which has been confirmed by other studies. The formation of vacuoles has been observed few hours after administration of a single dose of 2.0 g Na_3NTA, H_2O/kg bw. for rats. The changes developed during 1 to 6 hours after dosage and were decreased considerably after 72 hours. Dosage with 20 mg Na_3NTA/kg bw. caused no formation of vacuoles or other changes in the tubules (51).

Administration of 1.5 g Na_3NTA/kg bw./d for 13 days with stomach tube to rats induced hyperplasia, erosions, necrosis, and focal bleedings in kidney cortex and formation of cytoplasmic vacuoles in the proximal tubules (52). Dilatation of the renal pelvis and the proximal part of the ureter including hyperplasia and erosions was observed after administration of 2% (1000 mg/kg bw./d) Na_3NTA in the feed to rats for 28 days (39). After 7 weeks' administration of 1.5% H_3NTA (750 mg/kg bw./d) or 2% (1000 mg/kg bw./d) Na_3NTA in the feed to rats formation of vacuoles and nodular hyperplasia in tubules and changes in renal pelvis were observed. These changes disappeared after 5 weeks without "NTA" dosage; only very serious hydronephrosis was irriversible. This may indicate that a continuous administration of "NTA" is a condition of maintenance of the lighter lesions (58).

In a 2 years feeding study with rats the first cases of hydronephrosis were observed after 6 months in the dosage groups 0.15% (75 mg/kg bw./d) and 0.5% (250 mg/kg bw./d) Na_3NTA; the degenerative changes were even more pronounced and involved more animals after 12 months; later, serious inflammatoric changes arose. In the third dosage group of 0.03% (10 mg/kg bw./d) no effect was observed (61). In another study 20 mg/kg bw./d was given as a no-effect level (51,52).

5.5 Gastro-intestinal tract

Intake of more than 1 g Na_3NTA/kg bw. caused vomiting in dogs and the vomit contained blood, which may indicate changes in the stomach (60) or the oesophagus.

5.6 Heart and cardiovascular system

No information available.

5.7 Blood and blood forming organs

In a 10 weeks study in which rats received 1% (1500 mg/kg bw./d) Na_3NTA in the drinking water, hyperglucemia was observed (47), whereas in a 90 days experiment with dogs (169 mg Na_3NTA/kg bw./d) and rats (1% (500 mg/kg bw./d) Na_3NTA in the feed) no changes in the blood were found (60,17). The same was the case in a 2 years experiment with rats with up to 0.5% (250 mg/kg bw./d) Na_3NTA in the feed (61). However, in the same study the calcium chelate (CaNaNTA) caused an increase of hemoglobin concentrations in female rats dosed by 0.5% (61).

5.8 The central nervous system

See section 4.2.

5.9 The peripheric nervous system

No information available.

5.10 Bone

Like other chemicals which form strong complexes with divalent metal ions, "NTA" accumulates to a high degree in bone. At the same time "NTA" increases the zinc content in bone. However, in experimental animals no changes of the properties of bone caused by "NTA" have been observed (54,61).

5.11 Eyes

Instillation in rabbit eyes of 3 mg of a detergent production containing 11-35% Na_3NTA caused a weak eye irritation, but no permanent damage (60).

6. IMMUNOTOXICITY AND ALLERGY

No human cases of allergy to NTA or its salts have been published. For example Na_3NTA was not positive in the Draize test with 66 persons (60).

7. MUTAGENICITY, GENOTOXICITY

"NTA" has been surveyed for mutagenicity in several <u>in vitro</u> tests with cultures of bacteria, mammalian cells and plant cells; further in <u>in vivo</u> tests with banana flies (Drosophila) and mammals. Most investigations show low or no genotoxicity (see table 5)

Apparently, a genotoxic effect only shows up, when the cells are emptied of divalent metal ions. For example, a concentration of >2.5 mM Na_3NTA induced chromosomal aberrations in human lymphocytes (14), and a concentration of >7.3 mM increased V-79 cell rescue, which is a promotor test (48). Concentrations greater than 10^{-5} M induced mutations in the human cell line EUE (34).

8. CARCINOGENICITY

8.1 Human studies

No information available.

8.2 Animal studies

Administration via drinking water.

In a somewhat old study in which mice were exposed for 26 weeks to 0.5% (100 mg/kg bw./d) Na_3NTA in the drinking water, no difference between tumor incidence in treated animal or controls was reported (33). The experiment had, however, too short duration. A similar investigation with rats exposed during 84 weeks showed no increased tumor incidence either (45). The total dosage each animal received was 42 g "NTA".

Otherwise in a later study with rats exposed to 0.1% (150 mg/kg bw./d) Na_3NTA in the drinking water during 2 years an increased mortality and a significant increased incidence of kidney tumors were observed in the treated animals (32). In the exposed group 25 out of 183 rats had kidney adenomas, and 5 rats had kidney carcinomas. Of the controls 5 animals out of 192 had kidney adenomas.

From this study the tumor dose index (TD_{16}) for Na_3NTA can be calculated to be about 150 mg/kg bw./d, which corresponds to a carcinogen of intermediate potency (76).

Administration in the feed

In a two-years study rats were exposed to Na_3NTA in the feed at 3 dose levels: 0.03% (10 mg/kg bw./d), 0.15% (75 mg/kg bw./d) and 0.5% (250 mg/kg bw./d). In rats exposed to the two highest dosages an increased incidence of nephritis and nephrosis was observed, but no tumors (61).

Later the National Cancer Institute in USA was responsible for several more extensive feeding experiments with Fischer 344 rats and B6C3F1 mice exposed to both H_3NTA and Na_3NTA,H_2O (59). The highest dosage was in all experiments the maximal tolerable dosage (MTD) determined by a 8-weeks toxicity test.

In one study rats received 0.02% (10 mg/kg bw./d), 0.2% (100 mg/kg bw./d) or 2.0% (1000 mg/kg bw./d) Na_3NTA in the feed during 24 months. At the highest dosage of Na_3NTA,H_2O kidney tumors were observed in 13 of 24 male and 24 female animals compared to none of the controls, a statistically sig-

Table 5. Data from mutagenicity testing of "NTA"

Test system/effect	Dose	Response	Ref.
Mutation in fungi			
Aspergillus nidulans			
forward mutation	3.6 mM	-	23
malsegregation	45.5 mM	-	23
Schizosaccharomyces pombe			
forward mutation	40 µg/ml	-	46
Saccharomyces cerevisiae			
gene conversion	40 µg/ml	-	46
Neurospora crassa			
forward mutations	1%	-	69
Mutation in insects			
Drosophila melanogaster			
sex-linked recessive	feeding 50 mM	-	43
lethal test	inject 10 mM	-	43
sex-linked recessive	feeding 4.0 ppm	?	75
lethal test	inject 1.1 ppm	-	75
sex-linked recessive	feeding 50 mM	-	22
lethal test			
Mutation in bacteria			
Salmonella typhimurium			
(TA1535,TA1537,TA1538,			
TA98,TA100)			
gene reversion	40 µg/ml	-	46
Dominant lethal test in mice			
translocation test	50 mg/kg/d in 5 days	-	38
	0.1% in water in 7 weeks	-	37
	125 mg ip.	-	28
	1000 mg/kg po. in 5 days	-	28
Sister chromatid exchange (SCE)			
hamster ovary cells		-	15
human lymphocytes		-	15
Mutation in human cells			
EUE line	$>10^{-5}$M	+	34
lymphocytes	>2.5 nM	-+	14
lymphocytes	10^{-2}M	-	56
Mutation in mammalian cells			
hamster cells (V79)	$1.5x10^{-2}$M	-	19
rat kangaroo cells		+	41
rat embryo cells infected by RLV-virus cells	$5.2x10^{4}$	+	71
Mutation in plants			
bean root tips		-	41
DNA repair			
rat hepatocytes	$5x10^{-1}$ mg/ml	-	74

nificant finding; 12 of 48 animals had tumors in the urinary pelvis, and 5 of 24 females had bladder tumors. Furthermore, metastases (mainly in the lungs) were found in 10 out of 48 rats. In the other investigation rats received 0.75% and 1.5% "NTA" in the feed during 18 months, followed by 6 months intermission before killing. At the highest dosage level of H_3NTA 12 out of 48 female rats got bladder tumors. The incidence was not statistically significantly different in males, but one out of 48 males had a metastasing urinary tract tumor. The tumor incidence at the low concentration and at administration of the sodium salt was not statistically significantly increased.

In the third study mice received 0.75% (1,125 mg/kg bw./d) or 1.5% (2,250 mg/kg bw./d) H_3NTA, 0.25% (375 mg/kg bw./d) or 0.5% (750 mg/kg bw./d) Na_3NTA,H_2O in the feed for 18 months followed by 3 months intermission before killing. In the highest dose-group H_3NTA kidney tumors were found in 22 of 44 males. The incidence of tumors in females, and in males at the lower concentrations, was not significantly increased.

In the treated animals inflammatory changes in the urinary tract were observed more frequently. Lesions which in general occur in kidneys from older animals.

Administration by injection

One weekly subcutaneous injection for 75 weeks of 3.5 mg NTA dissolved in 0.05 ml tricapylin to 8 weeks old female Swiss mice induced local adenosarcomes (72).

Daily i.p. injection during 3 months of 5-7 mg FeNTA to male Wistar rats caused after 2 years kidney damage and malignant kidney carcinomas with metastases to other organs in 14 out of 18 animals. Animals exposed in a similar way to AlNTA got similar kidney damage, but not kidney tumors (25).

Interaction with other substances

In several animal studies secondary exposure to Na_3NTA (>0.5% in the feed) has been able to increase the effect of some model compounds for initiation of urinary cancers and thus react as a promotor (30,42,35,36). The model compound was the bladder carcinogen BBN (N-butyl-N-(4-hydroxybutyl)nitrosamine) or the kidney tubule carcinogen EHEN (N-ethyl-N-hydroxyethylnitrosamine). Contrary, there are animal studies in which "NTA" neither interacted with nor decreased the tumor rate. These were the chemicals NBBN (probably BBN!), DPN (Dipropylnitrosamine, liver carcinogen) and MNNG (N-methyl-N'-nitro-N-nitrosoguanidine, stomach carcinogen) (11).

9. REPRODUCTIVE TOXICOLOGY

Since "NTA" may bind essential metal ions such as Zn^{2+}, there have been speculations that the substance might be teratogenic and decrease the fertility, but Na_3NTA was neither embryotoxic nor teratogenic in rats exposed to 0.5% (750 mg/kg bw./d) or in mice exposed to 0.2% (400 mg/kg bw./d) of the chemical in drinking water day 6-18 in the pregnancy (70,62). A similar result was obtained in rabbits exposed to 250 mg Na_3NTA/kg bw./day (62).

No effects of "NTA" on sexual glands have been described, but interaction with Zn^{2+} metabolism means a potential for an effect on the fertility.

10. RELATIONSHIP BETWEEN EXPOSURE, EFFECT AND RESPONSE

10.1 Effects of short-term exposure

The formation of vacuoles in the tubule cells of the cortex is dose dependent in rats (51); the same is the degree of changes in the tubules (52). A direct proportionality between reduced utilization of feed, weight loss and changes in the kidneys has been reported (1). The data is summarized in table 6.

10.2 Effects of long-term exposure

The critical organ in both short-term and long-term studies is the kidney.

In several long-term animal bioassays with NTA and its salts an increase in the incidence of tumors in kidney has been reported in rats and mice. Furthermore, an increase of transitional epithelial tumors in renal pelvis, ureter and bladder has been reported in rats. (see table 7).

On the background of available data NTA, as the acid or the trisodium salt, has to be evaluated as carcinogenic in several independent studies involving rats and mice. A statistically significant increase in tumor incidence was demonstrated in the urinary tract, mainly in kidney and bladder. There were only a few or no tumors in controls. The tumorigenic dosage was from 0.1% (150 mg/kg bw./d) Na_3NTA in drinking water and 0.75% (375 mg/kg bw./d) H_3NTA in feed with a dose-response relationship.

The levels of exposure which cause significantly more tumors, give also rise to degenerative and inflammatory changes in the kidneys. A common viewpoint is that such changes are a precondition for development of tumors and that, therefore, only dose levels which are reprotoxic, induce tumors, and that the development of tumors - at least to a certain point - is reversible (2,3,11).

11. RESEARCH NEEDS

More information of occupational exposure conditions of NTA is needed. Development of chemical analytical methods for air samples is urgent. Further, epidemiological studies of "NTA" exposure are missing. The same is the case for inhalation studies with experimental animals, especially reproductive toxicity, embryo toxicity and teratogenicity studies. Finally, there is a need for more studies of the effect of NTA on the growing bone and interactions with other chemicals.

12. DISCUSSION AND EVALUATION

The NTA acid and its sodium salts have commercial importance and are included in this concluding evaluation. H_3NTA and salts are only slightly absorbed from the gastro-intestinal tract. The sodium salts are, furthermore, only slightly absorbed through the skin. The acid itself has not been tested by skin absorption but should be more skin penetrating than salts. The absorption by inhalation has not been studied.

There are no data available concerning health effects of "NTA" in humans. Most animal studies have been undertaken with oral administration of the compounds. This route of administration is not the most relevant as a basis for a workplace assessment.

Table 6. Dose-response in sub-chronical animal bioassays with "NTA"

Dose	Adm. route	Exposure time	Clinical sign	Microscopy of proximal tubules	Other finding ind the urinary tract	Ref.
RATS						
2%	feed	4 weeks	hydronephrosis nephromegalia 45% weight loss, decreased feed utilization	vacuoles degenerations necrose simple-nodular hyperplasia	erosions (ulcerations)	1
2%	feed	4 weeks	hematuria	-	hydronephrosis	6
1.5%	feed	4 weeks	crystaluria	-		
2%	feed	4 weeks	weight loss	-	hydrourether +	39
3.5%	feed	4 weeks	weight loss	-	hydronephrosis	
0.1%	tube	30 days	-	vacuoles hyperplasia	focal bleedings erosions hyperplasia necrosis	52
0.2%	feed	90 days	-			60
0.75%	feed	90 days	kidney/body weight ratio increased	light degeneration		
1%	feed	90 days	kidney/body weight ratio increased	serious degeneration		
2%	feed	90 days	hydronephrosis nephromegalia weight loss organ/body weight ratio increased			
2%	feed	90 days	weight loss	vacuoles nodular hyperplasia	erosions ulcerations hydronephrosis	58
DOGS						
0.03%	feed	90 days	-			17
0.15%	feed	90 days	-			
0.5%	feed	90 days	-			

Table 7. Urinary tract tumors in rats and mice exposed to "NTA" (modified from (11))

NTA type	Dosage (%)	(mmol/kg bw./d	(mg/kg bw./d)	Exposure time /duration (weeks)	Tumor incidence (tubules ephitelium)	(transition ephitelium)	Ref.
RATS							
Controls		0			5/391	0/391	11
Na_3NTA,H_2O	0.02	0.04	10	104	0/48	0/48	59
in feed	0.03	0.05	15	104	0/37	0/37	61
	0.15	0.27	75	104	0/31	0/31	61
	0.2	0.36	100	104	0/48	1/48*	59
Na_3NTA,H_2O in drinking water	0.1	0.52	150	101	29/183	0/183	32
Na_2NTA in water	0.5	0.85	200	84/104	3/60	0/60	45
Na_3NTA,H_2O	0.5	0.91	250	104	3/69	0/69	61
in feed	0.75	1.36	375	72/104	1/100	1/100	59
H_3NTA in feed	0.75	1.96	375	72/104	1/100	2/100	59
Na_3NTA,H_2O	1.5	2.73	750	72/104	2/100	2/100	59
in feed	2.0	3.64	1000	104	8/48	6/48	59
H_3NTA in feed	1.5	3.93	750	72/104	7/100	12/100	59
MICE							
Controls		0		85	0/80	0/100	59
Controls		0		26	1/77	0/77	33
Na_3NTA,H_2O in water	0.5	0.38	100	26	1/74	0/74	33
+ $NaNO_2$	0.5	0.38	100	26	0/76	0/76	33
Na_3NTA,H_2O	0.25	1.36	375	72/85	0/100	0/100	59
in feed	0.5	2.73	750	72/85	0/100	0/100	59
H_3NTA	0.75	5.89	1125	72/85	5/98	0/98	59
in feed	1.5	11.78	2250	72/85	28/83	0/83	59

* papilloma

Assumptions: 1) Rats consume 50 g feed/kg bw./d and consume 145 ml water/kg bw./d. 2) Mice consume 150 g feed/kg bw./d.

High single or multiple doses of H_3NTA and its salts ($\geq$2 g/kg bw./d) may result in toxic effects in experimental animals, mainly effect on the kidney. The adverse effects are probably due to the ability of NTA to bind divalent metal ions such as Zn^{2+}, Mg^{2+} and Ca^{2+}. No-effect level in long-term studies has been estimated to >20 mg/kg bw./d.

A daily dose of 0.1% (0.15 g/kg bw./d) H_3NTA and Na_3NTA in drinking water or 2% (1 g/kg bw./d) in the feed during 2 years induce tumors in the urinary tract, mainly in kidney tubules and urinary bladder, of rats. In mice

a similar dose of H_3NTA was tumorigenic in feeding experiments, but that dose was not obtainable with the sodium salt, because of its toxicity. Thus H_3NTA and its sodium salt were clearly carcinogenic in several independent animal studies, and a dose-response relationship was established.

TD_x (the tumor dose index) is around 150 mg/kg bw./d in the drinking water experiments, in which the uptake of the substance may be somewhat greater than from the feed, thus NTA may be classified as an intermediate potency carcinogen (low potency carcinogens have a TD_x >600 mg/kg bw./d) (76).

Furthermore, recent results of mutagen testing indicate that "NTA" in some instances is genotoxic, however, most mutagen test results are negative. Several investigations have also reported that "NTA" has a considerable ability to increase the effect of other mutagens such as chromates.

The critical effect of "NTA" at workplace exposures is the effect on the kidneys, including cancer. Cancer in animal develops, however, at exposures which affect the normal function of the kidneys. These are changes normally seen in older animals. The opinion of some scientists is that this adverse effect is a precondition for and the explanation of the development of tumors.

13. SUMMARY

Olsen SN, Jensen AA. Nitrilotriacetic acid (NTA) and salts. Nordic expert group for documentation of exposure limit values. Arbete och Hälsa 1989.

The literature concerning health effects relevant to a hygienic standard for nitrilotriacetic acid (NTA) and its salts has been reviewed.

NTA is used as a replacement for phosphates in detergents. It is mainly absorbed in the gastro-intestinal tract, less than 0.1% is absorbed through the skin. Absorption by inhalation has not been investigated. NTA does not undergo biotransformation but is excreted unchanged in the urine.

There are no relevant data concerning effects of NTA in humans. The acute toxicity of NTA and its salts in animals is low. Long-term exposure to rather high concentrations, however, exerts persistent toxic effects on the renal cortex which are manifested morphologically as vacuolisation of proximal convoluted tubular epithelium and exacerbation of age-related necrosis. No-effect level of the effects on the kidneys is estimated to be 20 mg/kg bw/d. The mechanism of the toxic effect is supposed to be a chelating of essential divalent metal ions such as calcium-, magnesium- and zinc-ions.

Very high NTA doses of from 0.14 g/kg bw/d in the drinking water or 1 g/kg bw/d in the feed for two years to mice and rats induced urinary tumors especially in the renal cortex and urinary bladder. The tumors occur at exposure levels which have some adverse effects on the kidneys normally seen in aged animals. Some scientists evaluate this effect as a precondition for the tumorigenic effect and classify NTA as a tumor promotor only.

NTA has been investigated in a huge number of different tests for genotoxicity and only found mutagenic in some cell culture systems, e.g. mutation in human lymphocytes, rat kangaroo cells and rat embryo cells infected with RLV virus. Furthermore, NTA increases considerably the mutagenicity of chromates in bacterial systems.

The critical effect of NTA and its salts is the toxic and tumorigenic effect on the kidneys. No specific occupational health limit has been enforced in any country.

Key words: Occupational exposure limit, NTA, nitrilotriacetic acid, sodium nitrilotriacetate, renal effects, cancer.
A Danish version is available in Arbete och Hälsa 1989: 76 references.

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Appendix. Occupational health limits for NTA in air.

Country	mg/m^3	ppm	year	comments	ref.
BRD	-		1988		5
Denmark	-		1988		2
Finland	-		1987		11
France	-		1987		12
Island	-		1978		9
Netherlands	-		1986		7
Norway	-		1984		1
Sovjet Union	-		1978		6
Great Britain	-		1988		4
Sweden	-		1988		3
USA (ACGIH)	-		1988		10
(NIOSH/OSHA)	-		1977		8

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ACETONITRILE

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1. PHYSICAL AND CHEMICAL DATA

Systematic name:	ethane nitrile
CAS No.:	75-05-8
Synonyms:	acetonitrile
	methyl cyanide
	cyanomethane
Formula:	CH_3CN
Molecular weight:	41.05
Melting point:	-45.7°C
Boiling point:	81.6°C (101.3 kPa)
Vapor pressure:	9.7 kPa (20°C)
	11.6 kPa (24°C)
	13.6 kPa (27°C)
Density (d20/4):	0.79
Flash point:	6°C
Conversion factors:	1 mg/m^3 = 0.586 ppm
	1 ppm = 1.706 mg/m^3

Acetonitrile at room temperature is a colorless liquid with an ether-like smell. When three persons were exposed to 70 mg/m^3 (40 ppm), all of them reported noticing the odor (34). A more recent publication reports the odor threshold to be 284 mg/m^3 (33).

Acetonitrile is soluble in most solvents: water, alcohol, benzene, carbon tetrachloride etc.

Production. Acetonitrile is a by-product of the production of acrylnitrile; acrylnitrile is produced by a reaction of propene, ammonia and oxygen (22). The ratio of acetonitrile to acrylnitrile is 1:35. The acetonitrile is recovered as a water azeotrope. The azeotrope is then dried and purified by distillation.

2. USES, OCCURRENCE

2.1. Uses

Acetonitrile is used primarily as a solvent in extraction processes, particularly to separate butadiene from other C4-hydrocarbons and to extract fatty acids from animal fats and vegetable oils. It is also used in the photography and perfume industries, and in chemical laboratories (22).

2.2. Air concentrations in the working environment

Occupational exposure to acetonitrile occurs primarily during its production and its use as a solvent.

In a chemical factory where tanks were internally coated with corrosion-resistant material, the measured concentrations of acetonitrile were below 29 mg/m^3 (17 ppm) (2).

Tobacco smoke contains acetonitrile. The smoke from 1 gram of tobacco contains about 0.16 mg acetonitrile (10).

2.3. Methods for analysis of air concentrations

Acetonitrile is sampled in large carbon tubes which have a capacity of 16.38 µg (0.297 µmol) (5). The samples are desorbed with benzene or toluene and analyzed by means of gas chromatography.

The detection limit is estimated to be 0.01 mg/sample. The studied range for a 10-liter sample was 31.4 to 140.2 mg/m^3 (31). The method is judged to be valid in the range 10 to 210 mg/m^3 (30).

3. KINETICS

3.1. Uptake

Dalhamn et al (8, 9) have shown that 74% of the total amount of acetonitrile in cigarette smoke is absorbed in the mouth, and that retention in the lungs is 91 $\pm$ 4.1%. This indicates that acetonitrile is easily absorbed, and that absorption is virtually complete. Workers exposed to extremely high air concentrations resulting from accidents have become ill, which can be taken as further evidence that acetonitrile is easily absorbed (2, 11, 12, 17).

When rats were exposed for 4 hours to undiluted acetonitrile via shaved stomach skin, some of the animals died: no analytical data were given, however (47).

3.2. Distribution

Acetonitrile is distributed throughout the body. In a case of acetonitrile poisoning which led to death after 6 days, analysis at autopsy showed acetonitrile in kidneys, liver, spleen and lungs, and traces in the pancreas and bladder. The metabolite cyanide (CN^-) was found in all these organs and also in the brain (12). In another case of poisoning, autopsy revealed cyanide in the blood, urine, kidneys, spleen and lungs, but only traces in the stomach contents and none in the liver (2).

3.3. Biotransformation

Acetonitrile is metabolized to cyanide in vivo (24). Among the metabolic pathways proposed is one via cyanohydrin:

$$CH_3CN \longrightarrow CH_2(OH)CN \longrightarrow HCHO + H^+ + CN^-$$

This reaction is dependent on cytochrome P-450, NADPH and oxygen; it has been confirmed by Freeman and Hayes (16) using rat hepatocytes, though they could not demonstrate either cyanohydrin or formaldehyde (15). Cyanohydrin is extremely short-lived, however, and the small additional amounts of formaldehyde would be difficult to distinguish from normally occurring metabolic formaldehyde.

The cyanide reacts further to thiocyanate with help of the enzyme rhodanese (E.C. 2.8.1.1.1.), which is found in the liver and also in the kidneys, adrenal glands, respiratory organs, and in rather high concentrations in olfactory organs (7, 23).

Freeman and Hayes (15) discuss the lag period in the microsomal metabolism and other relevant factors. They believe that other metabolic pathways are also used, such as nucleophilic substitution with glutathione (GSH), and with the help of GSH S transferase:

$$CH_3CN + GSH \longrightarrow CH_3SG + H^+ + CN^-$$

3.4. Elimination

Acetonitrile can be excreted as such or as a metabolite – usually thiocyanate – in urine, saliva and perspiration.

There is no information on elimination via the lungs.

Most data on excretion are obtained from cigarette smokers. A person who smokes 5 to 50 cigarettes per day excretes 11.76 µg /100 ml morning urine (average for 40 smokers). This can be compared with 0.29 µg/100 ml for non-smokers (29). Compared to non-smokers, smokers have concentrations of thiocyanate twice as high in urine and 3-4 times as high in saliva and blood serum (10).

Three subjects who inhaled acetonitrile in concentrations of 70 mg/m^3, 140 mg/m^3 and 270 mg/m^3 (40, 80 and 160 ppm) on different occasions showed no increase of blood cyanide or urine thiocyanate (34).

In long-term experiments with acetonitrile, 16-hour urine samples were taken from different animal species and analyzed for thiocyanate. Groups of rats exposed to 560 or 280 mg/m^3 (330 or 166 ppm) excreted an average 42 and 49 mg SCN^-/100 ml urine, respectively. Monkeys and dogs exposed to 600 mg/m^3 (350 ppm) excreted 9.7 and 13.5 mg SCN^-/100 ml urine respectively. The values also showed considerable variation within species, and the authors therefore concluded that thiocyanate in urine can not be used as an exposure index for acetonitrile (34).

When a dose of 31 mg/kg (0.75 mmol/kg) was given orally to male rats, 11.8% was excreted as thiocyanate within 24 hours; when the same dose was given intraperitoneally excretion was 4.4% (37).

3.5. Biological exposure indicators

Amdur (2) studied some cases of poisoning, determining cyanide in blood and thiocyanate in serum to see if these could be used as exposure indicators. Unfortunately, there were no exposure data for these cases.

Thiocyanate in urine has been measured in some animal experiments, but no dose-response relationship was found (34, 37). This indicates that urine thiocyanate can not be used as an exposure indicator for acetonitrile (cf. 3.4.).

4. GENERAL TOXICOLOGY

4.1. General observations

The LD_{50} for rats varies considerably with age, sex and method of administration: whether the acetonitrile is given in undiluted form or diluted in water, corn oil or Tergitol 7 (34).

Table 1. Acetonitrile: LD_{50} values for some animal species.

Species	Method of administration	LD_{50} (g/kg)	Ref.
Rat	gavage	1.32-6.70	34
Rat	p.o.	3.8	39
Rat	p.o.	2.46	1
Mouse	p.o.	0.27	42
Guinea pig	p.o.	0.18	34
Rat	i.p.	0.95	34
Mouse	i.p.	0.18	43
Rat	i.v.	1.68	34
Mouse	i.v.	0.61	32
Rabbit	skin	0.39-0.98	34
Rabbit	skin	3.93	39

Table 2. Acetonitrile: LC_{50} values for some animal species.

Species	mg/m^3	ppm	Time	Ref.
Rat	27,000	16,000	4 h	34
Guinea pig	9,500	5,655	4 h	34
Rabbit	4,800	2,828	4 h	34
Mouse	4,600	2,693	1 h	43

4.2. Factors that affect toxicity

Acetone potentiates the acute toxicity of acetonitrile (14, 35). It also retards the appearance of symptoms of poisoning: shaking and convulsions. These symptoms appeared 34 to 36 hours after an oral dose, and coincided with a rise in blood cyanide and a drop in blood acetone. Administration of sodium thiosulfate or a new dose of acetone counteracted the toxicity, which was connected to exposure to both solvents. The authors believe that these results reflect a bi-phasal effect in the metabolism of acetonitrile to cyanide (see 3.3.): an initial inhibition, followed by stimulation of this metabolism when the acetone is eliminated (14).

Mice can be protected against acetonitrile poisoning by sodium thiosulfate given in multiple injections, but not by sodium nitrite (both are used for cyanide poisoning) (45).

Dried and powdered thyroid glands from sheep, given to mice in diet, reduced the toxicity of acetonitrile by about 4 times but had no effect on cyanide toxicity (19). The active substance seems to be thyramine (46).

5. EFFECTS ON ORGANS

5.1. Effects on skin and mucous membranes

Pale to ash-grey skin and erythematous vesicular skin eruptions were observed in a group of workers exposed to an unknown concentration of acetonitrile (2).

Regarding skin irritation, Smyth and Carpenter (39) found acetonitrile comparable to acetone, and Zeller et al (47) observed no effect on skin of rabbits.

Undiluted acetonitrile (0.005 ml) caused damage to the eyes of rabbits, and 1 drop caused edema and severe inflammation of the conjunctiva (47).

5.2. Effects on respiratory organs

One person (of 3) exposed to 70 mg/m^3 (40 ppm) for 4 hours noticed nothing during the exposure, but a few hours later felt a slight tightness in his chest. The following day he reported that he had an icy feeling in his lungs, similar to that from inhaling menthol (34).

Another person (of 2) exposed to 270 mg/m^3 (160 ppm) for 4 hours felt a slight constriction of the bronchae about 5 hours after the exposure period, but nothing later (34).

Workers exposed to very high (but unknown) concentrations of acetonitrile experienced shortness of breath and pains and tightness in the chest 3 to 12 hours after the exposure (2).

Of 28 rats exposed to 280 mg/m^3 (166 ppm) for 90 days (7 h/day, 5 days/week), one had macrophage clumps in alveolae and another had atelectasis (34).

In another group of 26 rats, exposed on the same schedule to 560 mg/m^3 (330 ppm), only 3 were observed to have bronchitis, pneumonia, atelectasis, and macrophage clumps in alveolae (34).

A rhesus monkey exposed to 560 mg/m^3 (330 ppm) 7 hours/day for 99 days and then sacrificed had chronic pneumonitis, indicated at autopsy by diffuse proliferation of alveolar septa with monocyte infiltration and alveolar adhesions (34). The experiment was repeated with three other rhesus monkeys, which were exposed to 600 mg/m^3 (350 ppm) 7 hours/day for 91 days. The overall picture at autopsy was the same, with focal emphysema

and diffuse proliferation of alveolar septa. Pigmented foci with macrophage accumulations were also found in lung tissue (34).

Three dogs were exposed to 600 mg/m^3 (350 ppm) 7 hours/day for 91 days and then sacrificed. Histological examination showed focal emphysema and proliferations of alveolar septa in the lungs (34).

Rats that inhaled 4700 mg/m^3 (2800 ppm) acetonitrile 2 hours/day for 4 days developed dyspnea and lung hemorrhages (18).

Rats that inhaled acetonitrile at the LD_{50} concentration developed pulmonary edema. Neither sodium nitrite nor thiosulfate could prevent the development of the edema, which probably indicates that it was not induced by the liberated cyanide (3).

5.3. Effects on the liver

Workers exposed to high (unknown) concentrations of acetonitrile had temporary enlargement of the liver (hepatomegaly) (2). One worker who died 6 days after acetonitrile poisoning had 1.184 mg acetonitrile /100 g liver tissue at autopsy (12).

Central diffuse swellings were observed in the livers of 7 of 27 rats exposed to 1100 mg/m^3 for 90 days (34).

5.4. Effects on the kidneys

Albuminurea has been observed in workers exposed to high (unknown) concentrations of acetonitrile (2, 12). In one fatal case of poisoning, analysis at autopsy showed 1.355 mg acetonitrile/100 g kidney tissue (12).

Diffuse swellings in renal tubuli were observed in 8 of 27 rats after exposure to 1100 mg/m^3 (655 ppm) 7 hours/day for 90 days (34). The same effects were observed in 2 of 3 rhesus monkeys exposed to 600 mg/m^3 (350 ppm) 7 hours/day for 91 days (34).

5.5. Effects on the digestive system

After a latency period of 3 hours, vomiting was the first symptom observed in a person who had drunk 40 g acetonitrile in a suicide attempt (20). Workers exposed to high concentrations during an accident became nauseous and vomited after a latency period of 3 to 4 hours (2, 11, 12, 17).

5.6. Effects on the heart and circulatory system

After massive exposure, workers developed first a rapid pulse and then a slow and irregular pulse (2).

Workers exposed to high (unknown) concentrations in an accident showed below-normal blood pressure and elevated blood levels of cyanide and thiocyanate (2, 12).

Congestion in blood vessels of the dura mater (the hard, fibrous membrane around the brain) was observed in a rhesus monkey that had died on the 51st day of exposure to 1100 mg/m^3 (660 ppm) 7 hours/day (34).

5.7. Effects on blood and blood-forming organs

Microscopic examination of rats exposed to 1100 mg/m^3 (655 ppm) for 90 days revealed no changes in the spleen (34).

5.8. Effects on the central nervous system

In a case of fatal poisoning, autopsy revealed 0.022 mg HCN/100 g brain tissue (12), despite the fact that the patient had received medication for HCN poisoning: dicobalt tetracemate and hydroxy cobalamine.

Focal brain hemorrhages were observed in 1 of 5 rats exposed to 1100 mg/m^3 (655 ppm) 7 hours/day for 90 days (34). Subdural hemorrhages were also found in all 4 monkeys that survived exposure to 560-600 mg/m^3 (300-350 ppm) 7 hours/day for 3 months (34).

In acute toxicity studies, rats were given acetonitrile per os and the time from dosage to the first appearance of symptoms – trembling and convulsions – was measured. With a dose of 5370 to 6980 mg/kg body weight, these symptoms appeared after about 3 hours. When rats were given equal amounts of acetonitrile and acetone, the lowest dose group (800 mg/kg) developed convulsions after about 17 hours, but the latency increased with increased dose (14).

5.9. Effects on the peripheral nervous system

In a couple of serious cases of poisoning, tendon reflexes could not be elicited in the acute stage. These reflexes normalized as the patients recovered (2).

5.10. Effects on glands

Effects on the thyroid gland. One of nine persons exposed in an accident was afterward observed to have a somewhat enlarged thyroid, but no such change could be found in the person who died as a result of the accident (2).

It has been noted that an intramuscular injection of 0.05 to 0.1 ml acetonitrile causes exophthalmia and thyroid hyperplasia in rabbits (25, 26, 27, 28). The degree of exophthalmia could be related to the hyperplasia, and it could be prevented by pre-treatment with iodine (26).

Thyroid hyperplasia could also be induced by acetonitrile in rats and mice (12, 40), but the rats did not develop exophthalmia (12).

Effects on the adrenalin glands. No effect was noted in the adrenalin glands of rats that had received 18 mg acetonitrile /kg body weight (0.432 mmol/kg) subcutaneously 3 times a day for 4 days (41), but rats that had had their adrenalin glands surgically removed showed greatly increased sensitivity (up to 100 times) to acetonitrile, measured by LD_{50} determinations (6).

6. IMMUNOTOXICITY AND ALLERGIES

There are no reports discussing immunotoxicity or allergies.

7. MUTAGENICITY, GENOTOXICITY

Acetonitrile is not mutagenic in Ames' tests, either with or without metabolic activation (36).

Mice were given intraperitoneal injections of acetonitrile in a dose corresponding to 60% of the LD_{50}: a weak positive effect could be detected in a micronucleus test 24 hours later (36). In Saccharomyces cerevisiae strain D7, acetonitrile induced low levels of gene conversions in the presence of phenobarbital-induced liver homogenate, but no increase in the number of ile^+-revertants could be observed under any circumstances (36).

Acetonitrile induces mitotic aneuploidy in Saccharomyces cerevisiae, but does not induce either recombinations or point mutations (48).

8. CARCINOGENICITY

There are no cancer studies concerning acetonitrile. Nor does its metabolite cyanide seem to be carcinogenic (4).

9. REPRODUCTION TOXICOLOGY

The only available data are from animal experiments.

Male and female rats received subcutaneous doses of 0.05 ml acetonitrile daily for 2 months, after which they were mated. Their sexual functions seemed entirely normal (13). Rats that had inhaled 1100 mg/m^3 acetonitrile (655 ppm) 7 hours/day for 90 days had completely normal testicles on microscopic examination (34).

Mated Sprague-Dawley rats received by gavage doses of 0, 125, 190 or 275 mg/kg daily during days 6 to 19 of pregnancy. In the highest dose group there were a few cases of toxicity among the dams and some embryotoxic effects (increases in early resorptions and post-implantation losses). The young of rats in this group showed a higher incidence of incomplete skeletal ossification. Since this dose level caused some mortality among the dams, however, the authors concluded that the embryotoxicity was a reflection of the toxicity to the mothers. No teratogenic effects were observed at any dose level (21). Rats that received acetonitrile orally showed no changes in pregnancy, and there was no increase in resorption of entire litters or perinatal toxicity in the young, not even at doses that were lethal for the majority of the mothers (38).

Syrian hamsters exposed to 3100 or 6500 mg/m^3 (1800 or 3800 ppm) for 60 minutes showed no ill effects, and their young had no deformities (44).

Hamsters exposed to 8500 mg/m^3 (5000 ppm) were irritated by the vapor, indicated by profuse saliva secretion. Their young had skeletal abnormalities (dysrraphia). The effects were much more pronounced at exposure to 13,700 mg/m (8000 ppm) (44). The author believes it is the cyanide liberated from the acetonitrile in vivo that causes the fetal abnormalities, since injections of sodium thiosulfate counteracted the symptoms of poisoning and only a few anomalies were noted in rib bones.

10. EXPOSURE/ EFFECT AND RESPONSE RELATIONSHIPS

The relationship between exposure to acetonitrile and subjective symptoms in human subjects is given in Table 3. All 3 subjects exposed for 4 hours to 70 mg m^3 (40 ppm) noticed the odor, but after a couple of hours the sense of smell became "saturated." A few hours after termination of exposure one of the three felt slight discomfort in the form of tightness in the chest. The two subjects exposed to 135 mg/m^3 (80 ppm)

Table 3. Reactions after exposure to acetonitrile.

mg/m^3	ppm	Time	Reaction	Ref.
270	160	4 h	slight constriction in bronchae (1/2)	34
135	80	4 h	no reaction (0/2)	34
70	40	4 h	odor noted (3/3); slight tightness in chest (1/3)	34
30	17		no effect	2

reported no discomfort, but one of the two exposed to 270 mg/m^3 (160 ppm) reported becoming red in the face and feeling some bronchial constriction a few hours after the exposure. The concentration of thiocyanate in urine increased a bit in one of the subjects in the low-dose (40 ppm) group, but not in the others. The content of cyanide in blood did not change during the exposure in any of the 7 subjects (34).

Table 4. Effects of exposure to acetonitrile for some animal species.

Exposure mg/m^3	Exposure ppm	Time	Species, Effect	Ref.
27,000	16,000	4 h	Dog: all died.	34
27,000	16,000	4 h	Rat: LC_{50}.	34
9,500	5,655	4 h	Guinea pig: LC_{50}.	34
4,800	2,828	4 h	Rabbit: LC_{50}.	34
4,700	2,750	2 h/d, 4 d	Rat: anurea, dyspnea, hemorrhages in brain and lungs.	18
1,100	655	7 h/d, 90 d	Rat: temporary lung damage (10/27); focal brain hemorrhages, diffuse kidney inflammation (8/27); diffuse liver inflammation (8/27).	34
600	350	7 h/d, 91 d	Dog: hematocrit and Hb dropped, but rose toward end of exposure period.	34
560	330	7 h/d, 99 d	Monkey: irritability; postmortem: subdural hemorrhages, chronic pneumonitis, pleural adhesions.	34
560	330	7 h/d, 90 d	Rat: bronchitis, pneumonia, atelectasis, macrophage clumps (3/26).	34
280	166	7 h/d,	Rat: Macrophage clumps in lungs (1/28); atelectasis (1/28).	34

The lowest concentration of acetonitrile used in short-term tests on experimental animals is 4700 mg/m^3. Rats exposed to this concentration 2 hours/day for 4 days developed anurea, dyspnea and hemorrhages in various organs (18). No short-term inhalation studies at lower exposure levels have been reported, and it is thus impossible to state a dose-effect relationship for experimental animals.

With regard to long-term exposure to acetonitrile, there are no data for humans. For experimental animals, the exposure/effect relationships observed with 3 months of exposure to acetonitrile are shown in Table 4.

The lowest tested dose is 280 mg/m^3 (166 ppm), to which rats were exposed 7 hours/day for 90 days. One of 28 animals had atelectasis (collapsed alveolae) and accumulations of macrophages in the lungs. At 560 mg/m^3 (330 pm), three of 26 animals also developed bronchitis and pneumonia, and at 1100 mg/m^3 (655 ppm) 37% of the animals had temporary lung damage. In addition, the highest dose group had diffuse swellings in liver and kidneys, as well as focal brain hemorrhages (34).

Brain hemorrhages and effects on lungs were noted in monkeys after exposure to 560 mg/m^3 (350 ppm) for the same length of time (34).

11. RESEARCH NEEDS

Except for reports from a few accidents, there are no studies on the effects of occupational exposure to acetonitrile. Animal exposure studies covering periods longer than 90 days are lacking, and there are no epidemiological studies. Toxicokinetic studies on the role of cyanide and thiocyanate in acetonitrile poisoning are desirable. Such studies could also help identify biological exposure indicators.

12. DISCUSSION AND EVALUATION

There are no epidemiological studies of workers occupationally exposed to acetonitrile.

Acetonitrile at room temperature is considered relatively harmless. Since the boiling point is relatively low (about 80°C) there is risk for high air concentrations if it is heated. The cases of poisoning that have been reported occurred when acetonitrile was heated. The symptoms have usually appeared after a latency of a few hours. In these cases elevated levels of cyanide and thiocyanate have been found in blood. This probably indicates that the poisoning was not caused by acetonitrile per se, but by its metabolites. The symptoms are very similar to those of cyanide poisoning, and in these cases the blood cyanide level was also greatly elevated. Whether one or several factors cause the poisoning can not be determined from available data.

In the experimental study in which volunteers were exposed for 4 hours to 40, 80 or 160 ppm acetonitrile, no increases of cyanide in blood or thiocyanate in urine were observed. Two of the subjects reported tightness of the chest and bronchae. It is worth noting that these subjective symptoms didn't appear until a few hours after termination of exposure. The results of the study indicate that, with low-level exposure to acetonitrile, measurement of blood concentrations of cyanide or/and urine concentrations of thiocyanate can not be correlated with early symptoms.

Even though data on human exposure are limited, it appears that the critical effects are those on the respiratory passages. This is further indicated by results from animal experiments, where effects were noted in lungs of rats after 90 days of exposure to 280 mg/m^3 (166 ppm), the lowest dose tested.

When hamsters were exposed for 60 minutes to acetonitrile concentrations of 8500 mg/m^3 (5000 ppm) or higher during the 8th day of pregnancy, skeletal abnormalities were noted in the young. The females were also affected at these concentrations. Exposures of 6500 mg/m^3 (3800 ppm) or lower produced no abnormalities. If the exposed dams were also given intraperitoneal injections of sodium thiosulfate (the antidote to cyanide), the number of anomalies in the high dose groups dropped: this indicates their cause to be the metabolically formed cyanide.

13. SUMMARY

G. Heimbürger, P. Lundberg. Acetonitrile. Nordic Expert Group for Documentation of Occupational Exposure Limits. 86. Arbete och Hälsa 1989:.. pp. 151-176.

This summary of the literature is intended for use as a scientific basis for establishing occupational exposure limits.

Accidental exposure to acetonitrile has resulted in symptoms of poisoning within a few hours of exposure. Subjective symptoms, bronchial constriction and tightness in the chest, have been reported after 4 hours of exposure to 70 to 270 mg/m^3. The lowest dose studied in long-term animal experiments is 280 mg/m^3. This produced effects in the lungs of rats.

It has not been established whether the toxic effects are due to acetonitrile itself or to its metabolites, such as cyanide or thiocyanate. Judging from available data, the critical effect of exposure to acetonitrile is its effect on the respiratory system.

Original in Swedish; English translation. 48 references.

Key words: Acetonitrile, Occupational exposure limit, Respiratory effects, Cyanide, Thiocyanate.

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Appendix I. List of permitted or recommended maximum concentrations of acetonitrile in air.

Country	mg/m^3	ppm	Year	Note	Ref.
BRD	70	40	1988		5
Denmark	70	40	1988		2
Finland	70	40	1987		11
	105	60		15 min.	
France	70	40	1988	S.P.	12
Great Britain	70	40	1988		4
	105	60		STEL	
Iceland	70	40	1978		9
The Netherlands	70	40	1989		7
Norway	50	30	1989		1
Sweden	-	-	1988		3
U.S.A. (ACGIH)	70	40	1988-89		10
	105	60		STEL	
(NIOSH)	34	20	1978		8
(OSHA)	70	40	1989		13
	105	60		STEL	
U.S.S.R.	10		1978	gas	6

STEL = Short-term exposure limit

S.P. = Skin penetration

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METHYL FORMATE

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1. PHYSICAL AND CHEMICAL DATA

CAS No.:	107-31-3
Systematic name:	Methyl formate
Synonyms:	Methyl methanoate, Methyl ester of formic acid
Formula:	$C_2H_4O_2$
Structure:	$H-\overset{\overset{O}{\|}}{C}-O-CH_3$
Molecular weight:	60.05
Density:	0.987 g/ml
Boiling point:	31.3°C
Vapor pressure:	52.6 kPa
Odor threshold:	250-500 mg/m^3 (2, 32)
Conversion factors:	1 ppm = 2.5 mg/m^3, 1 mg/m^3 = 0.4 ppm

Methyl formate at room temperature is a colorless, flammable liquid with a pleasant aroma. It is soluble in water (1:3) and mixes with alcohol and ether.

2. USES, OCCURRENCE

2.1. Uses

Methyl formate is one of a number of alkyl esters used in industry. It is used as a solvent for methyl cellulose, as an insecticide and disinfectant, and as an intermediary in the production of pharmaceuticals. Methyl formate is also used as a hardener for phenol esters used to bond forms and cores for metal casting. It has been identified in cigarette smoke (19).

2.2. Air concentrations in the working environment

No published reports were found concerning basic monitoring of methyl formate in working environments. This might be explained by the lack of a generally accepted analytical method.

Monitoring of methyl formate around various operations in some Swedish aluminum foundries gave the following results: exposure measurements made during two work shifts yielded an average value of 2.5 mg/m^3 for block forming, with a geometric standard deviation of 1.6. For knocking-out and casting the values were below the detection limit of the sampling and analysis method (<4 mg/m^3 with a 5-liter air sample). For core removal, measurements showed a geometric average value of 11 mg/m^3 with a geometric standard deviation of 2.4 (36).

2.3. Methods for analysis of air concentrations

Sampling and analysis methods for methyl formate were developed for monitoring the working environment in foundries (36). The samples were taken according to Swedish National Board of Occupational Safety and Health Method 1013 ("Provtagning med adsorptionsrör och analys med gaskromatografi") (5) or by Method 1500, "Hydrocarbons 1311-36-126" in the NIOSH Manual of Analytical Methods (30).

Samples are taken with a pump flow of 10 to 200 ml/minute and a maximum sample volume of 5 liters. The sampling and analysis methods are based on adsorption on a solid adsorbent (activated charcoal) and eluation in carbon disulfide, followed by gas chromatographic determination with a flame ionization detector. The detection limit is 0.02 mg per sample, or 4 mg/m^3 for a 5-liter air sample (36).

Gas chromatographic methods for analysis of air samples and headspace analysis of biological materials are described in the literature (16, 19).

Direct-reading IR instruments are also described (22): the analytical wavelength is 8.5 µm and the detection limit is 0.2 mg/m^3.

3. KINETICS

3.1. Uptake

Methyl formate is absorbed via the lungs (4, 6, 37). This has been shown by symptoms of intoxication in workers exposed primarily by inhalation (11) and by a study in which hamsters were exposed to methyl formate by inhalation only (34).

Methyl formate is also absorbed in the digestive tract (4, 6, 37). This is supported by a study in which rabbits were given oral doses of methyl formate and its narcotic and lethal effects were noted (29).

Methyl formate is also absorbed by the skin (4, 6). One case report describes poisoning of a 19-month-old baby that was treated with a methyl formate disinfectant on a bare spot on the scalp. The baby showed symptoms of severe poisoning after about 20 minutes, and died a short while later (15).

3.2. Distribution

Analysis of body fluids in a case of poisoning showed distribution of methyl formate to brain, liver and stomach. Methyl formate, methyl alcohol and formic acid could be detected in brain and liver distillate: 0.23 mg/g in brain substance and 0.22 mg/g in liver (total amounts re-calculated to methyl formate). Only traces of methyl alcohol could be found in the stomach (15).

No information was found on the distribution coefficient of methyl formate in body tissues. Its distribution coefficient between vegetable oil and water is 1:2 at 25°C (29).

3.3. Biotransformation

In an in vitro experiment, increased oxygen consumption was noted in preparations of liver, kidney, striated muscle, spleen and cerebral cortex after exposure to methyl formate. The results indicated not only distribution of methyl formate in these organs, but also metabolic activity (8).

The oldest of the metabolic studies reports methyl alcohol and formic acid to be the primary metabolites, and asserts that methyl formate is biotransformed mainly to methyl alcohol, which is then oxidized to formaldehyde and formic acid (14).

Methyl formate is spontaneously hydrolyzed in body fluids, and is metabolized to methyl alcohol and formic acid (6):

methyl formate <—> methyl alcohol + formic acid <—> CO_2
formaldehyde <—> formic acid <—> CO_2

The amount of umetabolized methyl formate is small (11). There is some discussion as to whether the main biotransformation pathway goes via hydrolysis of methyl formate to methyl alcohol and formic acid, which are further metabolized to carbon dioxide, or goes via breakdown of methyl alcohol to formaldehyde and then to formic acid and carbon dioxide.

In the case of poisoning described above, body fluids were analyzed and methyl formate, methyl alcohol and formic acid were found in various organs. The minimal amounts of methyl alcohol in some fractions indicated that formic acid was formed primarily via formaldehyde (15). In an in vitro study it was noted that the formic acid fraction was oxidized in liver and striated muscle, but not in kidney; the methyl alcohol fraction was considered to be unmetabolized, however, and it was therefore concluded that there is no risk of classic methyl alcohol poisoning with exposure to methyl formate (8).

The symptoms shown by experimental animals that died after exposure to methyl formate were more like those of formic acid poisoning (vomiting, loss of consciousness) than those indicating a general reduction of central nervous system functions. The latter type are more common after exposure to the higher ester homologues (6), since methyl formate is much more readily hydrolyzed than other alkyl esters of formic acid.

Methyl formate can also be synthesized in vivo from methyl alcohol and formaldehyde by activation of alcohol dehydrogenase. This fact, taken together with the lipid solubility of methyl formate, raises the possibility that methyl formate, either directly or via lactate accumulation, is the main source of the toxic effects causing visual disturbances and blindness in cases of methyl alcohol poisoning (11, 23).

The symptoms seen in cases of acute formic acid poisoning, together with the low concentrations of methyl formate in body fluids, indicate a rapid hydrolysis of methyl formate to methyl alcohol and formic acid, followed primarily by biotransformation of formic acid to carbon dioxide. Only small amounts of methyl alcohol are broken down via formaldeyhyde.

A secondary breakdown of methyl alcohol via formaldehyde to more formic acid and then to carbon dioxide is possible, but this, like the balance between methyl alcohol and formic acid, is a matter of some discussion. Data from both animal experiments and case studies admit the possibility of several different primary biotransformations, in which both methyl alcohol and formic acid metabolism are conceivble.

3.4. Elimination

There are differing opinions on the biotransformation of methyl formate, primarily its quantitative aspects (6, 8, 11). It is probable that methyl formate is metabolized via methyl alcohol to formic acid and further to carbon dioxide, with a

secondary breakdown of the methyl alcohol via formaldehyde and formic acid to carbon dioxide (6, 11, 29). There is no information on excretion of unmetabolized methyl formate via either lungs or kidneys.

3.4.1. Respiratory passages

The methyl alcohol formed from methyl formate is eliminated via the lungs along with the carbon dioxide. There are no quantitative data for exposure to methyl formate. With skin exposure to methyl alcohol (absorbed dose 1.67 to 1.71 g), methyl alcohol excretion in exhaled air was 212 µg/min 30 minutes after exposure and 23 µg/min 300 minutes after exposure. Oral administration of methyl alcohol (absorbed dose 1.67 g) resulted in methyl alcohol excretion of 268 µg/min 30 minutes after exposure and 35 µg/min 300 minutes after exposure (10). Elimination after peroral and skin exposure was thus about the same.

3.4.2. Kidneys

Methyl alcohol formed from methyl formate can also be excreted in urine. There are no quantitative data. Exposure to vapors of methyl alcohol in concentrations of 300, 205 and 102 mg/m^3 for 8 hours resulted in methyl alcohol concentrations of 9.2, 6.4 and 3.5 mg/l urine immediately after termination of exposure, and 2, 1.7 and 1.5 mg/l 8 hours later. The half time for methyl alcohol was estimated to be 1.5 to 2 hours (33).

Unmetabolized formic acid is excreted in urine (37). Studies correlating exposure to formic acid with its excretion in urine showed that concentrations in urine increased 15 hours after termination of exposure. This indicates a long biological half time and thus a clear risk for accumulation (25).

3.4.3. Digestive tract

Elimination of unmetabolized methyl formate by the digestive tract was observed in a baby after accidental skin exposure (15). Data from animal experiments indicate that methyl alcohol is also excreted via the digestive tract (38).

3.5. Biological exposure indicators

There are no studies of the correlation between exposure to methyl formate and its metabolites in blood, urine or exhaled air. There is therefore no reliable biological exposure indicator for methyl formate. It is probably possible to show methyl formate uptake by metabolite analyses. Some experiments with methyl alcohol and formic acid, described below, indicate possible exposure indicators.

There are no studies correlating methyl alcohol in blood and in exhaled air. However, the connection between formic acid in urine and methanol in exhaled air has been studied: the absence of a correlation indicates that methyl alcohol in exhaled air reflects acute exposure, while formic acid reflects longer exposure (7).

On the other hand, several authors have demonstrated a good correlation between methyl alcohol in blood and in urine, and their results are in good agreement (3, 12). Average blood concentrations of 15 to 9 mg/l corresponded to average urine concentrations of 22 to 20 mg/l; the same study showed good correlations between methyl alcohol in exhaled air and in blood and urine. Exposure to 200 mg/m^3 methyl alcohol corresponded to a methyl alcohol concentration of about 40 mg/l in urine (3).

A correlation between methyl alcohol in air (thus indirectly methyl alcohol in blood) and formic acid in urine has been demonstrated. Average methyl alcohol concentrations of 111,

131 and 174 mg/m^3 resulted in increases of formic acid in urine (7).

A correlation between formic acid in blood and in urine has also been demonstrated. Increases of formic acid in urine from 13.3 ± 3.9 mg/l to 20.2 ± 7 mg/l corresponded to rises in blood from 3.2 ± 2.4 mg/l to 7.9 ± 3.2 mg/l (7).

Good correlations have also been demonstrated between both formic acid and methyl alcohol exposure and formic acid in urine. Exposure to 260 mg/m^3 methyl alcohol gave a formic acid concentration in urine of 80 mg/g kreatinin, and exposure to 9 mg/m^3 formic acid gave a formic acid content of 10 mg/g kreatinin (26).

It is possible to study the total uptake of methyl formate by enzymatic transformation of methyl alcohol and formic acid to methyl formate, followed by gas-chromatographic analysis (1).

4. GENERAL TOXICOLOGY

4.1. Toxic effects

Our knowledge of the toxic effects of methyl formate is incomplete, and based on only 8 published reports (11, 13, 14, 15, 18, 20, 29, 34). Four of these were published in 1940 or earlier, and four in 1960 or later. Only two of them discuss effects on humans: a case report of a poisoned baby and clinical finds from examination of exposed French workers (11, 15). One of the experiments on guinea pigs provides considerable information (34). In general, however, effects are not specifically reported.

The toxic effects of methyl formate can be divided into types: loss of consciousness, damage to organs and central nervous system effects.

4.1.1. Narcotic effects

Narcotic effects on man have not been studied .

There are several animal studies that report loss of consciousness, but without stating whether this is a direct narcotic effect or is caused by lung damage and consequent anoxia (11, 14). General information, without reference to specific research results, is given in one reference (14). Methyl formate is considered to have the weakest narcotic effect of all alkyl esters (29).

In one experiment, tadpoles and rabbits were used to study narcotic and lethal doses of various alkyl esters. The animals were divided into groups and exposed to different concentrations, and the time of appearance of various symptoms was then recorded. Exposure continued either until the animals died or until no new effects were observed.

For rabbits, both the ND_{50} (Narcotic Dose) and LD_{50} for methyl formate was 1,622 mg/kg. For the other esters, ethyl formate and higher alkyl esters, there was a weak drop of ND_{50} values but the LD_{50} remained the same. For tadpoles the picture was similar, except that the ND_{50} for all tested alkyl esters, including methyl formate, was lower than the LD_{50} (29). Neither does this study state whether the loss of consciousness is an expression of narcotic effect or an indication of toxic damage.

The effects of exposure to methyl formate were studied in experiments with guinea pigs. The level for narcotic effect/loss of consciousness was reported to be 125,000 mg/m^3 after 20 to 25 minutes, 62,500 mg/m^3 after 40 to 50 minutes, and 25,000 mg/m^3 after 120 to 150 minutes. Lower exposure levels did not result in loss of consciousness. The lethal concentration seems to be about 20,000 mg/m^3 (34).

4.1.2. Toxic effects

As early as 1935, Duquenois and Revel described the symptoms of French workers exposed to vapors from a solution containing methyl formate and some other alkyl esters. The exposure resulted in poisoning with CNS, visual and respiratory symptoms (11). A few years later, Flury and Neuman reported a study of methyl formate's effects on cats: toxic effects leading to vomiting and death were observed. The cats were exposed to 25,500 mg/m^3 for 120 to 180 minutes (13).

In 1940, Gettler described a case of a 19-month-old baby whose head was treated with a bactericide containing methyl formate. The baby developed symptoms of poisoning and died of heart failure (15).

4.2. Factors that affect toxicity

There is no information in the literature.

4.3. General observations

LD_{50} for rabbits, oral administration:	1,622 mg/kg	(31)
LCLO for guinea pigs:	25,000 mg/m^3	(37)
LC_{50} for mice:	7,500 mg/m^3	(20)
LC_{50} for guinea pigs:	50,000 mg/m^3	(37)

5. EFFECTS ON ORGANS

5.1. Effects on skin and mucous membranes

Schrenk et al, in a large study with guinea pigs, reported irritation to mucous membranes in nose and eyes after 8 hours of exposure to 8,750 mg/m^3, and the same symptoms after only two minutes of exposure to 25,000 mg/m^3 (34). The same study cites another report stating that human subjects experienced

neither eye nor nose irritation with one minute of exposure to 3,750 mg/m^3, although the odor was apparent. Another study reports that the irritative effects of methyl formate first appear at 8,750 mg/m^3 (32). Irritation of skin and mucous membranes is also mentioned in a review (37).

5.2. Effects on respiratory organs

Effects on lung function are reported in a case of poisoning: a 19-month-old baby developed cyanosis and irregular breathing after skin application of a solution containing methyl formate (15). The study of the French workers reports breathing difficulty and shortness of breath (11).

Larger doses were also reported to cause shortness of breath (dyspnea) in an experiment with rabbits to determine narcotic and lethal doses (29).

In the large exposure experiment with guinea pigs, the animals showed pronounced respiratory effects after 75 to 120 minutes of exposure to 25,000 mg/m^3 (34).

In the same study, the lungs of guinea pigs exposed for different lengths of time were given pathological examinations. Exposures to 125,000 mg/m^3 for 25 to 35 minutes, 62,500 mg/m^3 for 50 to 72 minutes, and 25,000 mg/m^3 for 150 to 175 minutes were all lethal to the animals. Bloody exudations were noted on lung surfaces. The lung examinations showed emphysema and edema, and lung vessels heavily congested with blood.

Lower exposures – 10 minutes at 125,000 mg/m^3, 30 minutes at 62,500 mg/m^3, 30 to 60 minutes at 25,000 mg/m^3 and 180 to 480 minutes at 8,750 mg/m^3 – were not lethal to the animals. Here, pathological examination of lungs showed slight blood congestion and indications of emphysema and edema. No such findings were made in animals from the three lowest exposure groups that were sacrificed 4 days after exposure, which indicates

that the effects are reversible. The animals with the highest exposure, 10 minutes at 125,000 mg/m^3, showed irreversible changes: slight swelling and edema. The guinea pigs exposed to 8,750 mg/m^3 for 30 to 60 minutes or 3,750 for 180 to 480 minutes showed no lung changes, either immediately after the exposure or 4 or 8 days later (34).

Henschler, in an unpublished work, reports toxic lung edema in mice exposed for 180 minutes to 1,250 mg/m^3 (20).

5.3. Effects on the liver

In the poisoning case, the pathological examination showed only that the liver was congested with blood; no histological examination was made (15).

The guinea pigs given medium-level exposures – 10 minutes at 125,000, 30 minutes at 62,500, 30 to 60 minutes at 25,000 or 180 to 480 minutes at 8,750 mg/m^3 – showed only slight liver enlargement. This was not seen in animals sacrificed 4 and 10 days after the exposure, however, except in the group exposed for 10 minutes to 125,000 mg/m^3. No pathological changes were found in the groups exposed to 8,750 mg/m^3 for 30 – 60 minutes or 180 – 480 minutes. No histological study was reported (34).

5.4. Effects on kidneys

Heavy blood congestion in a kidney is mentioned in the case report of poisoning (15). The study of the French workers included an exposure experiment: frogs given (unspecified) lethal doses also showed enlarged kidneys. No histological study is mentioned (11).

5.5. Effects on the digestive tract

Spastic, retching movements of the stomach wall were observed in guinea pigs at exposures ranging from 125,000 mg/m^3 for 10

– 20 minutes to 25,000 mg/m^3 for 75 – 120 minutes. This effect was not observed at concentrations below 8,750 mg/m^3, however (34).

5.6. Effects on the heart and circulatory system

The study of the French workers mentions patients with heart arrhythmia, and the same report also mentions heart effects in the form of tachycardia in guinea pigs exposed to methyl formate (11).

5.7. Effects on blood and blood-forming organs

There is no information in the literature.

5.8. Effects on the central nervous system

The study of the French workers mentions one patient who showed psychological disturbances such as euphoria, depression and loss of memory. Several of the exposed workers complained of visual problems, and one of them became completely blind, but he regained his sight about 2 weeks after termination of exposure. The same authors also reported an experiment in which exposed frogs showed coordination disturbances and deterioration of the nystagmus reflex (11).

Guinea pigs exposed to methyl formate showed signs of CNS effects – motoric disturbances and loss of coordination – after 10 to 20 minutes of exposure to 125,000 mg/m^3. Less pronounced disturbances of this type could be observed after longer exposures to lower concentrations, but were not observed at concentrations below 8,750 mg/m^3 (34).

5.9. Effects on the peripheral nervous system

There is no information in the literature.

5.10. Other organ effects

There is no information in the literature.

6. IMMUNOTOXICITY AND ALLERGIES

There is no information in the literature.

7. MUTAGENICITY, GENOTOXICITY

A case report describes three cases of leukemia in patients exposed to ethylene oxide. They had been working with sterilization of operation equipment, using a sterilizing liquid containing methyl formate. The authors speculate that the anti-bacterial effect of methyl formate may be expressed via an interaction with DNA, thus implying a possibility of mutagenic activity (21).

8. CARCINOGENICITY

There is no information in the literature.

9. REPRODUCTION TOXICOLOGY

There is no information in the literature.

10. EXPOSURE AND EFFECT / RESPONSE RELATIONSHIPS

No published reports were found that provide information on the relationship between dose and effect/response for humans. The relations between dose and effect/response for various

animal species are given in six of the reports mentioned above (13, 18, 20, 29, 34, 35).

An article by Amoore et al summarizes occupational exposure limits and odor thresholds, and the possibility of using the odor threshold as a warning signal for methyl formate is assessed (2). With an occupational exposure limit of 250 mg/m^3 and an upper odor threshold (at which everyone notices the odor) of 11,500 mg/m^3, methyl formate falls into a group of substances with odor thresholds too high to be useful as warning signals. Only 10% of subjects noted the odor of methyl formate at a concentraton of 250 mg/m^3 (2). In another study, the odor threshold was reported to be 5,000 mg/m^3 (28).

There is considerable individual variation in the ability to detect the odor of methyl formate (32). This work reports the lower threshold (the concentration noted by at least one exposed subject) to be 500 mg/m^3 and the upper threshold (the concentration at which everyone notes the odor) to be 6,875 mg/m^3.

Table 1 shows the results of inhalation studies made with laboratory animals. The table gives the species, concentration, exposure time and symptoms noted in the studies.

Table 2 shows the results of studies other than inhalation studies.

11. RESEARCH NEEDS

There is virtually no dose-effect or dose-response information for humans. There are no animal experiments on the effects of low exposures. Knowledge about effects on the central nervous system is particularly scanty. The biotransformation of methyl formate should be better understood, particularly since there are different opinions on the primary biotransformation path.

With regard to sampling and analysis of methyl formate in air, adsorbents other than activated charcol shold be tested and evaluated. Methyl formate has a tendency to diffuse through activated charcoal, which means that air volumes in samples must be extremely low.

Table 1. Inhalation toxicity of methyl formate.

Species	Conc$_3$ mg/m^3	Exposure (minutes)	Symptoms	Ref.
Guinea pig	125,000	25-35	All animals died.	(34)
Guinea pig	62,500	50-72	All animals died.	(34)
Rabbit	62,500	not given	All died after slight symptoms of narcosis, respiratory arrest, cramps.	(18)
Guinea pig	50,000 -62,000	120	Numbness, some died within 18 hours, 2 recovered.	(37)
Guinea pig	50,000 -62,500	60	2/3 died, 1/3 slowly recovered.	(37)
Guinea pig	50,000 -62,500	30	Pronounced drowsiness and numbness, recovery after 10 min.	(37)
Guinea pig	50,000 -62,500	5	Coughing, drowsiness, recovery after 10 min.	(37)
Cat	25,500	120-180	Lung edema, death.	(13)
Cat	25,000	90	Ataxia, narcosis.	(13)
Cat	25,500	20	Irritation of eyes and nose, drowsiness.	(13)
Guinea pig	25,000	150-175	All animals died.	(34)
Guinea pig	25,000	120-150	Loss of coordination, narcosis.	(34)
Guinea pig	25,000	75-120	Breathing problems, narcosis.	(34)
Guinea pig	25,000	6-15	Retching	(34)

(cont'd.)

Table 1 cont'd.

Species	Conc$_3$ mg/m^3	Exposure (minutes)	Symptoms	Ref.
Guinea pig	25,000	2-3	Irritation of eyes and nose.	(34)
Guinea pig	22,500 -25,000	60-120	Severe irritation of skin and mucous membranes, recovery after 10 min, no deaths, narcosis.	(37)
Guinea pig	22,500 -25,000	30	Drowsiness, severe eye watering.	(37)
Guinea pig	22,500 -25,000	1	Irritation of mucous membranes	(37)
Cat	15,000	60	Pneumonias, a few deaths after termination of exposure.	(13)
Cat	15,000	50	Irritation of mucous membranes, dizziness.	(13)
Guinea pig	8,750	480	Irritation of eyes and nose, retching, stomach cramps.	(34)
Mouse	7,500	180	Approximate LC_{50}	(20)
Guinea pig	3,750	480	Irritation in nose	(34)
Mouse	1,250	180	Sub-lethal lung edema	(20)

Table 2. Toxicity of methyl formate exposures in ways other than inhalation.

Species	Admin. method	Dose	Symptoms	Ref.
Rabbit	Oral	1622 mg/kg 1600 mg/kg	LD_{50} ND_{50}	(29) (29)
Rabbit	Subcutaneous injection		Death with severe cramps	(35)
Rabbit	Subcutaneous injection	4 x 0.5 mg/kg	Death from respiratory arrest, cramps.	(18)

12. DISCUSSION AND EVALUATION

With regard to man, the data given in this survey is mostly obtained from case studies of poisoning; other information on toxicity comes mostly from inhalation studies with experimental animals.

It is generally accepted that methyl formate is taken up via lungs, digestive tract and skin, and that it is distributed to brain, liver and stomach. Biotransformation is also understood, at least qualitatively. Methyl formate is metabolized to formic acid and methyl alcohol, and only minimal amounts remain unmetabolized. Whether further breakdown occurs via metabolism of methyl alcohol or of formic acid is a matter of debate. Observations from case reports and data from animal experiments indicate that both these pathways are possible.

A starting point for establishing occupational exposure limits might therefore be the formation of formic acid. There are proposals in the literature for a highest acceptable 24-hour excretion of formic acid in urine (26). This excretion can be used to calculate the highest permissible air concentration of methyl formate. Since understanding of the retention of methyl formate and its breakdown to formic acid is inadequate, however, such a calculation can not be used as a basis for occupational exposure limits.

The most important general toxicological effects seem to be those on the central nervous system, such as visual disturbances, which have been described in both experimental animals and man.

Irritation of skin and mucous membranes and effects on respiratory passages have been described in both man and experimental animals. There is no such documentation for effects on liver, kidneys, digestive tract or heart.

Only one study has presented a rough dose-effect calculation for irritative effects on human subjects. Other quantitative data come from animal experiments.

Methyl formate causes irritation only at fairly high concentrations, and the safety margin for damage to other organs may therefore be small. Moreover, long-term exposure to concentrations below the odor threshold may also have harmful effects. A comparison with methyl acetate can therefore be justified. Methyl acetate is reported to cause irritation at a concentration of 30,496 mg/m^3, nearly 4 times the irritation threshold for methyl formate. On this basis, the ACGIH has given methyl formate about 1/4 the threshold limit value of methyl acetate: 250 mg/m^3 (9).

13. SUMMARY

H Westberg, C-G Ohlson. Methyl formate. Nordic Expert Group for Documentation of Occupational Exposure Limits.

The literature on methyl formate was reviewed to obtain a basis for a discussion of occupational exposure limits.

Irritation of skin and mucous membranes, effects on respiratory organs, cardiac arrhythmia and effects on the central nervous system have been observed in humans as well as in animals. Effects on the optic nerve and blindness have also been reported.

Dose-effect relationships have been studied only in animal experiments, except for one report of irritative symptoms in man.

Data on dose-effect relationships for humans are not sufficient to support a statement of critical effect. Judging from animal data, the critical effect is that on the respiratory

organs. In one animal experiment respiratory effects were observed at concentrations of about 1,250 mg/m^3, three times the odor threshold for human subjects.

38 references.

Key words: Methyl formate, methanol, formic acid, skin and mucous membranes, central nervous system, blurred vision, blindness, occupational exposure limits.

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Appendix I. Maximum air concentrations of methyl formate stated in occupational health regulations or recommendations in some countries.

Country	mg/m^3	ppm	Year	Note	Ref.
BRD	250	100	1988	Irritative	4
Denmark	250	100	1988		2
Finland	250	100	1987		
	375	150		15 min.	8
France	250	100	1988		9
Great Britain	250	100	1987		3
	375	150		10 min.	
Holland	250	100	1989		5
	500	200		15 min.	
Iceland	250	100	1978		6
Norway	125	50	1989		1
Sweden	-	-	1987		10
USA (ACGIH)	250	100	1988-89		
	375	150		STEL	7
(OSHA)	250	100	1989		
	375	150		STEL	11

STEL = short-term exposure limit

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PAPER DUST

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APPENDIX. List of threshold limit values concerning dust (organic, cellulose or paper). 244

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1. BACKGROUND

Exposure to paper dust exists in all trades where papers are handled. High levels mainly occur in the paper producing industry but high levels also exist in the construction trade when attics are insulated with pulverized paper. Low grade exposure to paper dust can also exist among printing houses, book binderies and offices (59).

Documentation of the health effects of exposure to paper dust has been done almost exclusively by the paper industry. This document will therefore review exposure levels and health effects of exposure to paper dust based on studies from the paper manufacturing industry. The document will not review health effects associated with paper handling in offices, such as the problems with self copying paper.

Paper consists of compressed cellulose fibres. These are either purified from wood or produced from waste paper. When paper is produced the cellulose fibres are dissolved in water together with many additives. Then a slurry of the mixture is poured out on a moving wire screen that allows the water to drain off, leaving behind a mat of the blend that is then run around steam heated drying cylinders. The produced paper is then collected on large rollers which are cut or rerolled.

A lot of different qualities of paper are produced. The different qualities are made by varying the proportions of cellulose fibres and different additivies. In principal the following types of paper can be distinguished: printing paper, newsprint, craft paper, fibre board and soft paper.

Paper dust consists of cellulose fibres, cellulose particles and the rest comes from the used additives. The composition of paper dust is not completely known but some investigations have shown that about 80 % of the dust consists of organic materials. The remaining 20 % consists of inorganic materials most likely arising from the earlier mentioned additives (5, 14, 24, 70).

2. OCCURRENCE AND EXPOSURE

2.1 Occurrence

There are three main types of pulp: mechanical pulp, chemical pulp and pulp from waste paper. Pulp differs in regard to length of the cellulose fibres. From the point of dustiness this is an important characteristics as paper produced from pulp with short fibres has a higher tendency to emit dust. Chemical pulp has the longest fibres and waste pulp has the shortest fibres.

Different types of paper consist of varying proportions of different pulps. Simplified it can be stated that soft paper used in the production of napkins and toilet papers has high (80 %) proportion of waste pulp. More expensive qualities of paper, for instance printing papers, have on the other hand a high proportion of chemical pulp.

The pulp arrives at the paper mill either in large bales or as waste paper. Later on, the pulp is resolved in water in the pulp chest. The mixture (stock) is pumped into a mixture vat where different additives such as filling agents, coating agents and colours are added (see 2.2). The stock is then pumped through the head box to the wire screen where the water is drained off. Most of the water that remains is further eliminated through pressing and heating. The produced paper is then handled in different ways. It can be "crêped" in conection with the drying cylinder in the production of soft paper. It can also be coated or smoothed in the production of printing paper. Finally, the paper is collected in big rolls which later are cut, folded or rerolled into suitable products. This final production step is called converting.

The emission of dust in paper production depends on a lot of factors. The length of the cellulose fibres was mentioned earlier. Short fibres are considered to come loose from the web easier especially when the web has a high velocity.

The velocity of the web is also related to dust emission. Earlier

the paper machines and converting machines had slow velocities and consequently emitted less dust. Nowadays the velocities have markedly increased, particularly in soft paper mills and newsprint mills where velocities up to 1500 m/min exist. In smaller paper machines and in the production of different kinds of special paper the velocities are slower, often about 200 m/min (5, 36).

Paper with a high degree of moisture emits less dust than dryer paper. This can be observed for instanse in soft paper mills where production of paper towels, which are produced of a thicker and more moist paper, emits less dust than the production of toilet paper (70).

The dust levels in the paper mills depend also on occurrence and performance of evacuation pumps that often are situated above the paper machines, cutting machines and converting machines (7). The dust levels are also dependent on the function of the general ventilation and of the size of the factory hall.

In paper mills the dust exposure varies with different occupational categories (23, 24, 70). In years past, the workers who worked with the paper machines and the rolling machines were highly exposed. However, their exposure has been reduced during the recent years. Previously the machines were manoeuvred from control panels close to the machines but today most paper machines are operated from enclosed control rooms. Consequently, the extent to which the workers are exposed to dust has markedly decreased. High exposure levels occur however, with breakdowns, accidents and cleaning.

2.2 Additives

In paper production a lot of chemicals are added to the stock (2, 7, 8, 36, 39, 45). The most important additives are shown in table 1. The concentrations and the compositions vary from time to time and also depend on which paper qualities that are produced.

Table 1. List of the main additives used in the paper industry.

Filling agents	**Disperging agents**
Asbestos	**Coating agents**
Talc	Melanine resin
Titaniumdioxide	Casein
China clay	**Latexes**
Aluminiumhydroxide	Calciumcarbonate
Bariumsulphate	Aluminiumhydroxide
Wet strength agents	Bariumsulphate
Polyvinylamideresin	Colophony
Whitening agents	**Slime controling agents**
Retention agents	Organic bromic
Anti-foaming agents	compounds
Waxes	**Metylenbisthio-**
Fatty acids	cyanate
Talloilrosin	Pentachlorophenol
Dyes	Mercury compounds
Azodyes	Etylenediamine
Titaniumdioxide	

Occasionally for some of the additives, environmental samplings exists, but in most cases documented samplings are missing. However, it is of importance to get an opinion about the additives since they probably are one of the major constituents in the paper dust.

Asbestos was previously, at least in the Swedish paper industry, used as filling agents in some types of special paper (72). Furthermore, the talc that was used in paper mills was sometimes contaminated with asbestos (1). Asbestos was also used in paper mills for pipe insulations, machine insulations, packings and as brake backings for different machines (39). There are only a few published measurements of asbestos levels in paper mills. The levels are so out low and during recent years no asbestos has been detected (2, 5, 64).

Talc has been used both as a filling agent and as a coating agent. There are a few samplings where it is possible to approximate the air levels of talc (1, 70). The levels vary considerably during batching of talc and, for short periods, very high levels can be present. Ahling et al reported levels between 0,1 and 2,4 mg/m^3 (1) but Thorén et al reported that the talc batching gave a level of total dust of about 8 mg/m^3 (70). Finally the study by Gautam et al from India should also be mentioned where the authors by talc batching and handling of talc measured levels between 614 and 2757 mg/m^3 (29). The method of sampling was not mentioned in the article but probably the samplings were done during very short periods.

Wet strength agents are added especially in the production of soft paper. A common group of these agents is the polyvinylamide resins. In those compounds epichlorohydrin is present as a monomer rest (1). There are two studies from soft paper mills where levels of epichlorohydrin have been estimated (1, 23). Ahling et al found no detectable amounts (1), but Ericsson et al found levels about 0,1 mg/m^3 (23).

Formaldehyde is emitted from some additives, for instance some coating agents. Levels of formaldehyde in the paper mills have been estimated between < 0,1 mg/m^3 and up to 0,37 mg/m^3 (1, 2, 23, 36).

Printing paper can sometimes be coated with colophony. Probably colophony is a usual coating agent, but it is difficult to obtain information about its usage.

In the stock where the temperature is between 40 and 50 degrees C there are good conditions for growth of microorganisms. Many of these are slime producing and the slime complicates the paper production. Therefore slimicides are added to the stock.

Table 2. Number of bacteria and fungi in different kinds of paper mills. As a comparison, levels for a saw mill and for a sewage treatment plant, are also given.

Type of industry	Total amount alive bacteria per m^3 air	Total amount of spores per m^3 air	References
Soft paper mills			
Wet end	53 000-3.3 milj.	7 700-240 000	1
Wet end	-	40-2 900	34
Wet end	1 400	2 600	47
Rolling machine	19 000	3 200	2
Outdoors	-	40-19 000	34
Newsprint mills			
Wet end	1 100	230	1
Rolling machine	330	250	1
Paper mills*			
Wet end	7 400	280	58
Wet end	1 050	-	45
Rolling machine	150	85	58
Rolling machine	-	27 000	31
Rolling machine	210	-	45
Outdoors	190	350	58
Sawmill	8 000	-	1
Sewage plant	5 000-700 000	-	1

* Type of paper mill was not specified

Ahling et al have estimated levels of organic bromide to be between 0,008 and 0,29 mg/m^3 near to the wet end of a paper machine in a soft paper mill (1, 2). Chan-Yeung et al estimated 0,009 mg/m^3 tetrachlorofenol in a Canadian paper mill (19). No further measurements of slimicides were found in the literature.

At the wet end of the paper machines there is an aerosol of paper dust, microorganisms and additives. The levels of microorganisms in the different paper mills are shown in table 2.

From table 2 can be seen that the levels in the air vary quite a lot. The variations depend on different factors such as the circulation period for the stock, the levels of slimicides, the levels of microorganisms in the pulp and the enclosure of the paper machines (58).

However, there are only a few workers that are exposed to the aerosol at the wet end since the workers in a paper mill mainly work at the dry end of the paper machine.

2.3 Air concentrations in the occupational environment

Table 3 is a summary of published studies where personel samplings have been done of paper dust in different paper mills. Most of the studies are from Sweden and the majority are from soft paper mills. As expected the levels of total dust are highest in the soft paper mills. However, quite a great range in the means between the different investigations can be seen. Very high levels, i.e means over 10 mg/m^3 are shown by Ericsson and Billemyr et al from soft paper mills (23, 7). These two mills have similar production with a high intermixing of waste paper and high velocity on the paper machines.

The study by Billemyr et al (7) was done in the beginning of the 1970s and Thorén et al investigated the same mill 15 years later and found the total dust levels had markedly decreased (70).

The studies from the other paper mills show considerably lower levels. Eskilsson et al found 0,7 mg/m^3 in a study of a soft paper mill with a low intermixing of waste paper in the products and slow velocity paper machines (24).

Table 3 shows that the workers nearest the paper and rolling machines are exposed to higher dust levels than those working with converting machines. Furthermore, it can be seen that production of thick soft paper, i.e. paper towels, emits less dust than thin soft paper. This mirrors the fact that paper with a high degree of moisture emits less dust than drier paper.

Table 3. A list of levels of total dust in the production of different paper qualities. Personal samplings.

Type of process	Levels of total dust		Number of samplings	References
	Mean	Range		
Printing paper	1.6	<0.1-9.8	56	19
Paper board	0.4	<0.2-0.8	6	2
News print				
Pap and rol	0.1-0.5	-	-	1
Pap and rol	0.2	<0.1-0.9	14	2
Pap and rol	4.4	0.5-12.4	7	2
Soft paper				
Pap and rol	1.7	0.2-4.3	10	2
Pap and rol	12.0	2.8-55.2	9	7
Pap and rol				
Thick paper	0.6-1.2	0.3-1.5	4	23
Thin paper	5.0-14.0	1.0-55.2	37	23
Pap and rol	0.7	<0.4-2.1	16	24
Pap and rol	5.8	?		
Pap and rol	2.2	<0.1-8.2	7	70
Converting	4.4	0.2-16	8	2
Converting	3.2	0.6-5.2	-	7
Converting				
1976-1980	5.9-14.5	1.5-31.0	20	23
1981-1983	0.1-2.8	0.05-5.1	44	23
Converting	0.7-1.9	0.2-3.4	50	70
Waste paper	5.9	1.8-9.4	5	14
Waste paper	0.5	0.4-0.7	3	2

Pap and rol = Paper and rolling machines.

From other paper mills there are only a few investigations published. In one of these studies it could be seen that mills producing newsprint could have high levels of dust (5).

Stationary samplings of total dust are shown in table 4. Only four studies, all from Sweden, have been found. The studies strenghten the impression that the soft paper mills have the highest levels of total dust.

Table 4. A list of levels of total dust. In the production of different paper qualities. Stationary samplings

Type of process	Levels of total dust		Number of samplings	Referen-ces
	Mean	Range		
Printing paper				
Pap and rol	1.0	-	?	2
News print				
Pap and rol	0.4	0.3-0.5	2	1
Rolling machines	1.7	0.2-5.3	9	5
Pap and rol	1.0	<0.1-15	26	2
Soft paper				
Pap and rol	12.0	0.6-44.7	10	1
Pap and rol	1.4	0.4-3.2	7	2
Pap and rol	9.1	3.1-21.5	7	7
Converting	7.2	2.4-16	9	2
Converting	8.8	3.1-11.2	9	7
Converting	1.6	1.3-2.7	6	70*
Converting	1.0	0.3-1.7	6	70**

* Sampling 20 litres/min and ** Sampling 2 litres/min.

Pap and rol = Paper rolling machines

The levels of respirable dust have been studied in a few investigations. Mainly cyclone pre-samplers, have been used, i.e no particles with an aerodynamic diameter exceeding 7,1 um were sampled (4, 43). It should also bee mentioned that paper dust is a mixture of particles and fibres and we lack knowledge about the separation properties for fibre dust in a cyclon pre-sampler.

With personal samplings Heederik et al found 4,9 mg/m^3 close to papermachines in a Dutch soft paper mill (34). Thorén et al found in a Swedish soft paper mill 0,2-1,1 mg/m^3 near converting machines (70). In that study the respirable fraction, i.e that proportion of the dust that was obtained in a cyclon pre-sampler, varied between 15 and 69 %. Eskilsson et al found levels around 0,5 mg/m^3 on workers close to paper and rolling machines in a soft paper mill (24). Ahling et al found 0,4 mg/m^3 close to paper machines and about 1 mg/m^3 near converting machines in a soft paper mill (2).

A study by Thorén et al estimated the fibre concentration in paper dust through counting in a optical phase contrast microscope according to the rules concerning asbestos fibres (70). Fibre levels were found between 0,2-1,6 fibres/ml. Analysis of the sizes of the fibres with a scanning electron microscope showed that the fibres had a diameter between 1 and 5 um. The main part of the fibres were organic, probably cellulose fibres. There were also some inorganic fibres but not asbestos (64). Also the particles in the dust were analysed and it was found that the main part of the particles had a diameter below 5 um. They often consisted of the chemical elements aluminium and silica which probably originated from different mineral additives. A similar frequence of sizes were also shown by Ahling et al (2).

Many studies have done low temperature ashing of paper dust for removal of organic content. In those studies it has been found that between 5 and 25 % of the dust was inorganic material (5, 14, 24, 70).

In summary, workers in some soft paper mills have been exposed to high levels of total dust i.e 5 mg/m^3. From other types of paper mills only a few published samplings exist but they mainly show lower levels mostly below 5 mg/m^3.

3. Kinetics and toxicology

There are a lot of mainly experimental studies where the deposition and elimination of inhaled aerosols were investigated. The studies almost exclusively deal with particular aerosols. There are no studies concerning paper dust, which is a mixture of particles and fibres. The following review is hence based upon our knowledge of dust in general. The review is, in fact, mostly based on some excellent review articles dealing with the subject (15, 56, 68, 74).

From the functional point of view the respiratory tract can be separated into three parts, the naso-pharyngeal region, the tracheobronchial region and the pulmonary region. The anatomical conditions differ greatly among these compartments and hence also the depositing and elimination of dust differs greatly. For instance, in the nose there are narrow and winding passages which cause a turbulent flow and by that an increased depositing. On the other hand the bronchi are dichotomusly branched leading to an increased deposition of dust in the ramifications.

The most important single factor for deposit in the airways seems to be the aerodynamic diameter of the constituents. The aerodynamic diameter of a particle or a fibre is the diameter of a particle with a density 1 g/m^3 that has the same sedimentation velocity as a studied particle or fibre in question.

Figure 1 shows the pattern of deposition in the different compartments of the respiratory tract related to the aerodynamic diameter in the different particles in an aerosol. The diagram is based on a document published in 1966 that reviewed the

knowledge at that time (56). The diagram is, of course, only an approximation and the model was completed later but it is still valid for the must part.

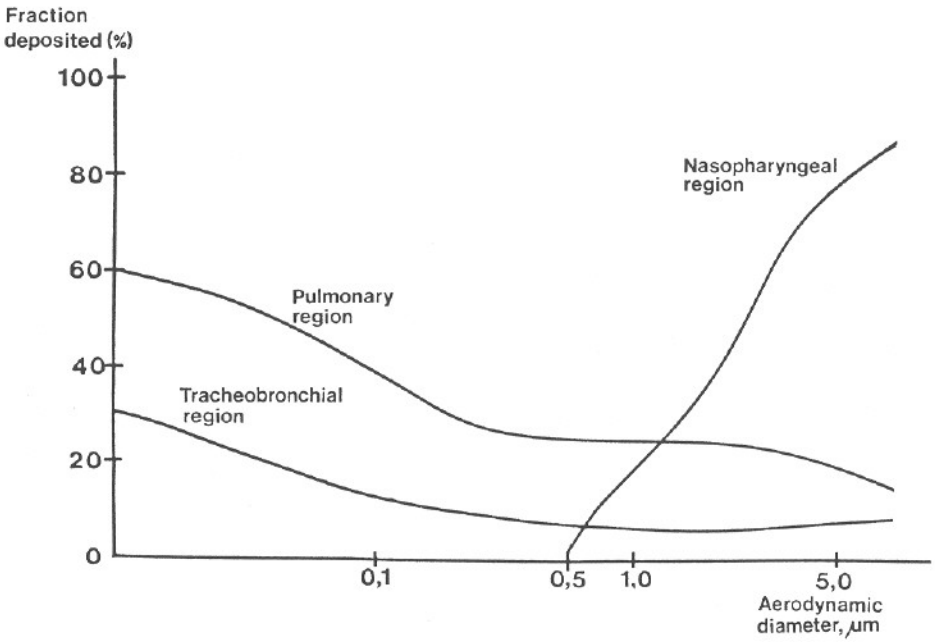

Figure 1. The relation between aerodynamic diameter and the pattern of deposition in the respiratory tract.

However, the model is not quite accurate during heavy work because then are the pattern of breath changed, the minute ventilation is increased and mouth breathing increases (78). Breathing through the mouth i.e. disengagement of the nose, should result in an increased deposit of large particles in the lower airways. Furthermore an increased minute ventilation causes per se an increased pattern of deposit in the airways with an increased central deposit (18).

An aerosol that has been deposed in the airways is more or less thoroughly eliminated through mucocilliary clearance, alveolar clearance, coughing or sneezing. With mucocilliar clearance means the ability in the airways to remove foreign substances by transportation in the mucus of the bronchus (74). In healthy individuals the velocity is about 10 mm/minute in the direction from the perifery to the throat where the polluting particles then are swallowed. There are a lot of situations where this transport is slowed down, for instance, with exposure to nitrous gases, sulphurdioxide, tobacoo-smoke and so forth. No studies concerning paper dust related to this topic have been found.

Foreign material in the nose also is transported away by mucocilliar clearance. And, in the nose clearance is directed towards the throat i.e. backwards. However, in the front of the nose the activity of the cilias is forward. Andersen et al have shown that the velocity is about 10 mm/min as in the lower airways (3). Andersen et al have also shown that the clearance is reduced by exposure to irritating gases but inert dust in levels as high as 25 mg/m^3 did not influence the clearance.

The material that has been deposited in the alveoli can only be transported away by alveolar macrofages. That process is called alveolar clearance. Studies concerning paper dust in this context have not been found.

4. EFFECTS ON DIFFERENT ORGANS

4.1 The skin

Fregert have investigated the slimicides that are used in the

Swedish paper industry and he found that many of them had sensitizing properties (28). Eczema has been found after exposure to slimicides containing organic bromide compounds (63). Paper mill workers exposed for methylene-bis-thiocyanate which is a common slimicide, were patch-tested with that substance (40). The investigation did not show any clear signs of sensibilisation.

Efskind screened prevalence of eczema among workers in a paper and pulp mill in Norway (22). He found that in the paper mill 1,3 % of the workers suffered from eczema that judged to be of occupational origin. The cause of the eczema was not mentioned.

Colophony can be used as a coating agent on printing paper and there are two reports about contact dermatitis from paper probably caused by colophony (6, 76).

In conclusion, there are no studies that have shown that paper dust per se could be harmful for the skin but exposure to slimicides and colophony seems to be a risk factor for eczema.

4.2 Upper airways

There are only two investigations, both cross-sectional studies, concerning symptoms from the upper airways among workers exposed to paper dust. Ericsson et al found in an investigation of soft paper workers that among those exposed to dust levels exceeding 5 mg/m^3 both smokers and non-smokers had a significant increased prevalence of throat irritation and crusts in the nose compared with prevalence of these conditions during previous employment (23). Workers exposed to dust levels below 1 mg/m^3 were used as referents in this study. In the study was a dose effect response concerning throat irritation but not concerning crusts in the nose.

Thorén et al investigated the symptoms in the upper airways among workers in a similar soft paper mill (70). In that study were used a similar questionnaire as in the study by Ericsson et al. Thorén et al found a significant increased prevalence of both crusts in the nose and throat irritation among workers exposed

to paper dust compared with an unexposed reference group. In this study the exposed were divided into three different categories of exposure: low, medium and high. The highest prevalence of symptoms was found in the medium exposed group, hence no dose response relation was found.

In both the studies cited above self-administered mailed questionnaire were used (23, 70). The questions dealing with symptoms from the upper airways were not validated.

4.3 Lower airways

4.3.1 Pulmonary function

The studies dealing with the pulmonary function are summarized in table 5. The earliest published investigation is by Ferris et al which studied 124 paper mill workers and compared those with 147 pulp mill workers. Both groups were measured as to forced vital capacity (FVC), forced exspiratory volume in 1 second (FEV_1) and peak exspiratory flow (PEF) (25). No differences between the groups were found in this study.

This cross-sectional study was followed up 10 years later when 91 of the original 124 paper mill workers were reinvestigated with regard to FVC, FEV_1 and PEF (26). Lung function decrement was found to be no more than the expected considering the increased age in the group.

In the first study of Ferris et al no samplings of total dust were done in the paper mill, nor was it mentioned which type of paper that was produced in the paper mill (25). In the follow-up study it was only mentioned that the paper mill workers had a minimal exposure (26).

Chan-Yeung et al investigated 278 workers in a Canadian paper mill without observing any decreased lung function (FEV_1 and FVC) compared with 496 unexposed referents (19). In that study there were done samplings of total dust and those varied between 0,1 and 9,8 mg/m^3, mean 1,6 mg/m^3.

Table 5. A list of studies on lung function of workers exposed to paper dust.

Exposure	Studied group	Referents	Result	Reference
Paper mill. Dust levels not given	124 paper mill workers	147 pulp mill workers	No difference in FVC, FEV_1, PEF	25
Stated as minimal	91 paper mill workers. Follow-up of the study above	109 pulp mill workers	No difference in FVC, FEV_1, PEF	26
Dust samplings, mean 1,6 mg/m^3	278 paper mill workers	498 foresters /office workers	No difference in FEV_1 and FVC	19
Dust samplings Three exp levels High >5 mg/m^3 Med= 1-5 mg/m^3 Low <1 mg/m^3	Soft paper workers, 115 high exp. 23 medium exp. 150 low exp.	None	Decreased FEV_1 and FVC among high exposed > 10 yrs. No decrease over a work shift	23
See (23)	Follow up of 13 high exp. life long non smoking workers from 23	14 life long non smoking officials	Increased P_{el}, decreased RV and MEF_{50}	42
Dust sampling Mean 5,8 mg/m^3	43 paper machine operators	40 office workers	No difference in FEV_1, FVC, MMEF, MEF_{50}, MEF_{25}. Decreased FEV_1, MMEF, MEF_{50}, MEF_{25} during a work week.	34
Dust samplings Three exp.levels High >5 mg/m^3 more than 10 yrs Low <1mg/m^3 Medium =the rest	54 high exp. 143 medium exp. 90 low exp.	79 office workers	No difference in FEV_1 and FVC	70

Ericsson et al investigated 1981 355 workers in a Swedish soft paper mill (23). In that study samplings were taken of total dust. The result of this have been presented in chapter 2.3. In the study all individuals were classified according to one of three exposure levels where the high exposed workers had worked in levels above 5 mg/m^3 and the low exposed in levels below 1 mg/m^3. The pulmonary function among the exposed were expressed as percent of predictive value compared with a national reference material in regard to age and sex.

Worker in the highest exposure levels with a period of employment exceeding 10 years no matter they were smokers had or non smokers a significant decreased FEV_1 and FVC compared with the low exposed group. Concerning FEV_1 the low exposed had 105 % of predicted value and the high exposed 88 % of predictived value. Concerning FVC the values were 100 % and 85 % respectively. Furthermore, there were significantly decreased FEV_1 (95 %) and FVC (94 %) among high exposed smokers no matter the length of the period of employment compared with the low exposed workers (99 % for both FEV_1 and FVC).

This study was the first that found signs of pulmonary function decrement after exposure to paper dust. The advantage with the study is that the exposure estimation is rather good among the investigated, i.e it is possible to distinguish a low exposed group and a high exposed group. A disadvantage of the study is that there is a lack of an unexposed control group. Concerning the exposure it also should be noted that the high exposed group in this mill had worked in levels of total dust that often markedly exceeded 10 mg/m^3.

At the same mill Järvholm et al did a follow-up study where all high exposed male non smoking workers employed more than 10 years were selected (42). Thirteen men were investigated and they were compared with 14 unexposed life long non smoking officials. In that study there was among the exposed a significant increased elastic recoil pressure (P_{el}) in the lungs by 100 % of the total lung capacity (100 % TLC), but there was also a similar tendency among the other levels of TLC. Furthermore the exposed had a

decreased residual volume (RV) and an increased MEF_{50} (Maximal expiratory flow at 50 % of FVC). The exposed also had a decreased TLC but the difference was not significant.

The lung function findings in this study support a restrictive impairment of the ventilation but the formal criterion i.e. a significant low TLC was not fulfilled.

Thorén et al investigated 366 workers in another Swedish soft paper mill (70). In that investigation there were no signs of impaired lung function. FEV_1 and FVC among 108 high exposed workers were not significantly reduced compared with 158 unexposed referents. High exposure was defined as work in levels exceeding 5 mg/m^3 more than 10 years. In the study there were also low and medium exposed workers and there were no signs of lung function impairment.

In this mill the dust levels were, in general, lower than in the mill Ericsson et al studied, meaning that the high exposed group, in general, was exposed to levels between 5 and 10 mg/m^3.

Heederik et al investigated 46 paper machine operators in a Dutch soft paper mill (34). The mean levels of total dust were 5,8 mg/m^3. There were no signs of impaired lung function FVC, FEV_1, MMEF (Maximal middle exspiratory flow), MEF_{50}, and MEF_{25} (Maximal exspiratory flow at 75 % of FVC), among the exposed compared with 40 unexposed referents.

The majority of the investigated 43 exposed and 39 unexposed were investigated with intradermal test on extract from different fungus spiecies that were present in the stock. Five exposed workers with a positive rapid reaction in intradermal test had a significant decreased MMEF, MEF_{50} and MEF_{25} ($p < 0,05$) and FEV_1 ($p < 0,01$) during a work week compared with 36 unexposed workers with negative skin tests.

In that study there was no impaired lung function in the dust exposed group as a totality, no information about the periods of employments was presented. But the study indicate that an

impaired lung function may occur during a work week and in that case exposure to microorganisms rather than exposure to paper dust should be an explanation. The study was a small one and in the analysis there were multiple statistical comparisons.

In the earlier cited study by Ericsson et al were also investigated FEV_1 and FVC were investigated over an 8-hour labour day without any significant changes found (23).

4.3.2. Symptoms and diseases in the lower airways

In the first study by Ferris et al 20 % of the workers reported cough with phlegm more than 3 months a year for more than 3 years (25). Compared with pulp mill workers there were no differences in regard to different smoking habits. There were also no significant differences between the groups concerning the prevalence of chronic obstructive pulmonary disease or bronchial asthma. Bronchial asthma was defined if the respondent had a history of bronchial asthma diagnosed by a physician and the condition was still present. Chronic obstructive pulmonary disease was diagnosed if the respondent admitted to a history of wheezing or whistling in the chest on most days or nights and/or shortness of breath that caused him to stop for breath when walking at his own place and/or mean FEV_1 less than 60 % of FVC. However, in the follow-up of the mortality Ferris et al found that 16 of the original 124 paper mill workers were decreased. Three of them had died from asthma or chronic obstructive pulmonary disease which resulted in a proportional mortality ratio (PMR) of 15 % (26).

Deprez et al studied information from 66 cities in the eastern part of USA and found that in the cities where there was paper and pulp industry, the number of hospitalized cases with the diagnosis asthma and/or chronic obstructive pulmonary disease was significantly increased compared with other cities (21).

Jäppinen studied 3250 workers at paper and pulp mills in southeast Finland (38). In the cohort was a subcohort of 392 paper mill workers. In that group there were no death from non malignent respiratory diseases.

Järvholm and Thorén et al found in two studies a significant increased prevalence of cough with phlegm for more than 3 months/year among workers exposed to soft paper dust compared with unexposed referents (42, 70). In that study there was also an increased prevalence of cough with phlegm in exposure levels below 5 mg/m^3 (70). In the analysis of the questions concerning cough with phlegm no information was presented about period of employment (42, 70). But there was no increased prevalence of cough with phlegm among the highly exposed (> 5 mg/m^3) soft paper mill workers in the studies by Ericsson and Heederik and co-workers (23, 34). Thorén et al found in the earlier cited cross-sectional study that among the exposed, i.e. soft paper workers, was a significant increased prevalence of reported bronchial asthma 4,9 % compared with 0 % among unexposed officals (70). The estimations are based only on information from self administered questionnaires. Heederik et al found that 15 % of the exposed reported bronchial asthma compared with 6 % among unexposed officials (34). Also in this study the information was based on information from questionnaires and the differences were not significant.

Robinson et al investigated the mortality in a cohort of 3572 paper and pulp workers from the northwest of the USA (62). The main objective of the study was to investigate the pulp workers and there were no distinguishable subcohort of paper mill workers. However, a subcohort of workers exposed to formaldehyde was studied which, in reality, was made up on workers in paper mills. In paper mills producing printing paper, the paper is often coated with agents which emits formaldehyde. In the total cohort there was no excess risk for death from non malignant respiratory diseases SMR 83 (confidence interval 90 % 65-105). In the analysis of the formaldehyde exposed subcohort non-malignant respiratory diseases were not mentioned.

Schwartz found in a PMR-study from the northeast of the USA no excess mortality in non-malignant respiratory diseases among 1071 paper and pulp mill workers(65).

Thorén et al have in two case control studies investigated the mortality from bronchial asthma and chronic obstructive pulmonary disease among workers in Swedish paper mills (69, 73). The first study was conducted in the soft paper mill where the earlier cited studies by Ericsson and Järvholm were carried out (23, 42). The study showed a significant increased relative risk (OR = 3,8) to die from bronchial asthma or chronic obstructive pulmonary disease among the exposed. There were only 12 cases in the study, six of them were exposed. In the study the exposure assessment were insufficient, it was only distinguished between employed and not employed. In the second study that was carried out in two paper mills producing printing paper there were no excess risk to die from bronchial asthma or chronic obstructive pulmonary disese among the process workers (73). In those mills the dust levels have been much lower compared with soft paper mills.

No increased mortality from bronchial asthma and chronic obstructive lung disease (SMR 90) were found among paper mill workers in Sweden when mortality data from 1971-1980 were linked together with the occupational information obtained from the 1970 National Census (71).

In a similar study there was observed an increased mortality from chronic interstiell pneumonia among Swedish paper mill workers (three cases versus one expected) (67).

4.4 Cardiovascular diseases

In a cohort study by Jäppinen there was a significant excess risk for ischemic heart disease (SMR 138, 95 % confidence interval 95-193) (38). Excess risks of the same magnitude were also observed among workers in the maintenance departments and power plants. The author speculates that exposure to sulphur compounds could explain the observed excess risk. Different smoking habits could not explain the observed risk excesses which were analysed in a later study (37).

In a study from Canada a correlation was found between dead death due to cerebrovascular disese among women and occurrence of paper

and pulp mills in their home district. (27).

5. ALLERGIES

Contact dermatitis is described under skin diseases 4.1. In addition to that no allergies are described in connection with exposure to paper dust.

6. TUMOURS

There are a lot of cancer epidemiological studies on paper and pulp mill workers (9, 11, 12, 16, 17, 20, 26, 30, 32, 33, 38, 41, 48, 49, 51 - 55, 61, 62, 65, 69, 71, 73, 75, 77). Exposure to paper dust occurs in paper mills but not in pulp mills. Consequently only studies where paper mill workers have been analysed as a entity have been reviewed in detail in the text and in table 6 (17, 38, 41, 49, 55, 62, 69, 73). In addition, also a case referent study is mentioned where paper dust exposure has been questionned among patients with different tumours (66).

Jäppinen et al distinguished two subcohorts of paper mill workers and board mill workers from a cohort with 3 545 persons that had worked in paper and pulp industry in Finland (38). Among 233 male paper mill workers they found a significant increased standard incidence ratio (SIR) 197 for tumours in trachea, bronchii, lungs and pleura and a non-significant increase, SIR 171, for stomach cancer. Among 823 male board mill workers there was also a significant increased SIR 222 for respiratory neoplasms but also non significant increases for colon cancer (SIR 239) and cancer in the urinary bladder (SIR 148). The risks estimated were further increased when analysed with regard to latency time and period of employments. The influences of different smoking habits were investigated in a later study but the observed differences could not explain the observed risk increases (37). The authors speculate about different explanations for their findings among them possible exposure to dyes or slimeicides. The exposure levels for paper dust were difficult to judge in this study but they probably were below 5 mg/m^3. No soft paper mills were included in the study.

Table 6. A list of studies in which an increase of tumours has been observed among paper mill workers or other groups exposed to paper dust.

Tumour site	Studied group	Result	Reference
Lung, pleura	Boardmill - cohort	SIR 222*	38
	Papermill - cohort	SIR 197*	38
	Softpapermill - case/ referent	OR 1.5	73
Lung	Papermill - PMR	PMR 134	55
	Different occupations case/referent	OR 1.4	66
Mesothelioma	Papermill - cohort	SIR 2.4	48
Stomach	Papermill - cohort	SIR 197	38
	Different occupations case/referent	OR 1.1	66
Colon	Papermill - PMR	PMR 152	55
	Papermill - cohort	SIR 239	38
Biliary tract	Papermill - cohort	SIR 1.8*	49
Urinary tract	Papermill - cohort	SIR 148	38
	Subcohort exp. to formaldehyde	4 obs vs 1 exp.	62
Prostate	Different occupations case/referent	OR 1.9*	66

* $P < 0.05$ OR = odds ratio
SIR = standard incidence ratio
PMR = proportional mortality ratio

Malker et al found, in a study in the Swedish Cancer Environmental Register, which is a linkage between national mortality data and occupation information in the National Census a relative risk of about three for malignant pleuramesothelioma among workers in the paper and pulp industry (48). The increased risk was based on 23 male cases. These 23 cases and 2 more female cases with malignant mesothelioma were further studied by Järvholm et al (41). In that study they found that 70 % of these workers had a certain or probable exposure to asbestos. 25 % of the workers had

been exposed to paper dust in connection with work with paper machines. The authors conclude that exposure to asbestos is probably the explanation for the found risk excess for malignant mesothelioma.

Malker et al have in one more similar study analysed the incidence of biliary tract cancer among different occupational groups in Sweden. They found a significant increased relative risk SIR 1,8 among workers employed in the paper and pulp industry. The risk excess was based on 25 cases (49).

Milham and Demers studied the mortality among 2113 paper and pulp mill workers in the USA and Canada. They distinguished 238 paper mill workers and in that group there were no significant risk excesses for different neoplasms (55). But there were insignificant increases of PMR among colon and lung cancers.

Robinson et al, investigated a cohort of 3572 paper and pulp mill workers from the northwest of the USA (62). A subcohort of 1261 men with a probably exposure to formaldehyde were separately analysed. In reality, that group consisted of workers in paper mills where coating agents have been used that emitted formaldehyde. In this group four cases of tumours of the urinary tract were found compared with one expected, analysed with 30 years of latency. No other risk excesses were observed in that group. No dust levels were mentioned in the study, but the mills produced coated paper i.e printing paper or paper board, a production that generally emit low lewels (< 5 mg/m^3) levels of paper dust.

In a case referent study, Siematycki et al investigated patients with 19 different tumours (66). As referents for each tumour the rest of the 18 tumours have been used. In the study the exposure to nine different dust qualities were investigated through personal interview. Concerning paper dust there were a mixture of different occupations not clearly stated but at least 9 % had worked in paper mills, 16 % in the printing industry and about 20 % had worked in offices. In the study a group with high exposure for paper dust was distinguished. The levels were not given, and there was risk excess for stomach cancer, lung cancer

and prostatic cancer.

Only the risk excess concerning prostatic cancer was significant, odds ratio 1,9 (95 % confidence interval 1,0-3,3) The study must be regarded as a hypothesis generating study. Furthermore on the descriptions of the exposure to paper dust were incomplete and the exposed individuals seemed to be exposed at a quite low level.

Thorén et al have in two case-referent studies, investigated the mortality in respiratory tumours among paper mill workers (69,73). In the first study there was a non-significant increase of the risk, odds ratio 1,5 among those employed in a soft paper mill (69). In that study the exposure evaluation was insufficient and was commented on earlier in chapter 4.3.2. In a second study there was also an increased risk among paper mill workers, but when the exposed were categorized in different occupation groups the risk excess seemed to originate from the maintenance workers which probably have been asbestos exposed (73). Among the workers employed in the paper making process there was no risk excess.

In both studies the smoking habits were unknown among the exposed and the unexposed. In both studies were therefore conducted a survey of the smoking habits among the living population around the paper mills. Those surveys indicated that smoking was more common among paper mill workers compared with the other inhabitants in the mill towns. The authors judged however that the differences in the smoking habits only partly could explained the observed risk excesses.

Carstensen studied lung cancer morbidity standardized for smoking habits among Swedish men based on information from the National Census and the National Cancer Register (17). In that study he found that paper and paper board workers had a significant decreased risk, standard incidence ratio SIR 67 (95 % confidence interval 49-93) for lung cancer.

In summary the literature show a divergent picture without any consistent findings. Furthermore the exposure is very sparingly

described in most studies making it is almost impossible to draw any conclusions about any explanations for the observed risk excesses. However, some tendences can be seen. In some studies there was an increased risk for lung cancer or respiratory cancer. Asbestos is probably an important confounder in these studies. Furthermore in some studies an increased risk for tumours in the gastrointestinal tract seems to appear. The explanation for this is unknown.

7. DISTURBANCES OF REPRODUCTION

Blomkvist et al investigated the outcome of pregnancy in a cohort of women who worked in the paper and pulp industry in Sweden (10). 890 deliverys and 899 children were identified. The women were divided in different occupational categories. Among 162 women who had worked in laboratories in different paper and pulp industries six children with serious deformations were born versus 2,9 expected. Among 176 women who worked with paper converting during the pregnance seven children were born with serious malformations versus three expected. Hemminki and Niemi have studied the occurrence of spontaneous abortions correlated with the occupation of the parents. They found in the study an insignificant risk increase of spontaneous abortions among women who had worked in the paper and pulp industry (35).

Kwa et al found in a case-referent study that among children tumours in the central nervous system were significantly associated with an occupation of the father in paper and pulp industry (44). The authors judged their finding as a random observation. Their observation could not been reproduced in a later similar case-referent study by Nasca et al (57).

8. EXPOSURE, EFFECT AND EXPOSURE RESPONSE RELATIONSHIPS

8.1 Effects of short term exposure

There are only two studies where the lung funtion has been investigated after short term exposure to paper dust. In the

study by Ericsson et al there was no impairment of the lung function during the course of one working day (23). In the study by Heederik et al there was an impairment during a working week among 5 workers with a positive skin test for microorganisms from the stock of the paper machines (34).

8.2 Effects of long term exposure

8.2.1 Dust levels beneath 5 mg/m^3

Two studies observed an increased prevalence of symptoms from the upper airways (23, 70). In one of the studies there was a partial exposure response relationship (23) but not in the study (70). No negative studies were found.

An increased prevalence of irritative symptoms from the lower airways as for instance cough with phlegm, have been reported in one study (70) but in two other studies there were no increases of such symptoms (19,23).

In all studies with these exposure intervals no lung function impariment among the exposed was found (19,23,70).

8.2.2 Exposure levels exceeding 5 mg/m^3

Two studies observed an increased prevalence of upper airway symptoms (23,70). In one of the studies there was a partial exposure effect relationship (23), but not in the other study (70).

Two studies observed an increased prevalence of irritative symptoms in the lower airways (42,70). In one study the increase was independent of the smoking habits (70), in the second study only non-smokers were investigated (42). In two other studies there was no increase of such irritative symptoms (23,34).

There are two studies where the exposure levels have been between 5 and 10 mg/m^3 where no impaired pulmonary function (FEV1 and FVC) has been observed (34,66). In one study, where the exposure

levels probably had been higher, exceeding 10 mg/m^3, a significant decrease of both FEV1 and FVC was observed among smokers regardless the period of employment and among workers employed more than 10 years regardless of smoking habits (23). In a follow-up study at the same paper mill on non smokers this lung function impairment could not be reproduced (42).

In the exposure interval exceeding 10 mg/m^3 rather than 5 mg/m^3 a significantly decreased residual volume, a significantly increased elastic recoil and a non-significant decrease of the total lung capacity were observed among non-smoking workers (42).

8.2.3 Occurence of diseases

An increased prevalence of asthma and chronic obstructive pulmonary disease are observed in some studies, those studies permit no conclusions concerning the effect of paper dust exposure or any exposure effect relationships (26, 34, 69, 70).

There are also a lot of observations in the literature where different tumours, mainly lung cancer and tumours in the gastrointestinal tract, are increased among groups of workers that could be assumed to have been exposure to paper dust. But also in those studies it is impossible to draw any conclusions about paper dust and eventual exposure effect relationships.

9. RESEARCH NEEDS

The prevalence of asthma and chronic obstructive pulmonary disease among groups exposed to paper dust should be more thouroghly investigated for example with longitudinal studies. The prevalence of symptoms from the upper airways should also be investigated and then mainly at exposure interval below 5 mg/m^3. As time goes on, cancer epidemiological studies also should be conducted. Furthermore, additional studies of characteristics of paper dust should also be done.

10. DISCUSSION AND CONCLUSIONS

Studies based on questionnaires indicate that symptoms in the upper airways can occur with exposure to low levels of paper dust (< 5 mg/m^3) as well as with exposure to high levels (> 5 mg/m^3). The distribution of the size of paper dust is such that breathing through the nose will reult in much of the dust being deposited in the nose. However, given current knowledge, it is impossible to draw any conclusions concerning exposure to paper dust and symptoms in the upper airways.

Concerning the lower airways exposure levels beneath 5 mg/m^3 seem not to cause any increased prevalence of irritative symptoms such as cough with phlegm. With higher exposure levels there are both negative and positive studies concerning irritative symptoms. This may strenghten the view that paper dust is not especially irritating to the lower airways. However, all studies are of cross-sectional design why in the studies there are probably a selection factor operating, i.e. person with respiratory symptoms could have changed occupation. Facts supporting the influence of paper dust on the lower airways include observations of an increased prevalence of bronchial asthma and chronic obstructive lung disease among paper mill workers. Among blue collar workers, particularly such groups exposed to dust, a decreased prevalence of respiratory diseases are expected. The reason for this is the healthy worker effect, i.e. disabled individuals leave their heavy and/or dusty works before their retirement. Consequently the observations of the reversed relationship among paper mill workers is suprising. However, from the studies it is impossible to draw any conclusions about the importance of paper dust.

There is no support in the literature that long term exposure to paper dust in levels beneath 5 mg/m^3 causes any impairment of FEV_1 and FVC. Concerning exposure to higher levels the situation is more unclear but probably exposure to very high levels (> 10 mg/m^3) causes some degree of impairment.

The critical effect level concerning the lower air ways (both lung function and irritative symptoms) with exposure to paper

dust seems to be 5 mg/m^3. Concerning malignances it is impossible to draw any conclusions about exposure to paper dust and those diseases. However, it should be mentioned that exposure to paper dust has not been frequent until the last 25 years. Given the latency periods the most tumours have, it is too early to do any cancer epidemiological studies on paper dust exposed groups.

11. SUMMARY

Kjell Thorén. Paper dust. Nordic Expert Group for occupational standards.

This document is a review of the literature concerning health effects of exposure to paper dust. Concerning symptoms from the upper airways these seem to occur with exposure levels beneath 5 mg/m^3.

Concerning the lower airways there is no support in the literature that irritative symptoms such as cough with phlegm will occur with exposure levels exceeding 5 mg/m^3. With higher exposure levels there is probably some increase of the symptoms.

There are no report in the literature that long term exposure to paper dust in levels exceeding 5 mg/m^3 causes any lung function impairment. With exposure to higher levels pulmonary function probably could be impaired at least in levels exceeding 10 mg/m^3.

An increased prevalence of asthma and chronic obstructive pulmonary disease is reported in paper mills.

The Swedish version is available in Arbete och Hälsa 1989:30. 78 references.

Keywords: **Paper dust, occupational exposure limit, respiratory symptoms, lung function, obstructive lung disease.**

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APPENDIX

Occupational exposure limits for airborne dust (organic, cellulose or paper).

Country	mg/m³	Years	Note	Ref
Denmark	5	1988	Organic total dust	2
FRG	6	1988	Fine dust	5
Finland	5	1987	Organic dust	10
	10		15 min	
France	10	1987	Paper fibre	11
Great Britain	5	1988	Respirable dust	4
	5		Total dust	
Iceland	5	1978	Organic total dust	8
The Netherlands	5	1989	Respirable dust	7
	10		Total dust (cellulose)	
Norway	5	1989	Organic dust	1
Soviet Union	-	1978		6
Sweden	5	1988	Organic total dust	3
USA				
(ACGIH)	10	1988-89	Paper fibres	9
(OSHA)	15	1989	Total dust	12
(NIOSH/OSHA)	5		Respirable dust	

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SUMMARY

Heimbürger G, Beije B, Lundberg P (eds). Criteria documents from the Nordic Expert Group 1989. Arbete och Hälsa 1989:37, pp 1-247.

The Nordic Expert Group is a standing committee with the task to produce 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 1989.

Key words: Acetonitrile, Criteria document, Diacetone alcohol, Hydroquinone, Methyl formate, Nitrilotriacetic acid, Nordic Expert Group, Occupational exposure limit, Paper dust, Toluene.

SAMMANFATTNING

Heimbürger G, Beije B, Lundberg P (eds). Kriteriedokument från den Nordiska expertgruppen 1989. Arbete och Hälsa 1989:37, s 1-247.

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 1989.

Nyckelord: Acetonitril, Diacetonalkohol, Hydrokinon, Hygieniskt gränsvärde, Kriteriedokument, Metylformiat, Nitrilotriättiksyra, Nordiska expertgruppen, Pappersdamm, Toluen.

APPENDIX

Documents published in English by the Nordic Expert Group.

Creosote	Arbete och Hälsa 1988:33, pp 7- 51
n-Decane and n-Undecane	Arbete och Hälsa 1987:40, pp 45- 73
Methyl bromide	Arbete och Hälsa 1987:40, pp 7- 44
Methylene chloride	Arbete och Hälsa 1987:40, pp 74-120
Methyl isobutyl ketone	Arbete och Hälsa 1988:33, pp 53- 76
Nitroalkanes	Arbete och Hälsa 1988:33, pp 115-163
Vinyl acetate	Arbete och Hälsa 1988:33, pp 77-113

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