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CRITERIA DOCUMENTS

FROM

THE NORDIC EXPERT GROUP

1988

G. Heimbürger and P. Lundberg (Eds)

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PREFACE

The Nordic Council is an 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 the Occupational Environment Matter initiated a project with a view to compile and evaluate scientific information on chemical agents relevant to health and safety at work and produce criteria documents. The documents are meant to be used by the regulatory authorities in the Nordic countries as a scientific basis for the setting of national occupational exposure limits.

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

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

Before 1987 the Expert Group consisted of the following members:

Børge Fallentin	Danish National Institute of Occupational Health, Denmark .
Bjørn Gylseth	National Institute of Occupational Health, Norway.
Torkell Johannesson	Department of Pharmacology, University of Iceland, Iceland.
Vesa Riihimäki	Institute of Occupational Health, Finland.
Ole Svane	Directorate of National Labour Inspection, Denmark.
Åke Swensson (Chairman)	National Institute of Occupational Health, Sweden.
Hans Tjønn	Directorate of Labour Inspection, Norway.
Ulf Ulfvarson	Department of Work Science, Royal Institute of Technology, Sweden.
Vesa Vaaranen	Institute of Occupational Health, Finland.

The documents accepted by the "old" Expert Group but published in 1988 are included in this volume.

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 of a numerical exposure limit value.

Search and collection of literature is executed by a secretariat headed by G. Heimbürger and located in the Institute of Occupational Health, Solna, Sweden. 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 secretariate. 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 1988. The names of those 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.

Gunilla Heimbürger — Secretary

Per Lundberg — Chairman

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CREOSOTE

by

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BACKGROUND

Creosote used for wood preservation is a mixture of distillates of coal tar. Coal tar is a by-product of coal carbonization (coking) in the steel industry. Creosote used in timber preservation is mainly a mixture of high-temperature coal tars (coking temperature above 700 °C, usually 1000-1350 °C). Coking temperature determines the chemical composition of a coal tar, and coals from different sources yield the same types of coal tars and coal tar distillation products in high temperature coking.

The beechwood creosote (wood creosote, CAS No. 8021-39-4) which contains guaiacol, creosol and cresol as main components is used as an antitussive. This medicinal product will not be dealt with in this document.

Exposure to creosote takes place by skin contact or by exposure to air containing volatile or aerosol components of the substance. Occupational exposure is probably most intensive in coal tar distillation, in wood impregnation with creosote and in the handling and processing of creosote treated wood.

Since the beginning of the eighties the use of creosote in wood preservation has decreased, although creosote-treated wood still has a superior position in railroad ties and marine pilings .

In the USA 98% of creosote produced is used for pressure treatment of wood. Other uses are non-pressure treatment of wood, as an animal or bird repellent and insecticide, as a component in tap hole refractory cement in ovens, as a frothing agent in mineral flotation and as a feedstock for the production of carbon blacks (38,56).

In Finland, the use of creosote varied from 11,236 to 29,641 tons per year during 1980-1985. Creosote used in Finland has been imported from Poland, West Germany, Denmark and the Soviet Union (25).

Reviews concerning risk assessment and exposure to coal tar and creosote have been published by national authorities in the USA (62,75). An assesment of the carcinogenic risk of coal tars and derived products, including creosote, has been published by the IARC (International Agency for Reasearch on Cancer, Lyon) (38).

PHYSICO-CHEMICAL DATA

CAS number 8001-58-9 (creosote oil)

Synonyms
English: creosote, brick oil, coal-tar creosote, coal-tar oil, creosote oil, creosotum, dead oil
German: Impregnieröl, Steinkohlenteeröl, Kreosotöl
Swedish: kreosot
Danish: kreosot, creosot
Norwegian: kreosot
Icelandish: kreosot
Finnish: kreosootti

Molecular weight: 94 to 252 (range of components)

Physical state (25 °C) and appearance: dark liquid, aromatic odor

Boiling interval: 175-450°C (range of components)

Vapor pressure at 25 °C: see table 3

Flash point: c. 100 °C.

Creosote used for preservation of wood is a mixture of distillation fractions of high temperature coal tar. Primary distillation fractions of high temperature coal tars are described in table 1.

Table 1. Distillation range and components derived from high temperature (above 700 °C) coal tars (56).

Product	Distillation range	Main components
Light oil	below 180 °C	toluene, xylene, benzene, indene
Carbolic oil	180-205 °C	higher alkylbenzenes, phenol and alkylphenols, indene, xylene, naphthalene
Naphthalene oil	200-300 °C	naphthalene, methylnaphthalene, alkylbenzenes, thionaphthalene, alkylphenols
Creosote oil / wash oil	230-290 °C	alkylnaphthalenes, naphthalene, diphenylacenaphthene, fluorene, higher phenols
Light anthracene oil	260-310 °C	anthracene, phenanthrene, carbazole, fluorene, pyrene
Heavy anthracene oil / base oil	above 310 °C	higher molecular weight PAHs
Medium-soft pitch	Residue	40-50% of PAHs with 4-7 rings

Commercial creosote is a mixture of distillation fractions of carbolic oil, naphthalene oil, creosote oil and light and heavy anthracene oils. Crude coal tar, mineral oil or pesticides have sometimes been mixed with commercial creosotes for economic or technical reasons.

More than 160 different chemical compounds have been identified in creosote (61). Less than 20 of these constitute the major portion of creosote. The main components of American and European creosotes are listed in table 2.

Table 2. Main components in samples of different American and European creosotes (31,31a,50,80).

	percentage (w/w)				
Compound	A	B	C	D	E
Acenaphthene	9.0	8.3	5.0	4.5	7.5
Alkylanthracenes (C_1)	4.0		0.02	0.03	0.08
Alkylbiphenyls (C_1)			2.4	2.6	2.8
Alkyldibenzofurans (C_1)			1.8	2.2	2.0
Alkylphenanthrenes (C_1-C_2)	3.0	3.0	2.3	1.5	1.5
Alkylphenols (C_1-C_2)			6.9	6.5	2.6
Alkylfluorenes (C_1)	3.0		0.3	0.6	0.4
Alkylnaphthalenes (C_1-C_4)	2.0	1.4	6.7	8.1	4.7
Anthracene	2.0	8.2	2.1	1.1	2.1
Benz(a)anthracene		1.1	0.5	0.2	0.7
Benzofluorenes	2.0	1.0	0.8	0.4	0.9
Benzofluoranthenes			0.2	0.08	0.4
Benzo(ghi)perylene			0.03	0.02	0.06
Benzo(a)pyrene		0.4	0.07	0.03	0.2
Benzo(h)thiophene		0.3	0.8	1.0	3.1
Biphenyl	0.8	0.8	2.3	3.4	3.2
Carbazole	2.0	3.9	0.7	0.3	0.9
Chrysene	3.0	2.8	0.8	0.4	0.2
Dibenz(a,h)anthracene			0.02	0.01	0.04
Dibenzofuran	5.0	3.9	3.8	4.3	4.9
Fluoranthene	10.0	7.5	2.8	2.2	3.1
Fluorene	10.0	5.2	4.6	5.3	5.8
Indene			2.0	0.9	1.6
1-methylnaphthalene	0.9	0.9	4.1	7.0	3.6
2-methylnaphthalene	1.2	2.1	6.4	11.3	6.2
Naphthalene	3.0	7.6	16.4	13.0	15.0
Phenathrene	21.0	16.9	5.7	5.7	6.0
Pyrene	8.5	5.3	2.0	1.1	2.8
Quinoline		2.0	1.1	1.0	1.8
Total (%)	90	83	83	85	84

A = American creosote (50)
B = American creosote (80)
C = German creosote (31,31a)
D = Polish creosote (31,31a)
E = Russian creosote (31,31a)

The concentration of benzo(a)pyrene in commercial creosote varies from 0.03 to 0.4% (10,16,31,70,80), that of benz(a)anthracene from 0.2 to 1.1 % (16,31) and dibenz(a,h)anthracene from 0.01 to 0.04 % (31).

The physico-chemical characteristics of several components of creosote are presented in table 3.

Table 3. Stuctural characteristics, boiling points, molecular weights and vapor pressures of creosote components (26,31,31a).

component	formula	number of rings	boiling point(°C)	molecular weight	vapor pressure (kPa at 20 °C)
Indene	C_9H_8	2	182	116.2	
Naphthalene	$C_{10}H_8$	2	218	128.2	720×10^{-6}
Quinoline	C_9H_7N	2	238	129.2	
2-Methylnaphthalene	$C_{11}H_{10}$	2	241	142.2	
1-Methylnaphthalene	$C_{11}H_{10}$	2	245	142.2	
Biphenyl	$C_{12}H_{10}$	2	256	154.2	
Dimethylnaphthalene	$C_{12}H_{12}$	2	268	156.2	
Acenaphthene	$C_{12}H_{10}$	3	279	156.2	120×10^{-6}
Dibenzofuran	$C_{12}H_8O$	3	287	168.2	
Fluorene	$C_{13}H_{10}$	3	293-5	166.2	
Methylfluorenes	$C_{14}H_{12}$	3	318	180.2	
Phenanthrene	$C_{14}H_{12}$	3	340	178.2	9×10^{-6}
Anthracene	$C_{14}H_{10}$	3	340	178.2	0.3×10^{-6}
Carbazole	$C_{12}H_9N$	3	355	167.2	
Methylphenanthrenes	$C_{15}H_{12}$	3	354-5	192.2	
Methylanthracenes	$C_{15}H_{12}$	3	360	192.2	
Fluoranthene	$C_{16}H_{10}$	4	382	202.3	0.4×10^{-6}
Pyrene	$C_{16}H_{10}$	4	393	202.3	0.4×10^{-6}
Benzofluorenes	$C_{17}H_{12}$	4	413	216.3	
Chrysene	$C_{18}H_{12}$	4	448	228.3	0.1×10^{-6}
Benzo(a)pyrene	$C_{20}H_{12}$	5	312	252.3	
Benzo(k)fluoranthene	$C_{20}H_{12}$	5	480	252.3	
Benz(a)anthracene	$C_{18}H_{12}$	4	435	228.3	
Dibenz(a,h)anthracene	$C_{22}H_{14}$	5		278.4	
Benzo(ghi)perylene	$C_{22}H_{12}$	6		276.3	

In a recent study aromatic amines, other nitrogen compounds and sulfur compounds were found in creosote used in Finland (31,31a). Of aromatic amines, aminofluorene (0.1-0.3 %) was detected in the creosote used in Finland. Of other nitrogen compounds benzonitrile (0.05-0.2%), quinoline (1.1-1.8 %), isoquinolines (0.2-0.5 %), indole (0.6-0.9%), cyanonaphthalene (0.2-0.6%), acridine (0.1-0.2 %), benzoquinoline (0.1 %), carbazole (0.3-0.9 %), cyanoanthracene (0.02-0.2%) and cyanofluorene (0.04-0.1%) were found. Of sulfur compounds benzothiophene (0.8-3.1%), dibenzothiophene (0.4-1.1%) and benzo(b)naphthothiophene (0.07-0.3%) were detected (31,31a).

The total amounts of unsubstituted polyaromatic hydrocarbons (PAHs) ranged from 15.1 to 21.3 % (3-6 rings) and from 1.8 to 4.8% (4-6 rings). The total amount of aromatic sulfur compounds ranged from 1.8 to 5.4 %, aromatic nitrogen compounds from 4.1 to 5.7 % and aromatic oxygen compounds (phenols, benzofurans etc.) from 11.0 to 14.6 % (31,31a).

TOXICOLOGY

1. METABOLIC MODEL

Since creosote is a complex mixture of phenolic, polycyclic aromatic, nitrogen and sulfur compounds, its metabolism can only be treated selectively and/or in general terms.

1.1. Absorption

1.1.1. Skin. There are no data concerning skin absorption of creosote itself. Cresols and other phenols are easily absorbed through the skin, and can also cause serious skin irritation and burns. Other aromatics can affect the skin absorption of phenolic compounds. It is probable that some low molecular weight aromatics with high systemic toxicity, such as biphenyl, naphthalene and pyridine, can also

be absorbed through the skin. Several coal tar PAH compounds have been detectad in the blood of volunteers after application to normal skin (73). Polycyclic aromatic hydrocarbons can be more or less readily absorbed through the skin and are detectable in the urine, as seen after topical applications of coal tar in the treatment of skin diseases (21). In experiments with mice ^{14}C-benzo(a)pyrene was almost totally absorbed and excreted in feces in 16 days after one topical application to the shaved skin (37). Both ^{14}C-labeled benzo(a)pyrene and 7,12-dimethylbenz(a)anthracene, percutaneously applied to mice, were rapidly absorbed through the skin and excreted in urine and feces. About 90% of both compounds were recovered in excreta during a 7-day follow-up period (69).

1.1.2. Lungs. No data are available concerning pulmonary absorption of creosote. The aromatic volatile creosote components are probably easily absorbed in the lungs. The main components of creosote vapor are naphthalene (30-70%) and methylnaphthalene (10-30%) (31,67). Other main components of creosote vapor are acenaphthene, benzothiophene, biphenyl, fluorene, indene, methylstyrene and phenol (31). In processes in which creosote is warmed or heated, PAH-containing aerosols are also produced.
Pure PAHs are readily absorbed in the lungs (76). Regional deposition and rates of clearance from the respiratory tract are dependent on the size and chemical composition of the particles, as well as on the structure of the hydrocarbon (32). For example, benzo(a)pyrene adsorbed on particles may take 20 times as long as free benzo(a)pyrene to be cleared from the lungs of mice (23).

1.1.3. Gastrointestinal tract. It is probable that many toxicologically active components of creosote are easily absorbed from the gastrointestinal tract. This is the case for PAHs, which have been shown to be rapidly absorbed by experimental animals (37).

1.2. Distribution

Data available on the distribution of creosote components in the body are limited . Phenolic compounds are bound to serum proteins, but are also distributed to internal organs such as the liver, spleen, kidneys and thyroid gland. Fat tissues are significant storage depots from which PAHs are released slowly (37).

1.3 Biotransformation

The biotransformation pathways of several components of creosote, e.g. alkylphenols, biphenyl and several PAHs, have been elucidated to varying extents. The biotransformation products of some components of creosote are well known. Naphthalene is hydroxylated to 1-naphthol (8,43) and 1-hydroxypyrene is formed from pyrene (41).

Many PAHs are metabolized by the cytochrome P-450 monooxygenase enzymes. They also induce this enzyme system. Phase 1 oxidative reactions yield arene oxides, phenols, quinones and dihydrodiols, phenol diols, diol epoxides and tetraols, as described in the metabolism of benzo(a)pyrene (37). Phase 2 conjugative steps yield glutathione conjugates and glucuronide and sulfate esters, which are subsequently excreted.

Epoxide and diolepoxide formation can yield metabolites with specific toxic capacity. Epoxide formation is catalyzed by aryl hydrocarbon hydroxylase enzyme in the cytochrome P-450 system. The action of epoxide hydratase and aryl hydrocarbon hydroxylase in special stereomeric molecular sites can yield a reactive diol-epoxide with strong carcinogenic properties. One of the best known of these is 7,8-diol-9,10-epoxide of benzo(a)pyrene (37).

The biotransformation of alkylsubstituted aromatic compounds takes place mainly by microsomal oxidation to more polar compounds. After conjugation they are excreted in urine.

1.4. Elimination

1.4.1. Lungs. No data concerning creosote are available. PAHs are not eliminated via exhaled air (37).

1.4.2. Gastrointestinal tract. Hepatobiliary excretion and elimination in feces is the major route by which metabolized PAHs are removed from the body, regardless of the route of absorption. In one experiment 70-75% of a subcutaneously injected dose of ^{14}C-3,4-benzopyrene was recovered in the feces of mice within six days following the injection (46,37). After topical application to the skin of mice, about 80% of the radioactivity of ^{14}C-benzo(a)pyrene and about 60% of thet of ^{14}C-7,12-dimethylbenz(a)anthracene was recovered in feces in seven days (69).

1.4.3. Kidneys. Some metabolites of aromatic and polyaromatic hydrocarbons are excreted in the urine. 1-Hydroxypyrene, a metabolite of pyrene, was found in excess in the urine of workers in a creosote pressure treatment plant (41). Naphthalene is excreted in urine as 1-naphthol (8,43).

Minor amounts of conjugated PAHs are excreted in urine. Four to 12% of a subcutaneously injected dose of ^{14}C-3,4-benzopyrene was eliminated in the urine of mice during a six-day follow up (46). After dermal application to mice 10% of the radioactivity of ^{14}C-labeled benzo(a)pyrene and about 30% of that of ^{14}C-labeled 7,12-dimethylbenz(a)anthracene was recovered in the urine in seven days (69).

Small-size PAHs (phenanthrene and fluoranthene) were detectable in the urine of workers exposed to coal tars in an anode plant (75). These compounds have not been detected in creosote exposed workers, but could be expected to be found after excessive exposure to creosote.

The importance of hepatobiliary metabolism and excretion in bile suggests that orally administered hydrocarbons would be excreted faster than compounds entering the systemic circulation without first passing through the liver. It was observed that 82% of an orally administered dose of 3-methylcholanthrene was excreted within 24 hours, while only 30% of an intraperitoneally administered dose was excreted in 72 hours (1).

1.5. Factors affecting the metabolic model

Enzyme induction in liver microsomes can enhance the metabolism of PAHs and increase the formation of reactive toxic metabolites. On the other hand, metabolic induction increases the metabolic clearance of PAHs (37).

2. TOXICOLOGICAL MECHANISMS

2.1. General toxicology

When creosote is given orally to experimental animals, acute toxic doses are as follows (48):

LD_{50} rat:	725 mg/kg
LDLo dog:	600 mg/kg
LDLo cat:	600 mg/kg
LDLo rabbit:	600 mg/kg

In a case of fatal ingestion of creosote, a multi-organ failure (liver, kidney, gastro-intestinal tract, heart) was attributed mainly to absorbed phenolic compounds (18).

The toxic effects of ingested creosote treated wood were studied in sheep and calves. Fine Douglas fir sawdust was pressure treated with creosote (40% creosote-60% sawdust, 3-4% phenolic compounds in creosote, w/v), mixed in water and administered to the animals by gastric tube. The acute fatal dose in sheep was estimated to be 4-6 g creosote/kg body weight. Daily administration to sheep of this creosote-treated sawdust in doses of 0.5 g/kg caused no apparent effect in 32 days, but 1.0 g/kg and 2.0 g/kg were fatal in 16 and 8 days, respectively. In calves daily dosages of 0.5 and 1.0 g/kg caused dose-dependent weight loss and starvation in 11 days. Signs of creosote intoxication included lethargy, dark-colored urine, liquid dark feces and loss of weight. Post-mortem examinations revealed inflammation of the gastrointestinal tract, cardiac hemorrhages, enlarged lymph nodes and degenerative changes in abdominal viscera (2,30).

2.2. Toxicological mechanisms

Exposure to creosote occurs mainly by inhalation of vapors and aerosols and by skin contact with creosote-treated wood. Exposure may result in direct toxic effects on respiratory organs and skin. The absorbed compounds may also elicit toxic effects in internal organs. With regard to exposure quantity and toxicological potency, the most interesting compounds are the carcinogenic and phototoxic PAHs. The most relevant target organ for toxic effects appears to be the skin.

PAH compounds are capable of inducing metabolizing cytochrome P-450 dependent microsomal enzymes in skin cells. In a study by Mukhtar et al. (59) crude coal tar was demonstrated to induce the monooxygenase enzymes aryl hydrocarbon hydroxylase, 7-ethoxyresorufin O-deethylase and 7-ethoxycoumarin O-deethylase, with increased formation of toxic PAH metabolites. In addition, ultraviolet light (UVB, 280-320 nm) caused microsomal enzyme induction, which had an additive or synergistic effect on microsomal enzyme induction caused by PAHs (59).

It is probable that other aromatic hydrocarbons in creosote can also elicit microsomal induction. The carcinogenic potency of different fractions of solvent-refined coal were studied. The high boiling (above 450^{o}C), neutral PAH fraction had clearly the highest tumor-initiating potency on mouse skin pretreated whit phorbol ester. The tumor-initiating activity of the distillates was not solely attributable to the concentration of benzo(a)pyrene or dibenz(a,h)anthracene, the presumed carcinogens. The overall initiating activity of complex mixtures of coal tar is highly dependent on interactions of many chemical carcinogens, and the relative concentrations of known carcinogenic PAHs are not the sole determinants of initiating activity (54). The PAH composition of coal tar derived solvents is very similar to that of creosote and skin contact with creosote may start the same kind of mechanism of tumor initiation and inhibition.

Certain PAHs in creosote (e.g. acridine, anthracene and phenanthrene) can absorb and emit light in the ultraviolet wavelength range and cause phototoxic skin reactions in sunlight (11). Phototoxic reactions are produced by UVA (wavelength 320-400 nm). Typically a phototoxic response involves a transient erythema that may be apparent immediately after exposure and is usually over within 1 or 2 days. The response is characterized by a localized burning sensation (27). The phototoxic reaction is believed to be mediated by the formation of a singlet oxygen in the presence of the phototoxic chemical and ultraviolet light. The singlet oxygen causes toxic responses in proteins, DNA and lipids of the skin (72). In one study of outdoor workers exposed to creosote, edema was reported to be a common symptom (57).

3. ORGAN EFFECTS

3.1. Skin, mucous membranes and conjunctiva

Exposure to creosote vapor can elicit irritative eye and skin symptoms, phototoxic skin reactions and skin discoloration.

3.1.1. Skin effects. Skin contact with creosote or exposure to creosote vapors can cause burning and itching of the skin. A phototoxic reaction in the form of markedly enhanced sunburns of skin exposed to ultraviolet light can arise from exposure to creosote vapor (55). Dermatitis was reported in 450 of 2,700 workers exposed to sawdust from of creosote-treated wood or dust from creosote-treated paper (40). Most of the cases had mild symptoms of redness and burning sensations and itching of the cheeks, nose, forehead and back of the neck resembling the appearance of mild erythema solare. In more severe cases intense burning was followed by deep bronze-brown pigmentation and scaling dermatitis. The fair-skinned workers seemed to be more susceptible, whereas negro workers showed a remarkable resistance to creosote (40). In one case report toxic and phototoxic skin reactions were observed in six workers after handling creosote impregnated ammunition boxes (35).

Workers handling tars and tar derivatives developed painful and burning skin sensations, often associated with erythema of the skin after exposure to sunlight (11). The best-known phototoxic compounds in coal tar are acridine, anthracene, phenanthrene and pyridine. These and other coal tar compounds can produce reactions which are nonimmunologic and can develop on the first exposure to these compounds. The longer wavelengths of ultraviolet light (320-400 nm, UVA) are responsible for the phototoxic skin reactions (11).

Dark coloring of the skin (melanosis) of the face and body was observed in a railway worker who had handled creosote impregnated railway sleepers. Anthracene was suspected as a causative agent (36). In Romania, 696 railway workers with exposure to creosote and other chemicals (mineral oil, coal and potassium dichromate) were studied. Dermatological manifestations were noted in 11.9% of them. The symptoms included phototoxic dermatitis, edema and melanosis of the skin, vesiculo-bullous eczemas and tar keratomas (57). In the melanosis of the skin the phototoxic chemicals stimulate the

melanocyte activity and are also incorporated in the basal cell layer of the skin, causing permanent discoloration resembling a tattoo.

In an American study of 329 creosote pressure treatment workers, 3 % had pustular folliculitis, mainly in the thigh regions. Most workers had been exposed more than 5 years, and some of them for over 20 years (26).
In a health examination of 11 workers in a pressure treatment plant, 2 cases of oil acne and 3 cases of pitch warts were detected; creosote was considered the probable causative agent. In addition 4 earlier cases of skin discoloration were reported by the workers (55).

A case of papillomatous wart-like skin growth was reported in a worker who handled railway sleepers (52). There is another case report of one creosote worker with multiple warts; microscopic examination revealed squamous cell papilloma (29).

3.1.2. Eye effects. Chemical conjunctivitis, with burning and tearing, photophobia, swelling of the lids and corneal scars, has been reported with chronic exposure to coal tar pitch volatiles (eg. creosote aerosols)(56). In a health effect survey in a pressure wood treatment plant 9/11 workers complained of burning, tearing and redness in the eyes (55). Corneal opacities which caused visual disturbances were seen in two gardeners who had used creosote as a pesticide (9). Among 450 workers with creosote skin burns, 15 % also had ocular symptoms: redness, photophobia and tearing. Corneal injuries, ranging from small isolated abrasions to permanent corneal scars and caused by sawdust from creosote-treated wood, were detected in 3 % of these workers (40). Naphthalene, the most abundant component of creosote vapor, can cause eye irritation at concentrations of 80 mg/m^3 (15 ppm) or higher (28). Peripheral lens opacities are produced in experimental animals by feeding them with naphthalene (28).

3.2. Respiratory system

No human data on respiratory effects are available. A liquid aerosol of coal, which has largely the same PAH composition as creosote, caused chemical bronchitis in guinea pigs after 12 days of exposure to 190 mg/m^3 (6 hr/day, 5 days/week).

3.3 Gastrointestinal canal

In a case of fatal creosote poisoning (drinking of 1 liter of creosote), petechial hemorrhages were found over the serosal surface of the lower jejunum and ileum (18).

3.4. Liver

There are no data available concerning liver effects of occupational exposure to creosote.
In a case of intentional fatal creosote poisoning (ingestion of one liter of creosote) liver histology showed degeneration and necrosis of hepatocytes with minimal inflammation. The morphological changes were assumed to have been caused by the phenolic compounds in the creosote (18).

3.5. Kidney

An acute tubular necrosis was established in the above-mentioned fatal case of creosote ingestion.

3.6. Blood and and blood-forming organs: Naphthalene, a major component of creosote, can cause acute hemolysis with liver and kidney damage after a massive exposure, e.g. accidental ingestion or inhalation (53). No hemolytic consequences are described in connection with occupational exposures.

3.7. Heart and circulatory system

Petechial hemorrhages were noted over the pericardium in the above case of fatal acute creosote poisoning by ingestion (18).

3.8. Central nervous system

Headache, giddiness, nausea, vomiting and/or copious salivation were reported by 113 out of 120 workers who had sprayed warmed creosote in a coal concentrate production plant (air concentration up to 10 mg/m^3)(24). Of 450 workers with creosote skin burns, 11 (2.4%) also complained of general symptoms such as depression, weakness, severe headache, slight confusion, vertigo, nausea and increased salivation (40).

3.9. Peripheral nervous system.
No data.

3.10.-3.11. Reproduction and fetus.
No data.

4. ALLERGY

No true allergy has been reported in connection with creosote exposure. Phototoxic dermatitis (so called photosensitization) is described in sections 2.2. and 3.1.1.

5. GENOTOXIC EFFECTS

Many creosote components have mutagenic properties in test systems. In particular some unsubstituted PAHs (e.g. benzo(a)pyrene) are well known experimental mutagens. Some creosote components (e.g. methyl naphtalenes) can also function as inhibitors of genotoxic effects(75).

5.1. Mutagenicity in test systems

Creosote and a coal-tar-creosote mixture were both mutagenic in Salmonella typhimurium TA 1537, TA 98 and TA 100 with microsomal activation; no activity was observed without microsomal activation, or in strain TA 1535 (71).

Similar positive results were reported in another study with Salmonella typhimurium TA 1537, TA1538, TA98 and TA100 in the presence of microsomal cell fraction. The strongest response was obtained with strains TA 98 and TA 100; no activity was observed with strain TA 1535 (12). The same compounds did not induce mutations in Escherichia coli strain WP2 (71). Fractions of creosote (separated by thin layer chromatography) were also mutagenic in Salmonella typhimurium TA98 in the presence of microsomal activation. The mutagenic activity in these fractions was ascribed primarily to benzo(a)pyrene and benz(a,h)anthracene, but also an unrecognized more polar fraction had remarkable mutagenic activity (16).

Both creosote and a coal-tar-creosote mixture induced a concentration-dependent mutagenic response in the L5178 mouse lymphoma cell system (TK+/-) with microsomal activation. A much higher concentration was required to induce a positive response in the absence of microsomal activation (58).

5.2. Mutagenicity of creosote vapors

Volatile components of creosote and coal tar were mutagenic with Salmonella typhimurium TA98 and TA100 strains in the presence of microsomal activation in the "taped plate assay": a bottom plate containing creosote and an agar top plate with test strain were taped together and incubated at 37 ^{o}C for 5 hours. Mutagenicity in the agar was determined normally after a further 48 hours of incubation (15).

5.3. Mutagenicity of contaminated surfaces

The contamination of work areas with creosote was studied by application of 5 ml of solvent (acetone or ethanol) on a work area surface. The solvent was mopped up with a paper tissue, extracted and tested for mutagenicity with Salmonella typhimurium strain TA98 with microsomal activation. A clear increase in surface mutagenicity was detected on the door of a

pressure cylinder, on the transport vehichle and on non-treated wood near the pressure cylinder in the treatment plant (14).

5.4. Mutagenicity of urine

The urine of rats given creosote (250 mg/kg i.p.) was mutagenic for Salmonella typhimurium TA98 and TA100 when tested in the presence of beta-glucuronidase and microsomal activation (higher activity) or with beta-glucuronidase alone (lower activity)(13).

5.5. Chromosome effects:
No data.

6. CARCINOGENICITY

Creosote contains many PAH compounds with mutagenic and carcinogenic properties. Some PAHs, heterocyclic nitrogen bases and aromatic amines in creosote have carcinogenic properties (75).

The U.S. Environmental Protection Agency (EPA) has collected data concerning the risks associated with exposure to carcinogenic chemicals (3). Two sets of information are used in the evaluation of each chemical: a grouping based on IARC criteria for classification and a potency factor estimate. The IARC classes used in this document are the following:

1. Human carcinogen (sufficient epidemiological evidence)
2. Probably carcinogenic to humans.
   2 A. Limited evidence of carcinogenicity in humans
   2 B. Sufficient evidence of carcinogenicity in animals
3. Cannot be classified as to its carcinogenicity to humans.

The potency factor is the reciprocal of the chemical dose which is estimated to cause a 10% life-time cancer risk. The hazard ranking of a substance is derived by combining both ranking systems. Evaluations for some creosote components are presented in table 4.

Table 4. EPA ranking of the risks associated with exposure to certain creosote components (3).

Component	IARC class	Potency factor	Hazard ranking
Acenaphthene	3	--	--
Anthracene	3	--	--
Benzo(a)pyrene	2B	500.0	High
Benzo(b)fluoranthene	2B	150.0	High
Benzo(k)fluoranthene	3	--	--
Benz(a)anthracene	2B	21.0	Medium
Chrysene	2B	5.0	Low
Creosote	2A	58.0	Medium
Dibenz(a,h)anthracene	2B	1000.0	High
Fluoranthene	3	--	--
Fluorene	3	--	--
Phenanthrene	3	--	--
Pyrene	3	--	--

6.1. Carcinogenicity in humans

6.1.1. Case reports. Three cases of skin cancer were reported in men occupationally exposed to creosote in timber preservation plants. In one worker warts had preceded skin cancer (38,63).

A metastasizing squamous cell epithelioma was detected on the hand of a worker employed for 33 years in carrying creosoted wood (22,38).

The British Medical Inspector of Factories reported 3,753 cases of epitheliomata from 1920 through 1945. Among these cases were 37 associated with exposure to creosote: 14/37 among workers treating timber with creosote, 8/37 associated with handling creosote in storage, and 10/37 among people using creosote as a releasing agent for brick moulds. Head, neck and arms were most often affected in the first two groups. Scrotal lesions were noted in the brick makers (34,38).

6.1.2. Epidemiological studies. The calculated crude mortality rate for scrotal cancer during 1911-1938 among brickmakers exposed to "creosote oil" was 29/1000 000 (9 cases), as compared to 4.2/1000 000 for the national average in Britain and rates of 1/1000 000 or less for groups not exposed to suspected skin carcinogens (33,38).

In a study of 123 Swedish workers exposed to creosote and arsenic between 1950 and 1980, 8 cases of different malignancies were detected as compared to 6 expected on the basis of national statistics. In a subgroup of 21 workers who had been exposed only to creosote for five years or more, 3 cancer deaths (leukemia, pancreatic and stomach cancer) were observed compared to 0.8 expected (5).

The IARC states that there is limited evidence that coal tar derived creosotes are carcinogenic to humans (38).

6.2 Carcinogenicity in animals

Several studies have confirmed the dermal carcinogenity of creosote in mice when applied repeatedly to the skin.

Creosote oil and anthracene oil were tested in groups of 50 male and female albino mice by twice-weekly dermal applications for at least 25 weeks. In the group receiving creosote oil, 10/19 animals surviving were found to have papillomas and 9/19 had large keratinizing carcinomas. In the group receiving anthracene oil, 8/20 surviving at 25 weeks were found to have papillomas and 6/20 had large keratinizing carcinomas (38,79).

In another study one drop (0.009 ml) of a 20% or 80% solution of creosote in toluene was applied three times a week for 44 weeks to the skin of two groups of 10 female C57I mice. Every mouse developed papillomas, and seven mice in each group developed epidermoid carcinomas, some of which metastasized to

pulmonary or regional lymph nodes. The time to papilloma appearance in 50% of the animals was 26 weeks for those receiving 20% and 21 weeks for those receiving the 80% solution. Control animals receiving toluene alone did not develop any neoplasms. Light creosote oil was tested in male C57Bl mice by applying one drop of a 50% solution in toluene three times a week for life. Of the 11 mice surviving 20 or more weeks of treatment, all developed skin tumors within 45 weeks (38,64).

Creosote oil (2% solution in acetone) was applied twice weekly for up to 70 weeks to a group of 30 female Swiss mice. Among the survivors 13/26 were found to have 23 skin tumors, of which 16 were classified as carcinomas. The average latency for development of the tumors was 50 weeks (38,49).

Undiluted creosote was applied twice weekly in amounts of 25 ul to the skin of 30 random-bred female mice. At the end of the experiment (28 weeks), the mice had an average of 5.4 papillomas per mouse and 82% had carcinomas. Similar application of creosote to another group of 30 mice for only four weeks followed by 32 weeks of observation resulted in no skin tumors. A third group treated with creosote for four weeks followed by twice-weekly applications of 25 ul of 0.5% croton oil in benzene developed 2.8 papillomas per mouse at 28 weeks and 4.4 papillomas per mouse at 36 weeks; 46% had carcinomas at week 44. A control group given croton oil alone also developed skin tumors at a lower rate (0.1 papilloma per mouse at 28 weeks), but, by 44 weeks, eight of 26 surviving mice given croton oil alone had 13 papillomas and one carcinoma (17,38).

A basic fraction of creosote was tested in mice for modifying effects on benzo(a)pyrene-induced tumorigenesis. A group of 100 female strain A mice was divided into five subgroups and painted three times a week (124-125 times altogether)

with a 1 % solution of the basic creosote fraction in benzene, 0.02% or 0.05% benzo(a)pyrene in benzene, or 0.05% benzo(a)pyrene in benzene containing 1% of the basic fraction of creosote. No tumor was found in any of the mice receiving the basic creosote fraction alone. However, the latent period before tumor appearance was shorter for the groups receiving benzo(a)pyrene and the basic fraction of creosote than it was for mice receiving benzo(a)pyrene alone, suggesting that the basic fraction of creosote shortened the latency of tumorigenic effects of benzo(a)pyrene (20,68). A phenolic fraction of creosote showed an enhancing effect on benzo(a)pyrene tumorigenity (20,38).

The IARC has stated that there is "sufficient evidence" that creosote and creosote oils are carcinogenic to experimental animals (38).

7. EXPOSURE INDICATORS

Exposure to creosote can take place via pulmonary absorption of volatile and aerosol components and via skin absorption of creosote components. Significant exposure to creosote aerosols is restricted mostly to processes in which creosote is warmed (e.g. pressure treatment of wood) or occasions when creosote-treated wood is heated (e.g. arc-welding in railway repair). The possibility of skin absorption is, however, obvious in all processes in which creosote or creosote treated wood is handled (31). Because of the many different compounds, chemical forms and routes of exposure there is no single ideal hygienic or biological indicator of creosote exposure.

7.1. Air concentration

7.1.1. Sampling of creosote aerosols. Creosote aerosols are collected on a filter (glass fiber with silver plate filter) and Soxhlet-extracted from the filter with hot benzene. The yield, which consists mainly of PAH compounds, is called coal tar pitch volatiles (CTPV) or particulate polycyclic aromatic

hydrocarbon (PPAH) and benzene-soluble matter (BSM). Many other solvents have also been used for the extraction of filters. The most common are cyclohexane, acetone, diethyl ether, dicloromethane, methanol and acetonitrile. Ultrasonic extraction has been found to be superior to Soxhlet extraction for most PAHs and solvents (4).

Creosote aerosols contain about 20 % large molecular PAHs. (19). Andersson and coworkers suggest a threshold limit value for coal tar PAHs of 100 ug/m^3, which corresponds to 0.2 mg/m^3 for total CTPV (3).

On the other hand the solvent extraction method has been criticized because of its poor reproducibility in the working environment (74).

7.1.2. Sampling of volatile components of creosote. To catch the volatile compounds in coal tar products, solid adsorbents have been added as a back-up behind the filter. Porous polymers such as Tenax GC and XAD-2 have been used for sampling from stationary sources and Chromosorb 102 for personal sampling of PAH in the workplace atmosphere. For desorption from solid adsorbents benzene (Chromosorb 102), pentane (Tenax GC) and dichloromethane (XAD-2) have been used (4).

7.1.3. Air exposure in workplaces. The most volatile creosote components are naphthalene, methylnaphthalene, acenaphthene, benzothiophene, biphenyl, fluorene, indene, methylstyrene and phenol (31,31a). Naphthalene alone represented 50-75% of volatile creosote components in the hygienic surveys made in the pressure treatment plants (31,31a,67).

The volatile components of creosote identified by Heikkilä et al. (more than 98% of all volatile compounds) are presented in table 5.

Table 5. The volatile components of creosote found in air in wood preservation plants and around repair and assembly of switches in railways, given as relative amounts (31,31a).

compound	its relative amount in creosote vapor
benzene	x
toluene	xx
xylenes	xx
trimethyl benzenes	xx
methyl ethyl benzenes	x
styrene	x
benzonitrile	x
phenol	xxx
benzofurane	xx
methyl styrenes	xxx
indene	xxx
cresols	xxx
methyl indene	xx
xylenols	xx
naphthalene	xxxxx
benzothiophene	xxx
quinoline	x
isoquinoline	x
methyl benzonitrile	x
methyl naphthalenes	xxxx
diphenyl	xx
dimethyl and ethyl naphthalenes	xxxx
acenaphthene	xxx
dibenzofuran	xx
fluorene	xx
dibenzothiophene	x
acenaphthylene	x

x-xx = less than 5 %
xxx = 5-15 %
xxxx-xxxxx = more than 15 %

Compounds with vapor pressure equal to or greater than that of acenaphthene can be found in the vapor phase in exposure situations. The 3-4 ring compounds beginning from fluorene are the usual constituents of the aerosols collected on the filter in the exposure situations (compare table 3, page 10).

Exposures to creosote vapors and aerosols in different workplaces are summarized in table 6.

Table 6. Air exposure to volatile creosote components, creosote aerosols, PAHs and benzo(a)pyrene in different workplaces.

Compound	Exposure level	Process
creosote vapors	0.3-10.6 mg/m^3	Pressure treatment of wood (31,31a,67)
	1.9-11 mg/m^3	Railway switch assembly shop (31,31a)
creosote aerosols	0.00013-0.20 mg/m^3 (max 1.67 mg/m^3)	pressure treatment of wood (55,67,74)
	0.02-0.059 mg/m^3	handling creosote treated pilings (6)
PAHs	2.3-130 ug/m^3	pressure treatment of wood (31,31a,55)
	0.4-22 ug/m^3 (max 36 ug/m^3)	railway switch assembly shop (31,31a,45)
	7.5-81 ug/m^3	rail switch welding (31,31a)
benzo(a)pyrene	0.04-0.07 ug/m^3	pressure treatment of wood (44)
	1.0 ug/m^3 (max)	railway switch assembly shop (45)

7.2 Skin exposure

The skin of workers in creosote wood treatment plants frequently becomes contaminated with creosote (31). Skin exposure is also common in the handling of creosote treated railway sleepers and telephone poles. There is no reliable method for estimation of skin exposure to creosote. Proposed methods involve estimations based on patch sampling from outside and inside of work clothing or biological monitoring (eg. in urine) of creosote components.

7.3. Biological monitoring

Exposure related excretion of urinary 1-hydroxypyrene, a metabolite of pyrene, was detected during the working week in a creosote impregnating plant. Much higher urinary 1-hydroxypyrene was found after dermal application of coal tar ointment (41). Urinary metabolites have also been monitored with exposure to coal tars. Elevated 1-hydroxypyrene levels were detected in the urine of workers in a coal tar distillation plant (42).

Urinary 1-naphthol has been detected after naphthalene exposure (8,43). For exposure to creosote vapors, 1-naphthol in urine could probably serve as a tool for biological monitoring.

Small size polycyclic aromatic hydrocarbon compounds (phenanthrene and fluoranthene) were detectable in the urine of workers exposed to coal tar aerosols in an anode plant (76). Methodological improvements have recently been made in the monitoring of urinary PAHs (7). 3-Hydroxy-benzo(a)pyrene has been proposed for biological monitoring of PAH exposure (42).

Analysis of urinary mutagenicity has sometimes been proposed for the biological monitoring of exposure to complex chemical mixtures including genotoxic components. In the context of exposure to coal tar pitch volatiles, both positive (47,60,65) and negative (77) results concerning the mutagenicity of urine have been reported. Increased urine mutagenicity was detected after treatment of psoriatic skin with coal tar (78).

The urine of workers in a creosote treatment plant was not found mutagenic with Salmonella typhimurium TA98 in the presence of beta-glucuronidase and microsomal activation (13).

Thus, it is possible that there is no single ideal biological indicator of creosote exposure.

8. RELATION BETWEEN EXPOSURE, EFFECT AND RESPONSE

8.1. Effects of acute exposure

Acute responses of relevance are eye and skin irritation and phototoxic dermatitis. No dose-response relation can be drawn from available vapor and aerosol exposure data.

8.2. Effects of long term exposure

Keratitis, skin discoloration (melanosis), toxic and phototoxic dermatitis, eczema, pitch warts and skin cancer are described as consequences from long-term exposure to creosote. No valid correlation between dose and response is available, except for experimental carcinogenicity in the skin of mice.

9. NEEDS FOR FURTHER RESEARCH

The chemical complexity of creosote makes it difficult to name the chemicals which specificially cause the toxic responses. Further studies for clarifying the compounds behind acute oral toxicity, dermal reactions and carcinogenity are indicated.

Epidemiological studies on cancer and mutagenic hazards among creosote exposed workers are needed.

Studies concerning the quantity and consequences of skin exposure are of primary interest in estimating the risk in creosote work.

Further investigation and development of methods for the biological monitoring of workers exposed to creosote are needed.

10. DISCUSSION AND EVALUATION

Creosote is a very complex mixture of chemical compounds derived from coal tar by distillation processes. Commercial creosote consists mostly of 2-6 ring cyclic aromatic hydrocarbons. Among these compounds are the known mutagenic and carcinogenic benzo(a)pyrene and dibenz(a,h)anthracene. Creosote is classified as an agent for which there is "sufficient evidence" of carcinogenity in experimental animals and "limited evidence" of carcinogenity in humans (38).

Most creosote components are poorly vaporized, and occupational exposure is usually connected with aerosol formation in the handling of freshly treated wood or when heating the creosote-treated timber, e.g. in welding in railway construction work. The percentage of carcinogenic PAHs in the volatile part of creosote is probably less than that in liquid creosote because of the slight volatility of these compounds. However, in the gas phase, there may be more of some highly volatile carcinogens such as aromatic amines (62).

Contamination and absorption in and through the skin is likely when creosote is handled. Creosote leakage from treated wood such as telephone poles may continue for many years after the treatment. It is obvious that the critical adverse effect of creosote is its carcinogenicity. Other harmful effects are eye and skin irritation and phototoxic skin reactions. Data regarding exposure-response relationships for the above effects are almost nonexistent. It is possible that in the occupational setting skin exposure to creosote is as important as exposure via inhalation. Prevention of skin contact and contamination is therefore of great importance.

Judging from exposure measurements around creosote pressure treatment of wood, the exposure to benzo(a)pyrene in these plants is comparable to exposure to benzo(a)pyrene in tobacco smoke (39). Creosote aerosol should be regarded as a probable carcinogen and exposure should be reduced to the least possible. Skin contact by creosote is likewise a probable cancer hazard, but the few cases reported might suggest that it is not a great one. Epidemiological studies are insufficient for drawing any conclusions regarding the cancer risks of occupational exposure to creosote.

11. SUMMARY

J. Liira: Creosote: 78. Nordic expert group for documentation of occupational exposure limits.

A survey of literature on creosote valuable as a basis for occupational exposure limits is presented.

Creosote, derived from coal tar by distillation, consists mostly of 2-6 ring polyaromatic hydrocarbons. Exposure to creosote vapors (naphthalene 50%) and aerosols (PAH compounds) takes place during wood treatment and handling of creosoted wood. The skin contact is, however, probably the most important route of exposure.

In humans phototoxic erythema, hyperpigmentation, desquamation, warts and carcinoma of the skin have been reported. Creosote is a skin carcinogen in experimental animals.

The probable carcinogenicity of creosote to humans is the critical health effect of long term exposure to creosote.

A Swedish version is available, 80 references.

Key words: Creosote, coal tar, occupational exposure limits, skin irritation, skin cancer.

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Appendix I. Occupational exposure limits for airborne creosote.

Country	mg/m^3	Year	Note	Ref.
BRD	-	1987	C, removed	2
France	-	1985	C	6
Great Britain[1)]	0.2	1986	C	1
Netherlands[1)]	0.2	1985	C	3
USA (ACGIH)[1)]	0.2	1987-88	C	5
(OSHA)[1)]	0.2	1977		4
(NIOSH)[2)]	0.1	1977		4

1) Benzene soluble fraction
2) Cyclohexane soluble fraction
C Carcinogen

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Methyl isobutyl ketone

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CONTENTS

BACKGROUND

Areas of use

Methyl isobutyl ketone (MIBK) is a solvent used in glues, paints and cleaners. MIBK is also used in plastic and in the oil industry. MIBK is flammable.

Chemical and physical data

Chemical name	Methyl isobutyl ketone
CAS No.	108-10-1
Synonyms	Hexon, isopropyl acetone, 4-methyl-2-pentanone, 2-methyl-4-pentanone, isobutyl methyl ketone, MIBK.
Basic formula	$C_6H_{12}O$
Chemical structure	$CH_3CH(CH_3)-CH_2-C(=O)-CH_3$
Molecular weight	100.16
Boiling point	116.85°C at 101.3 kPa
Vapor pressure	1.33 kPa at 30.0°C
Saturated concentration in air	40 g/m^3 at 25°C
Density at 20°C	0.798
Constants	1 mg/m^3=0.244 ppm, 1 ppm=4.10 mg/m^3

At room temperature MIBK is a clear fluid with a sweet odor. MIBK is sparingly soluble in water and has good solubility in alcohols, benzene, ether, acetone and chloroform.

1 METABOLIC MODEL

Methyl isobutyl ketone (MIBK) is a small molecule which penetrates fat easily (22). Unfortunately, information concerning the toxicokinetics of MIBK is lacking for both animals and man.

1.1 Uptake

1.1.1 Skin and mucous membranes

There is no information concerning uptake of MIBK through skin or mucous membranes.

1.1.2 Respiratory organs

There are no studies concerning uptake of MIBK via the lungs. Uptake through the lungs is probably rapid, since among guinea pigs an increased exposure to MIBK produced increased narcosis (25). At inhalation of 68,000 mg/m^3 (1.68 volume per cent) nine out of ten guinea pigs died within 3 h; dead was sooner at higher exposure levels (25).

1.1.3 Digestive tract

There is no information concerning uptake of methyl isobutyl ketone through the gastro intestinal tract.

1.2 Distribution

There are no distribution studies of MIBK, but some information can be obtained from its partition coefficients. The partition coefficients of MIBK are 79 for water/air, 90 for blood/air and 926 for oil/air (for comparison: styrene=5465 and acetone=86) (22). MIBK is ten times more soluble in oil than in blood and twelve times more soluble in oil than in water. This indicates that MIBK could accumulate in fat tissue.

1.3 Biotransformation

After intraperitoneal administration of MIBK to guinea pigs two metabolites were identified in serum: 4-hydroxy-4-methyl-2-pentanone and 4-methyl-2-pentanol (4). The most stable metabolite of MIBK is MIBK's alcohol, 4-methyl-2-pentanol, produced by reduction

(4). The hydroxylated ketone (4-hydroxy-4-methyl-2-pentanone) is formed through oxidation (4). Both metabolites can be conjugated with sulfuric acid or glucuronic acid or can enter the intermediary metabolism and be eliminated as carbon dioxide. They could also be hydroxylated, probably via the cytochrome P-450 system, to 3-hydroxy-2-pentanone and 4-methyl-4-hydroxy-2-pentanone, respectively (4).

1.4 Elimination

1.4.1 Respiratory organs

It is probable that MIBK is eliminated (exhaled) via the lungs. The carbon dioxide that is formed in its metabolism can be exhaled via the lungs.

1.4.2 Kidneys

MIBK has been detected in the urine of healthy subjects, thus indicating that an elimination in unchanged form in urine is possible (35). Whether the MIBK found in the urine is due to exposure to solvents or is a natural metabolite cannot be determined (35). It is also possible that metabolites are excreted in the urine, e.g. as derivates of glucuronic acids.

1.4.3 Digestive tract

No information is available.

1.5 Biological half times

The half time for MIBK in serum of guinea pigs was 66 min, and the elimination time was 6 h (4). The elimination time for the metabolite 4-hydroxy-4-methyl-2-pentanone in serum was 16 h (4).

1.6 Factors that can affect the metabolic model

No information is available.

2 TOXICOLOGICAL MECHANISMS

The toxicological mechanisms of MIBK are unknown. In animal experiments death probably has been caused by the paralyzing effect of MIBK on the respiration center in the CNS, by cardiac arrest, or through congestion due to increased secretion in the respiratory tract (21, 25). Panson and Winek (21) suggest that pulmonary edema or pulmonary bleeding is a less likely cause of death, since these changes were seldom noted in the lungs of dead animals that had been exposed to MIBK.

3 TOXICITY

MIBK has a low toxicity when administered orally. For rats, the LD50 value for peroral administration was 2080 mg/kg when the substance was administered as 20% emulsion in tergitol 7 surfactant (24). When MIBK was administered orally in a concentrated form to rats, the LD50 value was 5.7 ml/kg, corresponding to 4500 mg/kg (24). For mice, the LD50 value for peroral administration was 1900 mg/kg (33).

With intraperitoneal administration, the LD50 value for mice was 590 mg/kg (33).

Mortality from inhalation was studied for guinea pigs, rats and mice (table 1). When rats were exposed to 8200 mg/m^3 (2000 pm) for 4 h all animals survived (24). Also, when guinea pigs were exposed to 4100 mg/m^3 (1000 ppm) for 24 h, all animals survived (25).

Table 1. Mortality from inhalation of MIBK.

Dose mg/m^3	ppm	Duration of exposure	Species	Comments	Ref
74,200	18,100	45 min	Mouse	LC50	33
68,880	16,800	2 h	Guinea pig	9 of 10 dead	25
16,400	4000	4 h	Rat	All animals dead (6/6)	24
8200	2000	4 h	Rat	None dead (0/6)	24
4100	1000	24 h	Guinea pig	None dead (0/10)	25

4 EFFECTS ON ORGANS

4.1 Skin and mucous membranes

Irritation of the eyes was reported by 16 of 19 workers exposed to 330-2100 mg/m^3 (80-500 ppm) MIBK (16). The workers were exposed while centrifuging products in an industrial setting. This task was performed during only 20-30 min per 8 h-working day. The higher value of 2100 mg/m^3 (500 ppm) was registered in the vicinity of the centrifuge; in other parts of the setting the values were lower. When the centrifuge was not in operation the exposure to MIBK was low or zero. The methods used for exposure measurements are not described. There was probably a mixed exposure to acetone, since that also was in the process, but there is no information about the acetone exposure. A follow-up five years later included 14 of the original 19 workers. The exposure was then 430 mg/m^3 (105 ppm) in the vicinity of the centrifuge and 200 mg/m^3 (50 ppm) elsewhere in the industrial setting during 15-30 min per working day when the centrifuge was in operation and only one worker reported irritation in the eyes (2).

Twelve healthy subjects were exposed for 15 min to various concentrations of MIBK (23). A majority (number not reported) experienced irritation at the exposure to 410 mg/m^3 (100 ppm) (23). The tolerance limit for eye irritation was found to be 820 mg/m^3 (200 ppm) (23).

In mixed exposure to 80 mg/m^3 (20 ppm) or 20 mg/m^3 (5 ppm) methyl isobutyl ketone combined with NO_2 (1.8 mg/m^3 = 1 ppm) during radiation by mercury lamps, the time before onset of eye irritation was 27 and 23 sec, respectively, among the healthy subjects (31). This was significantly different from the time before eye irritation was experienced for ethanol, isopropanol, acetone or perchloroethylene (31).

Three of the 19 workers exposed to MIBK (330-2100 mg/m^3) had eczema on hands and forearms (16). When preventive measures (gloves and barrier creams) were introduced, the eczema disappeared (16).

4.2 Respiratory organs

At an exposure to 330-2100 mg/m^3 (80-500 ppm) (see 3.1) 13 out of 19 workers had complaints of nose and throat irritation (16). Two of the workers had bronchitis (16).

In cats bronchoconstriction was caused by inhalation of MIBK at exposure levels of 410 mg/m^3 (0.01%) (non significant) or 2100 mg/m^3 (0.05%) (significant) (33). The transpulmonary pressure was significantly increased at exposure to 4100 mg/m^3 (0.10%) (33). Intravenous administration of MIBK did not cause bronchoconstriction. It was suggested that MIBK stimulated irritant receptors in the airways of the cats, and the bronchoconstriction was caused by vagal reflexes.

Exposure to 68,900 mg/m^3 (1.68 volume per cent*) caused immediate reactions in the airways of guinea pigs: repetitive sneezing, salivation and coughing, and the guinea pigs started to scratch the nose intensively (25). The guinea pigs also showed a rapid decrease of breathing frequency (25). These phenomena can be explained by an irritating effect in the upper airways.

4.3 Liver

There was no effect on ornithine carbamyl transferase in serum (OCT) or liver pathology when 500 and 1000 mg/kg of MIBK was deposed intraperitoneally in guinea pigs (5). Both relative and absolute liver weight was higher in rats continuously exposed to MIBK at 820 mg/m^3 for two weeks and to 410 mg/m^3 for 90 days, when compared to controls (30). Exposure to 410 mg/m^3 MIBK for two weeks resulted in no effect on absolute or relative liver weight or liver pathology in rats, dogs, monkeys, and mice (30). There was no change in clinical serum tests indicative of normal liver function (e.g. bilirubin and alkaline phosphatase).

4.4 Kidneys

Urine of 19 workers exposed to 330-2100 mg/m^3 (80-500 ppm) MIBK during 20-30 min daily (see 4.1) showed no evidence of pathology when checked for proteins, albumins, globulins and cells (16).

Kidney weight (both absolute and relative) increased in Wistar rats (sex was not specified) after two weeks of continuous exposure to 410 mg/m^3 MIBK (30). This concentration had no effect on kidney weight in dogs, monkeys, and mice (30). At exposure to 820 mg/m^3 MIBK for two weeks and to 410 mg/m^3 for 90 days the increase of kidney weight in rats was

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* This study was performed in 1938, i.e. before gas chromatographic methods were available for determination of concentration levels. Thus, the exposure level must be regarded as approximate.

greater than that when the rats were exposed to 410 mg/m^3 for two weeks (30). In a histological examination of the kidneys, MacKenzie (18, 30) found hyaline droplets in the proximal tubules on the first day of sacrifice (18, 30). The changes in the kidneys appeared with a variable decrease in severity throughout the exposure. The finding was named hyaline droplet toxic tubular nephrosis. The tubular nephrosis was reversible and was completely gone between the third and fourth week after termination of exposure (18). Rats, dogs and monkeys were exposed to 410 mg/m^3 MIBK for 90 days; there was a visible kidney effect only on rats (17). The kidney weight increased, and histological examination revealed tubular nephrosis with hyaline droplets and in some cases also foci with tubular necrosis (17). There was a linear relationship between exposure time and the extension of the tubular nephrosis (17). Rats, which were sacrified at different intervals after termination of the exposure showed complete reversal of the kidney changes 60 days after a period of 15 days of exposure (17). In rats exposed for 90 days the reversal of the tubular changes progressed more slowly.

The described kidney changes in rat have been shown by only one research group. The sex of the rats was not reported. Histological examinations of kidneys in species other than rats are not described.

4.5 Blood and blood-forming organs

In 19 workers exposed to 330-2100 mg/m^3 (80-500 ppm) MIBK during 20-30 min per day there were no effects on hemoglobin or on red and white cell counts (16).

When rats were exposed for 15 and 90 days to 410 mg/m^3 (100 ppm) MIBK there were no changes in total white or red cell counts (17) and no change of hematocrit (17). There was no effect on hematocrit, hemoglobin, of red or white cell counts in monkeys or dogs after exposure to 410 mg/m^3 or to 820 mg/m^3 for two weeks (30).

4.6 Digestive tract

Of 19 workers exposed to 330-2100 mg/m^3 (80-500 ppm) MIBK during 20-30 min per day, 16 experienced nausea, 10 experienced vomiting and 6 experienced diarrhea (16). A follow-up study of 14 of the 19 workers made when the exposure had decreased to 200-430 mg/m^3 (50-105 ppm) during 15-30 min per day showed that the gastrointestinal disturbances had decreased: only two of the workers experienced nausea (2). However, it is difficult to evaluate these gastrointestinal disturbances since there was no reference group.

4.7 Heart and blood vessels

ECGs of the 19 workers exposed to 330-2100 mg/m^3 (80-500 ppm) MIBK for 20-30 min per day showed no disturbance of cardiac rhythm and no signs of coronary ischemia (16).

Cats exposed to 410 mg/m^3 MIBK developed pulmonary hypertension, vasoconstriction and a decrease in arterial blood flow (33). The effect on lung vessels increased with increased exposure to MIBK, but there was no effect on the peripheral vessels (blood pressure and peripheral resistance) (33). A study of the effects of intravenous injection of MIBK gave evidence of an effect on smooth muscle in the lung vessels which was independent of the route of administration (33). A dose of 8 mg/kg or higher causes an effect on the lung vessel, however no effect was seen after an injection of 4 mg/kg intravenously (33). The lethal dose of MIBK was higher than 64-128 mg/kg (33). Dogs developed pulmonary hypertension at an exposure of 2100 mg/m^3, and reduced myocardial function measured as maximal pressure increased velocity in the left cardiac chamber at an exposure of 41,000 mg/m^3 (33). With simultaneous inhalation of trichlorofluoromethane and MIBK the negative effects on cardiac muscles were enhanced (33).

4.8 Central nervous system

Odor threshold In a test with four subjects trained in odor analytic work the reported odor was experienced as sweet and the threshold was reported 1.9 mg/m^3 (0.47 ppm).(15). Hellman and Small used a trained panel and found that 100% of the persons could recognize MIBK at a level of 1.15 mg/m^3 (0.28 ppm) (11). A literature survey by Amoore and Hautala (1) reported the geometric mean of 2.9 mg/m^3 (0.68 ppm) for odor thresholds reported in different articles (which were not specified) (1).

Neurasthenic symptoms Of the 19 workers exposed to 330-2100 mg/m^3 (80-500 ppm) MIBK during 20-30 min per day, 16 were reported to have neurasthenic symptoms (16). In a follow-up study five years later when the exposure had decreased to 200-430 mg/m^3 (50-105 ppm) only three of the 14 remaining original workers and one later employed worker reported neurasthenic symptoms (2).

Behavior In experiments in which four baboons were exposed to 205 mg/m^3 (50 ppm) MIBK during seven days the response time to stimuli was increased (7, 8, 9). The test the baboons performed was a "delayed match to sample discrimination test" which measures the

functions associative learning, visual short memory and reaction time (10). The increased response time in the exposed baboons is to be judged as an extended reaction time. An exposure to a mixture of 205 mg/m^3 (50 ppm) MIBK and 294 mg/m^3 (100 ppm) methylethyl ketone had an activating effect, noted by a decrease in response time and an increase in the number of extra responses (10). Mice (N=40) exposed for 4 hours to 2700-3700 mg/m^3 (662-892 ppm) MIBK decreased their times of immobility in a swimming test after exposure (3).

Rats exposed to 100-200 mg/m^3 (25-50 ppm) MIBK for 3 h increased their response frequency (pressing a lever to get food) in a Skinner box. For some rats the increased response frequency remained for several days after the exposure (6).

In vitro experiments with creatine kinase from rabbit muscle and adenylate kinase from mouse brain showed that MIBK in millimolar concentrations irreversibly decreased enzyme activity (12). The decrease in enzyme activity was less than that seen with acrylamide or methyl-n-butyl ketone (12).

4.9 Peripheral nervous system

Minimal distal axonal changes could be seen in rats exposed to 6150 mg/m^3 (1500 ppm) MIBK during 6 h/d, five days a week for five months (27). The dose was so high that a narcotic effect was seen in the animals after 4 h each exposure day (27). The changes were seen in the distal part of the tibial and ulnar nerves and were described as: "many axons containing large numbers of dilated glycogen-filled mitochondrial remnants, adaxonal Schwann cell invaginations and rare focal swellings" (27). These effects may have been caused by the MIBK used in the investigation, which was not purified and contained 3% methyl n-butyl ketone (MBK) which alone gives severe neuropathy (27) and/or a compression neuropathy depending on the type of cage used for the rats (26).

In a later experimental model 98.8% pure MIBK (MBK<1%) was used. Four cats were given 150 mg/kg by subcutaneous injection (26). A narcotic effect and increased salivary secretion were seen in the cats shortly after injection twice a day (26). After 40 and 135 days biopsies were taken from the hind legs. On the biopsies pacini receptors, plantar nerves and interosse muscles were studied. Histologically these tissues appeared no different from biopsies from cats exposed to methyl n-butyl ketone (MBK) alone or in a mixture with MIBK (26).

4.10 Reproductive organs

There is no information available.

4.11 Embryos

Pregnant rats and mice were exposed to MIBK in concentrations of 0 mg/m^3, 1230 mg/m^3 (300 ppm), 4100 mg/m^3 (100 ppm), and 12,300 mg/m^3 (3000 ppm) (29). At the exposure to 12,300 mg/m^3 the rats showed signs of maternal toxicity in the form of effects on weight, kidney weight and food intake (29). In mice toxicity was seen in the form of death (3/25) and increase in liver weight (29). Fetal toxicity was seen in rat only at an exposure to 12,300 mg/m^3 as reduced fetus weight and a delay in skeletal bone development (29). In mice the fetal toxicity was seen as an increased incidence of fetus death, reduced fetus weight, and a delay in skeletal development (29). There were no exposure-related malformations in the two different species at the different exposure levels (29).

5 ALLERGY

No information is available.

6 GENOTOXIC EFFECTS

No information is available.

7 CANCEROGENIC EFFECTS

No information is available.

8 EXPOSURE INDICATORS

8.1 Air concentrations

MIBK can be determined in air by sampling in charcoal tubes (19). The sample is desorbed in carbon disulfide and analyzed by gas chromatography. NIOSH has validated a measurement range of 208-836 mg/m^3 for the above method, reporting a coefficient of variation of 0.064 and a standard deviation of 17 mg/m^3 (20). Different absorbents were tested for sampling of MIBK by Levin and Carleborg (13). They found that recovery was high for XE-

348 with diethyl ether (94-101%). For charcoal tubes the recovery was 61-100%, with the lower value recorded after two weeks' storage of the sample at room temperature (13).

8.2 Biological indicators

MIBK in blood and urine from non-exposed humans can be determined with gas chromatography and mass spectrophotometry (34, 35). There is no information concerning the relation between exposure and MIBK in blood or urine. There is no information concerning excretion of biotransformation products.

9 EXPOSURE-EFFECT AND EXPOSURE-RESPONSE RELATIONSHIPS

9.1 Effects of short-term exposure

9.1.1 Acute, reversible effects (tables 2 and 3)

Irritation of the eyes is reported by human subjects at an exposure level of 410 mg/m^3 (23). The tolerance level for eye irritation was reported to be 820 mg/m^3 (23).

Behavioral disturbances have been reported in the rat at exposure to 100-200 mg/m^3 (6) and in the mouse at 2700-3700 mg/m^3 (3). The differences in effects may be due to different methods of measuring the disturbances in behavior, but may also be due to differences between the species.

Pulmonary hypertension was seen in cats at an exposure to 410 mg/m^3 and in dogs at an exposure to 2050 mg/m^3 (33).

9.1.2 Chronic effects

There is no information available for man.

Narcosis and deaths occur in rats exposed to 16,400 mg/m^3 and in guinea pigs exposed to 68,880 mg/m^3.

9.2 Effects of long-term exposure (table 4)

9.2.1 Reversible effects

In man nausea, vomiting, and diarrhea have been reported after 20-30 min per day of exposure to 330-2100 mg/m^3 during three months to one year (16). Undefined neurasthenic symptoms were present in a majority of workers exposed to 330-2100 mg/m^3 during 20-30 min per working day (16). Irritation of airways was reported for four of 14 workers exposed to 200-430 mg/m^3 for 15-30 min per working day (2).

In rats, exposure to 410 mg/m^3, 24 h/day for 14 days caused an increase in liver weight and toxic tubular nephrosis in the kidney (30). In studies on baboons the reaction time was impaired with an exposure of 205 mg/m^3, 24 h/day for seven days (7, 8, 9).

9.2.2 Permanent effects

There is no demonstrated evidence of permanent effects in man. In animals who survived the exposure to MIBK there are no reports of a permanent effect.

Table 2 Exposure-effect relationships in man for single exposures of MIBK.

Exposure/dose mg/m^3	ppm	Duration of exposure	Effect	Ref
330-2100	80-500	20-30 min	Eye irritation	16
820	200	15 min	Subjective tolerance level for eye irritation	23
410	100	15 min	Eye irritation in a majority	23
2.8	0.68		Odor threshold - mean value in a literature survey	1
1.9	0.47		Odor threshold for four persons trained in odor analytic work	15
1.15	0.28		Odor threshold - recognition level for a trained odor panel	11

Table 3 Exposure-effect relationships in different species for single exposures of MIBK.

Exposure/dose mg/m^3	ppm	Duration of exposure	Species	Effect	Ref
41,000	10,000	5 min	Dog	Impairment of myocardial function	33
12,300	3000	ca 3 h	Guinea pig	Irritation of airways and mucous membranes	25
2700-3700	660-890	4 h	Mouse	Toxic behavioral effect in swimming test	3
2100	500	5 min	Dog	Pulmonary hypertension	33
410	100	5 min	Cat	Pulmonary hypertension, vasoconstriction in lung vessels	33
100-200	25-50	3 h	Rat	Behavioral effect - response frequency in a Skinner box	6

Table 4. Exposure-effect relationships in man for long-term exposure to MIBK.

Exposure/dose mg/m^3	ppm	Duration of exposure	Effect	Ref
330-2100	80-500	20-30 min/work-day,3 months-1 yr	Nausea, vomiting, diarrhea, neurasthenia, irritation in eyes and airways	16
200-400	50-100	15-30 min/work-day for 5-7 yrs	Neurasthenia in 4 of 14, irritation in airways in 2 of 14	2

10 RESEARCH NEEDS

There is no information available about dose-response relationships in man concerning the effects of MIBK on the CNS (e.g. reaction time, behavioral effects), the upper airways and mucous membranes or kidney function. Toxicokinetic studies with human subjects should be made with MIBK alone and in mixture with other solvents. Skin penetration of MIBK should be assessed.

11 DISCUSSION AND EVALUATION

At exposure to high levels of MIBK, the most serious risk is death due to its narcotic effect. Of 19 workers exposed to 330-2100 mg/m^3 during 20-30 min per work day for three months to one year, 16 experienced neurasthenic symptoms (16). At a follow-up five years later when exposure had decreased to levels of 200-430 mg/m^3 only three of the remaining 14 workers and one later employed worker experienced neurasthenic symptoms. In 19 workers exposed to 330-2100 mg/m^3 MIBK during 20-30 min per work day the following symptoms were reported: nausea in 17, vomiting in 10, and diarrhea in 6 (16). In the five year follow-up, when the exposure had decreased to 200-430 mg/m^3 during 15-30 min per work day, the symptoms had decreased. Only two of the 14 remaining workers experienced nausea (2). Irritation of eyes was experienced by 17 of the 19 workers exposed to 330-2100 mg/m^3 (16). At the follow-up five years later, when exposure had decreased to 200-430 mg/m^3, only one worker experienced irritation in the eyes. When 12 healthy

subjects were exposed to various levels of MIBK, a majority experienced eye irritation at exposure to 410 mg/m^3 (23). Irritation in airways was experienced by 13 of the 19 workers exposed to 330-2100 mg/m^3 MIBK (16). At the follow-up five years later, with decreased exposure (200-430 mg/m^3), only two of 14 workers experienced airway irritation. Examination of blood and urine from the 19 workers exposed to 330-2100 mg/m^3 MIBK showed no effect on blood or kidneys.(16). The report of the 19 workers, which was followed up five years later after decreased exposure, is the only investigation of occupational exposure to MIBK (2, 16). In evaluating these reports, it must be borne in mind that the exposure levels were not precise, that the exposure was of short duration each working day, and that there may have been simultaneous exposure to acetone (2, 16). Unfortunately there are no toxicokinetic studies concerning uptake and elimination of MIBK in man. There are no dose-response relationship studies of MIBK in man. In occupational exposures, MIBK often occurs in combination with other organic solvents. Reports concerning interaction in man between various solvents and MIBK are missing. Healthy persons exposed to a combination of NO_2 (1.8 mg/m^3) and MIBK developed eye irritation at levels as low as 20-80 mg/m^3 (31). The odor threshold is between 1 and 3 mg/m^3.

In baboons an effect on the nervous system could be recorded at an exposure to 205 mg/m^3, 24 h per day for seven days. When a mixture of MIBK and methylethyl ketone (MEK) was used in the exposure of the baboons there was an activating effect on the CNS, compared to a depressive effect when the baboons were exposed to the two solvents separately (10). This implies that interactions between MIBK and other compounds may vary and are complicated. When MIBK and trichlorofluoromethane were simultaneously inhaled by dogs there was a potentiating of the negative effect on cardiac muscles (33). An evaluation of the mutagenicity of MIBK is impossible since no studies have been made. MIBK probably has no teratogenic effect, since studies on rats and mice have not shown any malformations. Fetal toxicity was seen at an exposure to 12,300 mg/m^3 MIBK in rats as reduced fetus weight and a delay in skeletal bone development (29). In mice the fetal toxicity was seen as increased incidence of fetus death, reduced fetus weight and a delay in skeletal development (29). There is no investigation concerning cancer in relation to MIBK exposure.

Guidelines in setting the occupational exposure limits for MIBK should be the levels for the CNS effects and the irritative effects.

12 SUMMARY

M. Hagberg. Methyl isobutyl ketone. 79. Nordic expert group for occupational standards.

A review of current literature for methyl isobytyl ketone (MIBK) is presented as a basis for discussion of occupational exposure limits. Neurasthenic as well as gastrointestinal symptoms in man have been reported for exposure levels of 330-2100 mg/m^3 during 20-30 minutes per day. Irritation of nose, throat, and eyes in man was reported at levels of 205-430 mg/m^3. When MIBK exposure was combined with NO_2 (1.8 mg/m^3) irritation of eyes was reported at levels of 20-80 mg/m^3. The odor threshold is between 1 and 3 mg/m^3. When mice and rats were exposed to MIBK (levels of 1230-12,300 mg/m^3) there was no increase in fetal malformations. Fetal toxicity was seen at an exposure to 12,300 mg/m^3 MIBK in rats as reduced fetus weight and a delay in skeletal bone development. In mice the fetal toxicity was seen as increased incidence of fetus death, reduced fetus weight and a delay in skeletal development. In setting occupational exposure limits, attention has to be focused both on the CNS effect and on the irritative effects of MIBK.

A Swedish version is available in Arbete och Hälsa 1988:20; 35 references.

Keywords: CNS, irritative effects, methyl isobutyl ketone, occupational exposure limits, occupational health.

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Appendix I. Occupational exposure limits for airborne methyl isobutyl ketone.

Country	mg/m3	ppm	year	note *	ref.
BRD	400	100	1988		5
Denmark	210	50	1988	S	2
Finland	210	50	1987	S	10
	315	75		15 min	
Iceland	210	50	1978	S	8
The Netherlands	410	100	1985	S	6
Norway	210	50	1984	S	1
Great Britain	205	50	1987	S	4
	300	75		10 min	4
Sweden	200	50	1988		3
	300	75		KTV	
USA (ACGIH)	205	50	1987-88		9
	300	75		STEL	
(NIOSH/OSHA)	410	100	1978		7

*S = Skin; KTV = Short-term value; STEL = Short-term exposure limit

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VINYL ACETATE

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CONTENTS

BACKGROUND

Vinyl acetate is one of the most important monomers in the plastics industry. It is used in the production of polyvinyl acetate emulsions and resins, polyvinyl alcohol, polyvinyl butyral, vinyl chloride-vinyl acetate copolymers, ethylene-vinyl acetate resins and emulsions and for other purposes. Exposure to vinyl acetate may occur, in addition to the above-mentioned production lines, in the manufacture of vinyl acetate and in industries using polymers containing vinyl acetate monomer. Polyvinyl acetate is used in adhesives, paints, as a binder in paper coatings and nonwoven fabrics, in textile treatment, solution coatings, inks, gum bases, and factory prefinishing of ceiling elements. Polyvinyl alcohol is employed in paper sizing and coating, as a textile warp sizing and finishing agent, as a fibre, as a component in adhesives, as a film, and as a thickener in latex coatings. Polyvinyl butyral is used as an adhesive film in the production of safety glass and wash primers for steel.

A NIOSH document on occupational exposure to vinyl acetate was published in 1978 (51). IARC published a monograph on vinyl acetate, polyvinyl acetate and polyvinyl alcohol in 1979 and on vinyl acetate in 1986 (31,32).

Physical and chemical properties (31,32,51,71)

CAS number:	108-05-4
Systematic name:	vinyl acetate
Synonyms:	acetic acid vinyl ester, 1-acetoxy-ethylene, vinyl A monomer, acetic acid ethylene ester, ethanoic acid ethenyl ester, ethenyl acetate, ethenyl ethanoate, vinyl acetate monomer, vinyl ethanoate, acetic acid ethenyl ester

Molecular formula:	$C_4H_6O_2$
Structural formula:	$H_2C{=}CH{-}O{-}\overset{\overset{O}{\|}}{C}{-}CH_3$
Molecular weight:	86.09
Description:	colourless liquid with sweet to sharp odour, irritating
Density:	d_4^{20}=0.9317, vapour density 3 (air=1)
Melting point:	-93.2°C (71)
Boiling point:	72.2°C (71)
Vapour pressure:	13.3 kPa at 23.3°C, (71), 15.3 kPa at 25°C (32)
Solubility:	in water at 20°C 2.5 g/100 ml (51), 2.0 g/100 ml (32), soluble in ethanol, ether, acetone, benzene, chloroform, and in most organic solvents
Conversion factors:	1 mg/m^3 = 0.284 ppm 1 ppm = 3.52 mg/m^3
Purity of technical products:	99.9 %
Impurities:	ethyl acetate 323 mg/kg, water 240 mg/kg, methyl acetate 175 mg/kg, acetaldehyde 6 mg/kg, acrolein 1 mg/kg (according to 31,32 typical for vinyl acetate produced in Western Europe); stabilators: hydroquinone 3-5 or 14-17 mg/l or diphenylamine 200-300 mg/l
Odour threshold:	odour threshold about 0.4-5 mg/m^3 (0.12-1.4 ppm) (22,16,26,61,51). Reversible olfactory fatigue has been reported to follow short exposures (less than 4 hours) to 70 mg/m^3 (19.5 ppm) (51). In water solutions, a vinyl acetate concentration of 1.022 µmol/l has been suggested as the odour threshold (6).

TOXICOLOGICAL DATA

1 METABOLISM

1.1 Uptake

The primary routes of occupational exposure to vinyl acetate are inhalation of vapour and contact of the liquid with the skin and eyes (51). In humans, no quantitative information on uptake is available. In the few animal studies available, vinyl acetate administered orally or by inhalation was rapidly absorbed (17,64).

Studies with rabbits exposed by inhalation to unspecified concentrations of vinyl acetate showed an uptake of about 70% (17). The degree of retention did not change during the exposure. One minute after stopping the exposure a rapid decrease was noted in the concentration of vinyl acetate in expired air. No vinyl acetate was found in the blood of the rabbits during or after the exposure. These findings suggest that inhaled vinyl acetate is rapidly broken down in the body (see 1.3).

When rats were exposed by inhalation in closed exposure chambers to different concentrations of vinyl acetate (approximate initial concentration 2700-4850 mg/m^3, i.e., 770-1380 ppm), the decline curve of vinyl acetate in the atmosphere showed a nonlinear pattern with zero-order kinetics during the first half of the experiment, followed by first-order kinetics when the concentration of vinyl acetate in the air was low (64). It was suggested that the ventilation rate in rats was the limiting factor of the pulmonary uptake.

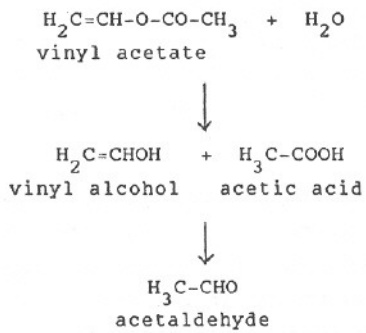
1.2 Distribution

No published data were found on the distribution of vinyl acetate in humans or in animals. Vinyl acetate, as such, may

not be efficiently distributed in the tissues, as it seems to be rapidly hydrolyzed by blood esterases (17,64).

1.3 Biotransformation

Vinyl acetate is rapidly hydrolyzed by esterases to acetic acid and (via a theoretical unstable intermediate, vinyl alcohol) to acetaldehyde in several biological systems (17,27,54,64).



Acetaldehyde will subsequently be oxidized in the liver by aldehyde dehydrogenase (with possible contribution by aldehyde oxidase and xanthine oxidase) to acetic acid, which, after conversion into acetyl coenzyme A, would enter normal intermediary metabolism of two carbon compounds, mainly via the tricarboxylic acid cycle. A small portion will participate in the synthesis of endogenous compounds, but the majority is ultimately oxidized to carbon dioxide. Minor pathways may include the dismutation of acetaldehyde to ethanol (and the reoxidation of the ethanol back to acetaldehyde) and the binding of acetaldehyde to macromolecules (proteins, neuropeptides, nucleic acids, membrane structures) and to smaller molecules (amino acids, biogenic amines, sulphhydryl compounds, cofactors).

In vitro, rapid (1-2 min) hydrolysis of vinyl acetate has been reported in human, rat and mouse whole blood, plasma and intact or hemolyzed washed erythrocytes, in diluted samples of human, rat and mouse plasma, and whole blood, in whole-blood cultures of human lymphocytes, in diluted rat or mouse liver homogenate, and in microsomal, mitochondrial, 1000xg supernatant and cytosolic fractions from rat liver and lungs (17, 27,54,64).

Enzymes from various biological sources have been shown to hydrolyze vinyl acetate in vitro. These include purified carboxyl esterase from porcine liver, purified butyrylcholinesterase from human plasma, purified acetylcholinesterase from human erythrocytes, and porcine pancreatic lipase (13,64).

The hydrolysis of vinyl acetate to acetaldehyde appears to be very rapid also in vivo. Rabbits inhaling an unspecified concentration of vinyl acetate were not found to have any vinyl acetate in their blood during or after the exposure (17). Rats exposed to vinyl acetate (by inhalation) until they lost consciousness had, on the average, 10.4×10^{-3} mmol/l of acetaldehyde (45.8 µg %) in their blood. As the rats became unconscious after acetaldehyde inhalation at a mean acetaldehyde concentration of 6.9×10^{-3} mmol/l (30.4 µg %), some accumulation of acetaldehyde was thought to occur in vinyl acetate intoxication (17).

Calculations of metabolic elimination rates in rats exposed by inhalation to 880-4200 mg/m^3 (250-1200 ppm) of vinyl acetate indicated that at constant concentrations up to 2300 mg/m^3 (650 ppm) vinyl acetate is metabolized in linear correlation with atmospheric concentration (64). Above this level, a saturation phenomenon could be observed (64). The pharmacokinetics of vinyl acetate in rats was not influenced by pretreatment with diethyldithiocarbamate (a compound known to inhibit monooxygenase-mediated biotransformation), which

suggested that monooxygenases - which could form an epoxide on the vinyl group of vinyl acetate - do not play an important role in the metabolism of this compound. The biotransformation of vinyl acetate to acetaldehyde in rats exposed by inhalation was further demonstrated by exhalation and transient increase of acetaldehyde in the air of the closed system (64).

Rats exposed to vinyl acetate by inhalation (10-500 mg/m^3, i.e. 2.8-142 ppm, for 6 months, 5 h/d, 5 d/week) showed a transient decrease in cytochrome P-450 and microsomal protein content in the liver (28). However, vinyl acetate did not bind to cytochrome P-450 in vitro in phenobarbital-induced rat liver microsomes, nor did it degrade cytochrome P-450, cytochrome b_5, heme, or NADPH-cytochrome c reductase, or enhance CO-inducible NADPH oxidation (33).

Vinyl acetate has been reported to undergo a slow enzyme-catalyzed conjugation with glutathione in the presence of dialyzed rat liver supernatant (10). Accordingly, an intraperitoneal injection of vinyl acetate to guinea pigs (500 mg/kg), mice (300 mg/kg) and rats (450 mg/kg) decreased the content of non-protein thiols in the liver by 50 % (within 30 min), 23 % (after 4 h), and 10 % (effect significant only after 4 h), respectively (29). After a chronic intermittent exposure (5 h/d for 6 months) to 10, 100 or 500 mg/m^3 (2.8, 28 or 142 ppm) of vinyl acetate, an approximate reduction of 20 % in the -SH content of the liver was observed, with no obvious dose-response (29). Boyland and Chasseaud (11) observed the GSH level of the liver to have decreased to 70 % of the control value in vinyl acetate treated rats 30 min after intraperitoneal injection (746 mg/kg, i.e., 0.8 ml/kg). Two hours after treatment, however, it was elevated to 134 %.

1.4 Elimination

There are no published studies on the elimination of vinyl acetate in humans.

In experimental animals, the excretion of vinyl acetate metabolites appears to be rapid and occurs mainly through exhaled air (CO_2), with minor contribution of urine and faeces (the urinary or faecal metabolites were not identified) (27).

When radiolabelled vinyl acetate was given to rats orally, within 96 h the major proportion (87%) of the administered radioactivity was eliminated in the expired air, and 1.2% was found in faeces and 3% in urine (27).

When rats were exposed to radiolabelled vinyl acetate by inhalation, within 96 the greatest portion (70 %) of the recovered radioactivity was found in expired air and a minor proportion in faeces (3.9%) and in urine (3%) (27).

The main metabolite of vinyl acetate in the expired air of rats exposed by inhalation or orally appears to be carbon dioxide (27). Also acetaldehyde has been detected in the exhaled air of rats exposed to vinyl acetate in a closed system (64). The decline of the initial vinyl acetate concentrations of about 4750 or 2100 mg/m^3 (1350 or 600 ppm) in the air of the closed system was accompanied by a transient increase of acetaldehyde, reaching a peak of about 290 mg/m^3 (160 ppm) or 110 mg/m^3 (60 ppm), respectively, at about 0.5 or 0.4 h, respectively, after the start of the experiment. Gas liquid chromatographical analyses of the exhaled air of rats treated intraperitoneally with different doses of vinyl acetate, showed no presence of vinyl acetate.

1.5 Biological half-times

No half-times have been given in the literature for vinyl acetate in experimental animals or humans. Studies on the gas uptake, metabolism and kinetics of vinyl acetate in rats and

mice indicate that vinyl acetate is very rapidly hydrolyzed in the blood with a half-time comparable to the in vitro figures (64).

In vitro vinyl acetate (2.21×10^{-3} mol/l rat blood) was reported to be completely transformed into acetaldehyde within 1-2 minutes. Effective formation of acetaldehyde could also be detected 3 min after the addition of vinyl acetate in human and rat whole blood, plasma, and in a suspension of intact or hemolyzed washed erythrocytes (17). The spontaneous hydrolysis of vinyl acetate was measured to be much slower than the enzyme-mediated reaction with half-times of 4.5 and 3 h in a buffer solution at pH 7.4 and 8.0, respectively (64).

1.6 Factors affecting metabolism

No data were found in the literature on the metabolism of vinyl acetate in humans.

In rats, the pulmonary uptake of vinyl acetate is limited by the maximum ventilation rate of the species (64). Pretreatment with diethyldithiocarbamate, an inhibitor of microsomal monooxygenation, did not influence the pharmacokinetics of vinyl acetate in rats. As the hydrolysis of vinyl acetate produces acetaldehyde, factors influencing the metabolism of acetaldehyde (see 73) may also be important with regard to vinyl acetate exposure.

2 MECHANISMS OF TOXICITY

As vinyl acetate is rapidly hydrolyzed in the body, its toxic effects are probably mediated by metabolites, of which acetaldehyde is the most reactive one. No evidence exists in favour of the epoxidation of vinyl acetate, and thus the toxicological significance of vinyl acetate epoxide is unknown.

The possible toxicological mechanisms of acetaldehyde have been dealt with in a previous volume of this series (73). Although the toxicological mechanisms of vinyl acetate are poorly known, they can be expected to be similar to those of acetaldehyde. Acetaldehyde is able to bind to amines, amino-acids, proteins (including hemoglobin), phospholipids, and nucleic acids.

Vinyl acetate has been reported to bind to glutathione (10) and accordingly causing a slight reduction in hepatic glutathione levels (11,29). Vinyl acetate has also been shown to decrease transiently cytochrome P-450 and microsomal protein content in the liver of rats (28). Vinyl acetate also inhibited noradrenaline-induced oxidative metabolism of hamster brown fat cells in vitro (58).

The oral LD_{50} of vinyl acetate was 2920 mg/kg bw in rats (65) and 1613 mg/kg bw in mice (21).

In rabbits, the LD_{50} of vinyl acetate after dermal application ranged between 2329 and >4659 mg/kg bw (65,67).

The LC_{50} of vinyl acetate (exposure time 4 h) is 11400-14450 mg/m^3 (3250-4100 ppm) for rats, 5150-5400 mg/ m^3 (1460-1550 ppm) for mice, 21750 mg/m^3 (6180 ppm) for guinea pigs, and 8800 mg/m^3 (2500 ppm) for rabbits (15,51, 65,68).

Vinyl acetate and acetaldehyde are both able to induce DNA-DNA cross-links (42,60) which may explain their genotoxicity in short-term tests (see section 5).

3 EFFECTS ON ORGANS

3.1 Skin and mucous membranes

Experience from the industry indicates that continued dermal contact with vinyl acetate may cause irritation and blister

formation (unpublished, see 51). According to a questionnaire study in three production units of a Gulf Coast chemical plant, 3 out of 21 vinyl acetate workers reported dermatitis (16). Noted effects on the skin included dryness of hands and irritation between the fingers. Two workers had experienced skin rashes.

According to an unpublished volunteer study, vinyl acetate can cause eye irritation at 250 mg/m^3 (71.5 ppm) (51), while studies performed in industry suggest that concentrations as low as 20 mg/m^3 (5.7 ppm) can irritate the eye (16).

Vinyl acetate has been reported to cause irritation of the eyes at concentrations of 7000 mg/m^3 (2000 ppm) (20) in rats, and at 651 mg/m^3 (185 ppm) in dogs (unpublished, see 51).

Ocular application of 466 mg (0.5 ml) of vinyl acetate caused severe irritation of the eyes and corneal burns in rabbits (67).

3.2 Respiratory organs

In the production of vinyl acetate - at vinyl acetate TWA (Time Weighted Average) concentrations of 18, 27 and 29 mg/m^3 (5.2, 7.7 and 8.2 ppm) and peaks of 435-1150 mg/m^3 (123.3-326.5 ppm) in nonroutine operations in the three units studied - two workers out of 21 reported upper respiratory tract irritation and one "a hurting of the chest" from breathing vinyl acetate at high concentrations. Three subjects exposed to 76 mg/m^3 (21.6 ppm) of vinyl acetate reported hoarseness and cough, and one of them had upper respiratory tract irritation at 15 and 20 mg/m^3 (4.2 and 5.7 ppm). It was concluded in the study that long-term exposure to vinyl acetate at concentrations between 18 and 35 mg/m^3 (5-10 ppm) produced no serious chronic effects according to a review of medical records and contemporary clinical examinations.

Although one observer noted hoarseness at 15 mg/m^3 (4.2 ppm), concentrations up to 35 mg/m^3 (10 ppm) were unlikely to produce irritation of the respiratory tract (or eyes) in most workers. However, exposure to 76 mg/m^3 (21.6 ppm) of vinyl acetate appeared to cause upper respiratory tract (and eye) irritation in most workers (16).

In the literature from the Soviet Union, impairment of ventilatory function and symptoms of chronic bronchitis have been reported among workers exposed up to 140 mg/m^3 of vinyl acetate (40 ppm) in polyvinyl acetate plants. The frequency of the effects observed was related to the degree and length of exposure. The workers were, however, exposed also to other chemicals such as various aldehydes and vinyl copolymers (1,4,5,36).

Exposure of rats (4 males and 4 females) to vinyl acetate at a concentration of 7000 mg/m^3 (2000 ppm) for 6 hours per day, 5 days a week, for 3 weeks caused nose irritation and respiratory difficulty. Microscopic examination showed increased numbers of macrophages in the lungs of the female rats (20).

Irritation of the respiratory tract has been observed at 530 mg/m^3 (150 ppm) in mice and at 1760 mg/m^3 (500 ppm) in rats exposed to vinyl acetate for 6 hours a day on 6 days per week for 4 months (27).

In white mice, an unspecified concentration of vinyl acetate produced irritation of the respiratory tract, and microscopic analysis showed acute hemorrhagic inflammation, with pneumonia in some of the studied animals. Capillaries of the lung, septa and bronchial walls were dilated, and the lungs were scattered with interstitial, subpleural or parenchymal hemorrhagic foci (23, as reported in 51).

A concentration-dependent increase in emphysema and lung atelectases (and disturbed blood circulation in other organs)

was observed in rats after exposure by inhalation to 13.2 and 68.0 mg/m^3 (3.7-19.3 ppm) of vinyl acetate for 4 months (62).

3.3 Liver

No human data were available.

Exposure to vinyl acetate at 350, 880, 2200, or 7000 mg/m^3 (or 100, 250, 630, or 2000 ppm respectively), 6 hours/day, 5 days/week for 3 weeks did not cause histopathological changes in the rat (4 males and 4 females) liver (20).

In another study exposure of rats to 100 and 500 mg/m^3 (28 and 142 ppm) of vinyl acetate, 5 hours per day, 5 days a week for 10 months caused fatty degeneration of hepatic parenchyma, proliferation and extension of smooth endoplasmatic reticulum and changes in the biliary canaliculi (15).

3.4 Kidney

No human studies were available.

Gage (20) observed that exposure to 350, 880, 2200, or 7000 mg/m^3 (100, 250, 630, 2000 ppm) of vinyl acetate for 6 hours/day, 5 days/week, for 3 weeks did not cause histopathological abnormalities in the kidneys (or lung, liver, spleen, and adrenal tissue) of albino rats. Urine examinations of rats exposed to 880 mg/m^3 (250 ppm) of vinyl acetate did not reveal any disturbances in renal function.

3.5 Gastrointestinal tract

No human or relevant animal data were available.

3.6 Blood and the blood-forming organs

Deese and Joyner (16) reported that there were some differences in the results of haematological studies on vinyl acetate operators (average exposure 18-35 mg/m^3, i.e. 5-10 ppm, mean length of service 15.2 years) and control operators. All values, however, fell within normal limits and the number of invidivual abnormalities was not strikingly different in the two groups.

No relevant animal data were available

3.7 Heart and the circulatory system

Changes in some measures of the cardiac function (phase structure of systole of the left ventricle) (3) and changes in the electrical activity of the heart (2) have been reported among workers in polyvinyl acetate plants exposed to up to 140 mg/m^3 (40 ppm) of vinyl acetate. The workers were exposed to e.g. various aldehydes and other vinyl copolymers besides vinyl acetate. The reports cited above, however, do not contain enough data to evaluate them for our purposes.

In an unpublished study (as reported in 51) four dogs were exposed (via inhalation) to 320 mg/m^3 (91 ppm) of vinyl acetate 6 hours/day, 5 days/week, for 6 weeks. Two and a half weeks later the same dogs were again exposed to vinyl acetate: 278 mg/m^3 (79 ppm) for 2 weeks, and then 655 mg/m^3 (186 ppm) for one week. No circulatory abnormalities were observed in the treated animals.

3.8 Nervous system

According to an unpublished volunteer study (see 51) impairment of the sense of smell was observed in all four subjects at 70-250 mg/m^3 (19.5-71.5 ppm) of vinyl acetate after exposure for 0.5-4 h in a test chamber. The olfactory

fatigue seemed to recover in 10 minutes. The experiments were conducted on 4 consecutive days.

Gofmekler (22) studied the concentration of vinyl acetate which could produce a conditioned response. For this purpose two subjects were exposed (via inhalation) to vinyl acetate and their brain electrical activity was recorded on an electroencephalograph (EEG). The vinyl acetate stimulus was reinforced with light after 10-15 sec of exposure (which caused a desynchronization in the EEG). Through association with light, exposure to vinyl acetate could become a conditioned stimulus, producing EEG desynchronization before the light stimulus was presented. Gofmekler (22) found the minimum effective concentration to produce the conditioned change to be 0.32 mg/m^3 (0.09 ppm). The maximum inactive concentration was 0.21 mg/m^3 (0.06 ppm). The significance of these results cannot be evaluated.

Bartenev (7) studied the effect of vinyl acetate on CNS by monitoring two indices of the reflex activity of the foot of an exposed rabbit, the time for muscle tension reflex development to attain a value of 0.7 kg and the muscle tension value when the reflex was attained. The minimum concentration of vinyl acetate that affected the CNS of rabbit, determined by flexor reflex changes, was between 125 and 250 mg/m^3 (35.5 and 71 ppm).

Bartenev (7) also studied the effect of vinyl acetate on conditioned reflex activity in three rabbits. Exposure to 25-50 mg/m^3 (7-14 ppm) of vinyl acetate for 37 min was high enough to alter the ability of the rabbits to differentiate between quantitatively similar but qualitatively different visual stimuli. Disturbances in the conditioned reflex activity were then seen at a concentration one-fifth of that causing changes in unconditioned reflex activity.

3.9 Reproductive organs

No human or animal studies were available.

3.10 Foetus

No published human or animal data were available.

4 ALLERGIC EFFECTS

No human or animal data were available.

5 GENOTOXICITY

An increased frequency of chromosome aberrations was observed in workers engaged in the production of polyvinyl acetate (63).

Vinyl acetate induced micronuclei in mouse bone marrow erythrocytes in vivo at intraperitoneal doses of 1000 and 2000 mg/kg in olive oil (49). Vinyl acetate was also reported to induce sperm head abnormalities in mice (52,53).

Vinyl acetate did not induce point mutations in the Ames Salmonella/microsome test with or without metabolic activation (8,12,18,43,48). It was inactive also in the SOS chromotest with Escherichia coli (12). In cultured mammalian cells, in contrast, vinyl acetate was an efficient inducer of chromosome damage without metabolic activation (25,35,49,50,54).

Acetaldehyde has been reported to be the reactive metabolite responsible for the chromosome-damaging effect of vinyl acetate (54). Acetaldehyde caused chromosome damage in cultured human lymphocytes (14,25,30,34,39,54,55,60,69), in CHO (Chinese hamster ovary) cells and in rat skin fibroblasts (9,59,56,69). In vivo acetaldehyde was reported to induce sister-chromatid exchanges (SCE) in bone-marrow cells of

Chinese hamster and mice (40,55) and recessive lethal mutations in Drosophila (72). In cultured mammalian cells vinyl acetate and acetaldehyde both induced DNA-DNA cross-links (42,60), which may explain their chromosome damaging effect in these cell systems.

6 CARCINOGENICITY

An association between lung cancer risk and exposure to 19 chemicals, including vinyl acetate, was studied in workers of a US synthetic chemical plant (70). Of the 4806 male workers ever employed in the plant, 42 died (28.2 expected, $P < 0.01$) from lung cancer during the study period (1942-1973). No association between lung cancer and exposure to vinyl acetate could be detected.

Vinyl acetate (8800 mg/m^3 or 2500 ppm for 4 hours/day, 5 days/week for 52 weeks) did not cause tumors in rats (45, 46,47). Lijinsky and Reuber (44), on the other hand, observed an increased number of tumors of the uterus, thyroid and liver in rats (20/sex/dose) exposed to vinyl acetate in drinking water (0, 11.6 and 29 mmol/l) (0, 1000, and 2500 mg/l) for 5 days/week for 100 weeks. The numbers of adenocarcinomas of the uterus and liver neoplasms were significantly higher in the high exposure group than in the control group. The increase in C-cell neoplasms of the thyroid, in the higher exposure group, was only marginally significant, but the consistency with which they occurred suggested (according to the authors) that they were due to the treatment. The number of animals used for the experiment was small. Also the (possible) instability of vinyl acetate in the drinking water of the animals makes it difficult to evaluate the findings of Lijinsky and Reuber (44).

Preneoplastic enzyme-altered foci (EAF) were not observed in newborn rats exposed to vinyl acetate (200 and 400 mg/kg bw/day) for three weeks with a subsequent promotion by phenobarbital (0.05% in drinking water) (41).

Epithelial metaplasia of bronchi was observed in rats exposed to 10, 100 and 500 mg/m^3 (2.8, 28, and 142 ppm) of vinyl acetate for 5 hours per day, 5 days a week for 10 months (15). Such changes were not seen in control animals.

The international Agency for Research on Cancer has evaluated the carcinogenicity of vinyl acetate to be inadequate to both humans and experimental animals (32).

7 METHODS FOR MONITORING EXPOSURE

7.1 Ambient air concentrations

Integrative sampling methods, such as solid sorbent tubes (see e.g. 51 for references), midget impingers (16) and grab-sampling methods, such as sampling bags (24) have been used for the collection of vinyl acetate.

Solid sorbent devices are best suited for personal sampling because of their relatively small size. They require less careful handling than liquid sorbents and are efficient and easy to use. NIOSH (51) has recommended a solid-sorbent sampling method in which a 1.5 l air sample is drawn through a sampling tube containing 300 mg Chromosorb 107 sorbent. It is possible to collect very small amounts of vinyl acetate with this method, the quantitative limit is 0.5 µg of vinyl acetate/300 mg of solid sorbent (19,66,see also 51). A sampling tube containing charcoal inhibited with hydroquinone and calcium sulphate as the drying agent has been reported to be a sensitive sampling method over the range 7-28 mg/m^3 (2-8 ppm). The lower limit of detection for an 18 l air sample is 1.3 mg/m^3, i.e. 0.37 ppm (37,38). For more complex matrices, such as air in the vicinity of chemical waste dumps, gas chromatographical/mass spectrometrical analysis of samples trapped by Tenax has been recommended (57).

Vinyl acetate has been determined by polarography, infrared absorption spectroscopy, bromometry, paper chromatography, colorimetry, and gas chromatography (see e.g. 51 for references). NIOSH (51) has recommended a gas chromatographic method with a flame-ionization detection for the analysis of vinyl acetate in the workplace air.

7.2 Biological monitoring

No determinations of vinyl acetate in human blood, urine or other biological fluid have been done after occupational exposure to vinyl acetate. Considering the low concentrations of vinyl acetate in workplaces and its rapid hydrolysis to acetaldehyde in biological systems, it is probably not possible to monitor vinyl acetate in biological samples from workers. There are techniques for the determination of acetaldehyde in blood, but such measurements have not been done in workers occupationally exposed to acetaldehyde.

8 EXPOSURE-EFFECT-RESPONSE RELATIONSHIPS

A continued contact with vinyl acetate liquid has been reported to irritate the skin, resulting in severe irritation and blistering (16, see also 51).

Irritation of the respiratory tract and eyes was reported in workers exposed to vinyl acetate vapour at concentrations of 76 mg/m^3 (21.6 ppm) or greater (16).

Impairment of ventilary function and symptoms of chronic bronchitis (1,4,5,36) and some subclinical changes in heart function (2,3) have been observed in workers exposed to up to 140 mg/m^3 (40 ppm) of vinyl acetate in polyvinyl acetate plants. Concomitant exposure to other chemicals than vinyl acetate, such as aldehydes and vinyl copolymers, complicates the evaluation of these results.

Deese and Joyner (16) did not find any chronic effects, according to medical records and recent clinical examinations, after a long-term occupational exposure to a mean concentration of 18-35 mg/m^3 (5-10 ppm) of vinyl acetate.

Irritation of the respiratory tract was observed at a concentration of 528 mg/m^3 (150 ppm) in mice and at 1760 mg/m^3 (500 ppm) in rats exposed to vinyl acetate for 6 hours a day, 6 days a week, for 4 months (27). Exposure of rats to 7000 mg/m^3 (2000 ppm) of vinyl acetate for 6 hours per day, 5 days a week, for 3 weeks resulted in irritation of the eyes, nose and the respiratory tract (20). Irritation of the eyes and lacrimation was observed in dogs exposed to 651 mg/m^3 (185 ppm) of vinyl acetate for one week (unpublished, see 51). Severe irritation and mild corneal burns were seen in rabbits after ocular application of 466 mg (0.5 ml) or more of vinyl acetate (67).

Exposure to 10, 100 and 500 mg/m^3 (2.8, 28 and 142 ppm) of vinyl acetate for 10 months, 5 days per week, 5 hours a day has been reported to cause epithelial metaplasia of bronchi in rats (15).

Fatty degeneration of hepatic parenchyma, proliferation and extension of the smooth endoplasmatic reticulum and changes in the biliary canaliculi in rat liver have been observed in rats after exposure to 100 and 500 mg/m^3 (28 and 142 ppm) of vinyl acetate for 10 months, 5 hours per day, 5 days a week (15).

Vinyl acetate at 125-250 mg/m^3 (35.5-71 ppm) has been reported to affect the CNS of rabbit (as judged by flexor reflex changes), and concentrations between 25 and 50 mg/m^3 (7-14 ppm) have been found to cause disturbances in the conditioned reflex activity (7).

TABLE 1. SUMMARY OF THE EFFECTS OF VINYL ACETATE ON HUMANS.

Concentration mg/m^3	ppm	Type of exposure	Duration of exposure	Effect or response	Ref.
68-250	19.5-71.5	Inhalation	<4 h	Olfactory fatigue	51
≥76	≥21.6	Occupational	mean 15.2 yr	Irritation of the respiratory tract and eyes	16
up to 140	40	"	-	Impairment of ventilatory function and symptoms of chronic bronchitis	1,4,5,36
"	"	"	-	Changes in the phase structure of systole of the left ventricle	3
"	"	"	-	Changes in the electrical activity of the heart	2
2.1-4.6	0.6-1.3	Inhalation	2 min	Detection of odour	51
0.7-1.0	0.2-0.3	"	2-3 h	"	22
0.4	0.1	"	-	"	26
1.8	0.5	"	-	"	61
-	-	Occupational	-	Increased number of chromosome aberrations in blood lymphocytes	63
0.2-0.3	0.06-0.09	Inhalation	2-3 h	A conditioned response change in the electrical activity of the brain	22

TABLE 2. SUMMARY OF THE EFFECTS OF VINYL ACETATE ON ANIMALS.

Concentration mg/m^3	ppm	Type of exposure	Duration of exposure	Species	Effect or response	Ref.
7000	2000	Inhalation	3 wk	Rat	Irritation of the respiratory tract and eyes	20
1760	500	"	6 h/d, 6 d/wk for 4 wk	Rat	"	27
528	150	"	"	Mouse	"	27
651	185	"	1 wk	Dog	Irritation of the eyes and lacrimation	51
125-250	35.5-71.0	"	40 min	Rabbit	Changes in unconditioned reflex activity	7
100, 500	28, 142	"	10 mo, 5 h/d, 5 d/wk	Rat	Liver: fatty degeneration of hepatic parenchyma, proliferation and extention of smooth endoplasmatic reticulum and changes in the biliary canaliculi	15
25-50	7-14	"	37 min	Rabbit	Disturbances in conditioned reflex activity	7
13.2, 68	3.7-19.3	"	4 mo	Rat	Lung: conc.-depend. emphysema and atelectases	62
10, 100, 500	2.8, 28, 142	"	10 mo, 5 d/wk	Rat	Epithelial metaplasia of bronchi	15

A higher number of adenocarcinomas of the uterus, C-cell adenomas and carcinomas of the thyroid, and neoplastic nodules of the liver were found in animals exposed to vinyl acetate in drinking water - 11.6 and 29 mmol/l (1000 and 2500 mg/l) - for over 100 weeks, 5 days a week, compared to control animals. Only the number of adenocarcinomas of the uterus in the higher exposure group was significantly increased by the treatment (44). The study did not fulfill the standards of an adequate carcinogenicity study. Other limited evidence available was not suggestive of a carcinogenic effect.

9 RESEARCH NEED

Data concerning especially the long-term effects of vinyl acetate in humans is meagre. Further human and animal studies are needed to evaluate the possible adverse health effects of vinyl acetate exposure at concentrations which are relevant to occupational situations.

More animal experiments and studies on vinyl acetate-exposed subjects are needed to evaluate the carcinogenicity and possible genetic risk of vinyl acetate to humans.

10 EVALUATION

A short-term exposure to vinyl acetate causes irritation of the respiratory tract and eyes. In sensitive individuals irritation of the respiratory tract and eyes have been reported to occur already after exposure to 15 or 20 mg/m^3 (4.2 and 5.7 ppm, respectively). In general, vinyl acetate concentrations of 76 mg/m^3 (21.6 ppm) cause these effects. Olfactory fatigue has been observed after exposures (for less than 4 hours) to 19.5 ppm (70 mg/m^3) of vinyl acetate monomer. Continued contact with liquid vinyl acetate irritates the skin. The chronic health effects of long-term exposure to vinyl acetate have been studied in two investigations only. No serious effects were found.

The effects of vinyl acetate on different organs of test animals were usually found at concentrations well above those measured at workplaces. It is difficult to evaluate the possible adverse effects of vinyl acetate on different organs of humans on the basis of the animal studies done so far.

There are no published data indicating that vinyl acetate is teratogenic in experimental animals or in humans. Vinyl acetate has been shown to be an efficient inducer of chromosome damage in cultured mammalian cells, however. The reactive metabolite of vinyl acetate, acetaldehyde, is likely to be responsible for these mutagenic effects.

Vinyl acetate given in drinking water to rats has caused tumours. Exposure by inhalation, on the other hand, did not cause tumours in rats. According to the International Agency for Research on Cancer, the evidence for the carcinogenicity of vinyl acetate is inadequate, regarding both experimental animals and humans. Because vinyl acetate is genotoxic in experimental test systems, its carcinogenicity should be further clarified by animal studies and by epidemiological (and cytogenetic monitoring) studies on vinyl acetate-exposed worker groups.

The critical effect of occupational exposure to vinyl acetate is irritation.

11 SUMMARY

J. Mäki-Paakkanen and H. Norppa: Vinyl acetate. 80. Nordic expert group for documentation of occupational exposure limits.

Survey of the literature on vinyl acetate to serve as a background for a discussion of occupational exposure limits.

Exposure to relatively low concentrations (15-20 mg/m^3) of vinyl acetate may irritate the respiratory tract and eyes.

Vinyl acetate has caused mutagenic effects in many test systems. The genotoxic metabolite of vinyl acetate seems to be acetaldehyde, which has been shown experimentally to be both mutagenic and carcinogenic.

In one cytogenetic study an increased frequency of structural chromosome aberrations was observed in workers exposed to an unspecified concentration of vinyl acetate.

Results of the experimental studies done so far do not allow evaluation of the long-term health effects of vinyl acetate to humans. It is recommended that the exposure limit value of vinyl acetate should be based on the irritating effects.

A Swedish version is available in Arbete och Hälsa 1988:26, 73 references.

Key words: vinyl acetate, occupational exposure limit, hydrolysis by esterases, acetaldehyde, irritation of the respiratory tract and eyes, mutagenicity, carcinogenicity.

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APPENDIX Occupational exposure limits for airborne vinyl acetate.

Country	mg/m^3	ppm	year	note	ref.
FRG	35	10	1988		5
Denmark	30	10	1988		2
Finland	35	10	1987		11
	70	20		15 min	
France	30	10	1987		12
Great Britain	30	10	1988		4
	60	20		10 min	
Iceland	30	10	1978		9
Netherlands	30	10	1985		7
Norway	30	10	1984		1
Soviet Union	10	3	1978	g	6
Sweden	35	10	1987		3
	50	15		STV	
USA (ACGIH)	30	10	1988-1989		10
	60	20		STEL	
(NIOSH)	15	4	1983	c	8

c=ceiling
g=gas
STEL=short-term exposure limit
STV=short term value

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NITROALKANES

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CONTENTS

BACKGROUND

The use of nitroalkanes in the Nordic countries is not widespread. The following possible fields of use for nitromethane, tetranitromethane, nitroethane and 1- and 2-nitropropane have been found in the literature:

Nitromethane

- solvent in coatings and adhesive for cellulose esters and synthetic resins
- intermediary in the synthesis of dyes, textiles, surfactants, insecticides, pharmaceuticals
- propellant or fuel additive
- stabilizer in halogenated alkanes, aerosols and pastes for inks.

Tetranitromethane

- ingredient in liquid explosives
- octane number improver in diesel fuels
- analytical laboratory nitrating reagent
- rocket propellants
- byproduct in the manufacture of trinitrotoluene

Nitroethane

- solvent in coatings and adhesives for cellulose esters and synthetic resins
- intermediary in the synthesis of organic dyes, insecticides, pesticides, nitroplasticizers, pharmaceuticals and some other organic chemicals
- propellant
- extractant in petroleum fractionation
- recrystallization solvent

1- and 2-Nitropropane

- thinner and solvent for cellulose derivatives, lacquers and dopes
- solvent in vinyl resins for industrial coatings and printing inks
- solvent in synthetic finish removers
- solvent for oil- and spirit-soluble dyes for molded plastics
- extractant for purification, separation, recrystallization and recovery of natural and synthetic resins, tars, coating materials, fats and oils
- reaction medium, initiator, catalyst and solvent in polymer technology
- synthesis of amines, nitrated alcohols and acids, and chloronitroparaffins
- manufacture of explosives

PHYSICAL AND CHEMICAL PROPERTIES

Chemical name	**Nitromethane**
CAS no	75-52-5
Structural formula	CH_3NO_2
Molecular weight	61.04
Density	1.127
Melting point	- 29°C
Boiling point (101.3 kPa)	101°C
Solubility	Soluble in organic solvents, sparingly soluble in water
Vapor pressure (20°C)	3.66 kPa

Saturation concentration (20°C)	90g/m^3
Conversion factors	1 ppm = 2.50 mg/m^3
(25°C, 101.3 kPa)	1 mg/m^3 = 0.401 ppm
Appearance and odor	Colorless liquid with a mild, fruity odor
Chemical name	**Tetranitromethane**
CAS no	509-14-8
Structural formula	$C(NO_2)_4$
Molecular weight	196.04
Density	1.637
Melting point	14.2°C
Boiling point (101.3 kPa)	125.7°C
Solubility	Virtually insoluble in water, soluble in many organic solvents
Vapor pressure (20°C)	1.11 kPa
Saturation concentration	90 g/m^3
Conversion factors	1 ppm = 8.02 mg/m^3
(25°C, 101.3 kPa)	1 mg/m^3 = 0.1247 ppm
Appearance and odor	Colorless to slightly yellow liquid or solid. The vapor has a pungent odor and causes tears
Chemical name	**Nitroethane**
CAS no	79-24-3
Structural formula	$CH_3CH_2NO_2$
Molecular weight	75.07
Specific gravity	1.045
Melting point	- 50°C
Boiling point (101.3 kPa)	114.1°C

Solubility	Slightly soluble in water (4.7% by wt at 25°C) soluble in many organic solvents
Vapor pressure (20°C)	2.1 kPa
Saturation concentration	61 g/m^3
Conversion factors	1 ppm = 3.07 mg/m^3
(25°C, 101.3 kPa)	1 mg/m^3 = 0.326 ppm
Appearance and odor	Colorless liquid with a mild, fruity odor
Chemical name	**1-Nitropropane**
CAS no	108-03-2
Structural formula	$CH_3CH_2CH_2NO_2$
Molecular weight	89.09
Molecular formula	$C_3H_7NO_2$
Density	0.998
Melting point	-108°C
Boiling point (101.3 kPa)	132°C
Saturation concentration	36 g/m^3
Solubility	Slightly soluble in water, soluble in many organic solvents
Vapor pressure (20°C)	0.99 kPa
Conversion factors	1 ppm = 3.64 mg/m^3
(101.3 kPa, 25°C)	1 mg/m^3 = 0.274 ppm
Appearance and odor	Colorless liquid with a mild fruity odor
Chemical name	**2-Nitropropane**
CAS no	79-46-9
Synonyms	dimethylnitromethane, isonitropropane, nitroisopropane, 2-NP

Molecular formula	$C_3H_7NO_2$
Structural formula	$CH_3CH(NO_2)CH_3$
Molecular weight	89.09
Density	0.992
Melting point	-93°C
Boiling point (101.3 kPa)	120°C
Saturation concentration (20°C)	63 g/m^3
Solubility	Slightly soluble in water, soluble in many organic solvents
Vapor pressure (20°C)	1.70 kPa
Conversion factors	1 ppm = 3.64 mg/m^3
(25°C, 101.3 kPa)	1 mg/m^3 = 0.274 ppm
Appearance and odor	Colorless liquid with a mild, fruity odor

TOXICOLOGY

1. METABOLISM

1.1. Absorption

1.1.1. Respiratory tract

Nitromethane

No human data were found.

Rats apparently absorbed nitromethane from inhaled air, since systemic effects were found after inhalation exposure (12), but no quantitative studies on respiratory absorption were found.

Tetranitromethane

No studies were found.

Nitroethane

No human data were found.

Rats absorbed about 60% of the inhaled nitroethane when exposed to an air concentration of 3030 mg/m^3 (1000 ppm) (61).

1-Nitropropane

No human data were found.

Rats absorbed 1-nitropropane from inhaled air (10), but no quantitative studies were found.

2-Nitropropane

No human studies on the absorption of 2-nitropropane via lungs have been published. However, case reports of fatal occupational exposures show that 2-nitropropane is absorbed via lungs (18,29,53).

Rats which were exposed by inhalation for 6 h to 75 or 560 mg/m^3 (20 or 154 ppm) absorbed at least 40% of the inhaled 2-nitropropane (51).

1.1.2. Gastrointestinal tract

No human data on gastrointestinal absorption of nitroalkanes were found.

No quantitative animal data on the gastrointestinal absorption of nitroalkanes were found, but there are animal experiments (e.g. LD_{50} determinations) indicating that absorption occurs (54).

1.1.3. Skin and mucous membranes

No data on penetration through human skin were found. No systemic effects or weight loss were observed after the application of pure nitroalkanes in five daily treatments to the skin of rabbits. The observations were not described in detail, so the reliability of these results cannot be ascertained (43).

1.2. Distribution

Data were found only for **2-nitropropane**.

Muller et al (48) dosed rats intraperitoneally with radioactive 2-nitropropane (50 mg/kg) and measured the radioactivity in various tissues 4 h, 40 h or 8 days after dosing. High concentrations were observed in the lungs, liver, kidneys, adrenals, bone marrow and spleen. The high concentration in fat after 1 h indicates that 2-nitropropane is initially deposited in fatty tissues, but the values after 40 h and 8 days showed that the redistribution of radioactivity (2-nitropropane and its metabolites) is quite rapid and complete. The distribution of radioactivity after 8 days is explained by the fact that the compound is metabolized to isopropanol, acetone and carbon dioxide which are utilized in normal C_1 and C_2 metabolism.

1.3. Biotransformation

No human data were found.

The metabolism of nitroalkanes is not well understood. However, the mixed function monooxygenase system in liver microsomes degrades them (46,55,64). Well-known inducing agents modify enzymatic activity, e.g. the activity of uninduced rat liver microsomes is very low or undetectable, whereas induced microsomes by phenobarbital and 3-methylcholanthrene are active (64). The differences between species are considerable, e.g. uninduced mouse liver microsomes denitrify 2-nitropropane (46), but uninduced rat liver microsomes do not (64).

Nitromethane

Phenobarbital-induced rat liver microsomes bind nitromethane. An unstable cytochrome P-450-NO complex is formed and nitrite and formaldehyde are produced when the microsomes are incubated with 50 mM nitromethane. The splitting of nitric oxide and the formation of cytochrome P-450-NO complex is not seen to occur with nitroalkanes other than nitromethane and tetranitromethane. However, pig liver microsomes do not produce cytochrome P-450-NO complex (55).

Tetranitromethane

Tetranitromethane binds to phenobarbital-induced rat liver microsomes and creates a cytochrome P-450-NO complex. No

formaldehyde is formed (unlike with nitromethane), but NO is released from the complex as nitrite. The pig liver microsomes lack the ability to bind tetranitromethane (55).

Nitroethane

Nitrates have been found in rabbit blood in amounts proportional to the duration and intensity of nitroethane exposure. The amount of nitrite formed was small and much of it is oxidized in the blood (56). Also a number of flavoenzymes oxidize nitroethane with generation of a superoxide radical (35).

1-Nitropropane

The microsomal cytochrome P-450 system denitrifies 1-nitropropane and nitrite is formed (64).

2-Nitropropane

The microsomal cytochrome P-450 system denitrifies 2-nitropropane to acetone and nitrite (46,55,64). The denitrification activity of uninduced rat liver microsomes is very low or nonmeasurable, while microsomes induced by phenobarbital and 3-methylcholanthrene are active (64). The differences between species are, however, significant; e.g. uninduced mouse liver microsomes actively denitrify 2-nitropropane (46).

After a single intraperitoneal injection of high doses (1.1 g/kg or 1.7 g/kg), or repeated injections with smaller doses (7 daily doses of 0.11 g/kg) or exposure to at least 2770 mg/m^3 (760 ppm), nitrite was observed in rat heart, lungs, kidneys, and spleen (10).

Carbon dioxide, acetone and isopropanol are the major radioactive metabolites found in rats and chimpanzees after intraperitoneal or intravenous injection of ^{14}C-labelled 2-nitropropane. The radioactivity excreted in urine consists primarily of one or more polar metabolites, whose structures are unknown. Preliminary results suggest that rats and chimpanzees form different conjugates (48).

Horseradish peroxidase oxidizes 2-nitropropane to nitrite and acetone, making use of hydrogen peroxide to form nitropropane radical species that can reduce oxygen to superoxide anion radicals. These probably form hydroxyl radicals which might attack nitropropane (14,15). Some flavoenzymes, e.g. mammalian D-amino acid oxidase, oxidize 2-nitropropane and generate superoxide radicals (35).

Hydroperoxides can support the denitrification of 2-nitropropane even in uninduced mouse liver microsomes (47) and a free-radical chain oxidation is initiated and propagated by superoxide (39).

1.4. Elimination

No data on elimination of nitroalkanes are found for humans.

1.4.1. Lungs

Animal data on respiratory excretion are available only for **2-nitropropane**. Rats exposed to ^{14}C-labelled 2-nitropropane at 75 mg/m^3 (20 ppm) or 560 mg/m^3 (154 ppm) excreted about 50% of the radioactivity as carbon dioxide during a follow-up period of 48 hours. After the 75 mg/m^3 (20 ppm) exposure 3.7% was recovered unchanged, while after the 560 mg/m^3 (154 ppm) exposure 21.9% of the activity was excreted unchanged (51). Müller et al (48) obtained very similar results and demonstrated that exhalation is also the principal route of elimination of radioactivity in chimpanzees after intravenous administration (10 mg/kg) of radioactive 2-nitropropane.

1.4.2. Urine

Animal data were found only for **2-nitropropane**. Rats exposed for 6 h to 75 or 560 mg/m^3 (20 or 154 ppm) of 2-(^{14}C)-nitropropane excreted in urine 8 and 11% of the recovered radioactivity, respectively (51). Müller et al (48) obtained similar results in rats and chimpanzees.

1.5. Rate of elimination

No human data for any nitroalkane were found.

Animal data are available only for **nitroethane** and **2-nitropropane**.

Nitroethane

Nitroethane disappears rapidly from the body; only 14% of an intracardial dose was recovered in rats after 3 hours, and by 30 h essentially all the dose had been cleared from the blood, lungs, liver and muscle (44).

2-Nitropropane

The disappearance of 2-nitropropane is also rapid: only 12% of the original radioactivity was found in the rat carcass 40 hours after an intraperitoneal dose (50 mg/kg) (48).

1.6. Factors affecting the metabolic model

2-Nitropropane may affect its own metabolism: cytochrome P-450 is degraded after in vitro incubation of phenobarbital-induced rat liver microsomes with 2-nitropropane and NADPH (33). 2-Nitropropane also destroys hepatic cytochrome P-450 in vivo in rats after an intraperitoneal injection (50 mg/kg) (67).

2. TOXICOLOGICAL MECHANISMS

The molecular mechanisms of nitroalkane toxicity are not well known. The acute toxicity of tetranitromethane stems from its irritating properties, which are apparently due to its marked acidity (1). The reactivity of one nitro group and the liberation of nitrogen oxide from tetranitromethane might also contribute to the toxicity. The known metabolites of other nitroalkanes hardly explain their toxicity; e.g. very high doses are needed to produce even minimal increases of methemoglobin levels (9,10,11,12,13). The formation of free radicals in peroxidase-catalyzed oxidations might contribute to the toxicity of nitroethane and 2-nitropropane; the morphological damage in liver cells, for example supports the participation of peroxidation (67).

3. EFFECTS ON ORGANS

3.1. Skin and mucous membranes

Nitromethane

No human data are available.

Animals exposed to 1250 mg/m^3 (500 ppm) showed no marked conjunctival irritation, and there was no notable increase in blinking or discharge (43).

Tetranitromethane

Tetranitromethane is a potent irritant to skin and mucous membranes. It reacts with skin surfaces with the subsequent formation of pigmented areas owing to its reactivity with proteins (3,38). Eye contact can cause ulceration and conjunctival inflammation, and in more severe cases burns, severe pupillary changes and paralysis of the eye muscles (1).

Nitroethane

No human data are available.

Severe eye irritation has been noted in animals exposed to 1540 mg/m^3 (500 ppm) (43).

1-Nitropropane

In exposure experiments, a majority of human volunteers experienced conjunctival irritation at 1-nitropropane concentrations exceeding 360 mg/m^3 (100 ppm) (58).

2-Nitropropane

No data are available.

3.2. Respiratory organs

Nitromethane

No human data were found.

Lungs of rabbits exposed to 250 and 1860 mg/m^3 (98 and 745 ppm) for 1 month showed focal areas of hemorrhage and congestion of the alveolar and alveolar duct walls. Interstitial edema of the walls and alveolar wall necrosis were also present. Frank

pulmonary edema occurred in some animals. The dose-response relationships were not reported. The lungs of similarly exposed rats did not show any histopathologic changes (41).

Tetranitromethane

Workers handling melted trinitrotoluene which was giving off fumes of tetranitromethane (a byproduct of the synthesis) suffered severe lung edema. One of the three described cases was fatal. The exposure levels were unknown. The workers had been exposed for more than two weeks (38).

Tetranitromethane irritates mucous membranes and the respiratory tract. Cyanosis, bronchopneumonia and lung edema are possible acute effects in humans (17).

The irritating property of tetranitromethane has been reported to constitute a serious industrial nuisance and to limit the efficiency of workers who during World War I had to handle trinitrotoluene from which tetranitromethane had not been removed by sulfitization (52,57).

The acute toxicity of tetranitromethane in rats and mice after inhalation and intravenous exposure is consistent with acute pulmonary irritation and death due to respiratory failure; the possible formation of nitrogen oxides does not explain this effect because the toxicity of equimolar doses of nitrogen dioxide was lower (36).

Sievers et al (57) exposed cats to tetranitromethane fumes from crude trinitrotoluene. The animals developed pulmonary edema when exposed for 1-3 days to 24-72 mg/m^3 (3-9 ppm). Only mild irritation of the respiratory tract (not specified in detail) was seen at 0.8-3.2 mg/m^3 (0.1-0.4 ppm).

2-week inhalation exposures of rats to tetranitromethane at concentrations of 28, 40 and 60 mg/m^3 (3.5, 5 and 7.5 ppm) induced dose-related histopathologic changes. The changes were attributable to irritation of the epithelium in the tracheobronchial tree and the alveoli. The severity of lung edema correlated closely with mortality. Secondary effects were pneumonia and structural changes in lung architecture (36).

Cats exposed to 80 mg/m^3 (10 ppm) for 20 min became sick and died within 10 days (17). Eleven of 19 rats exposed to 51 mg/m^3 (6.35 ppm) for 6 months died during the exposure with evidence of pulmonary irritation, edema and pneumonia. The surviving animals developed pneumonitis and bronchitis. Two dogs survived similar exposure conditions without any injury (31).

Concentrations ranging from 27 to 200 mg/m^3 (3.3 to 25.2 ppm) caused irritation of mucous membranes and acute pulmonary edema in cats (57).

Nitroethane

No human data are available.

Rats and mice exposed by inhalation to 3100 mg/m^3 (1000 ppm) for 13 weeks showed degenerative and inflammatory changes in the olfactory epithelium; the changes were less severe at 1000 mg/m^3 (350 ppm) (23).

1-Nitropropane

No human data are available.

High doses (1800 mg/m^3; 500 ppm) caused irritation in the upper respiratory tract of rabbits (43).

2-Nitropropane

No human data were found.

After 1, 3 and 6 months of exposure to 750 mg/m^3 (207 ppm) rats exhibited an increased incidence of lung edema and other pulmonary abnormalities, such as dark hemorrhagic foci scattered over all lobes of the lung. Rats exposed to 100 mg/m^3 (27 ppm) demonstrated a milder response (41).

3.3 Liver

No human data are available.

The morphological changes (e.g. fatty infiltration) in the livers of guinea pigs after nitroalkane exposure are most prominent for 2-nitropropane, followed by nitroethane and nitromethane in decreasing order (43). Morphological changes

have also been observed in the livers of rats after exposure to nitroethane and nitromethane (68).

Nitromethane

No human data were found.

Liver damage was produced in dogs with large single oral doses of nitromethane: 1.5 g/kg (more than LD_{50}) produced central congestion and areas of hepatic edema as well as focal periportal and midzonal necroses. After a dose of 1.0 g/kg, the liver had midzonal necrosis, and after 0.5 g/kg fatty changes were seen in periportal and midzonal areas and there were areas of hemorrhage. A dose of 0.125 g/kg produced mild fatty changes with a few lymphocytes in the portal areas. The liver cells were regenerating 48 hours after the dosage (66).

Rats which received 2% nitromethane in their drinking water for one week had numerous lymphocytes in the periportal areas of the liver; in rats which received 0.25% nitromethane in drinking water for 15 weeks the cytoplasm of the hepatocytes was granulated and the nuclei were prominent, and numerous lymphocytes were seen in the periportal areas. The rats receiving 0.1% nitromethane showed less prominent hepatic changes (66).

Tetranitromethane

No data were found.

Nitroethane

No human data were found.

Rabbits died after 3 hours of exposure to 15,400 mg/m^3 (5000 ppm), and the autopsy showed mild to severe liver damage (43).

Exposure of rats and mice to 3100 mg nitroethane/m^3 (1000 ppm) for 13 weeks (6 h/day, 5 days/wk) resulted in hepatocellular vacuolization. Less frequent vacuoles were observed in mice similary exposed to 1100 mg/m^3 (350 ppm) (23). Rats exposed for 2 years to 610 mg/m^3 (200 ppm) for 7 h/day, 5 days/week showed no differences from controls concerning ALAT and GOT activity or bilirubin amount in serum (22a).

1-Nitropropane

No data were found.

2-Nitropropane

Two men were exposed to unknown concentrations of 2-nitropropane during the application of an epoxy resin within a tank. One of them died 18 hours after the exposure, with evidence of liver necrosis. The other also became ill but survived. They both developed toxic hepatitis; the liver biopsy showed a predominantly centrilobular degeneration hepatitis (18).

Four painters died of liver failure after being exposed to unknown concentrations of 2-nitropropane. (The maximum concentration estimated from vapour pressure and room temperature was 62,000 mg/m^3 (17,000 ppm)). The total exposure time in each case was relatively short (6 to 16 hours in broken shifts); the longest exposure was over a three-day period. The characteristic finding was the destruction of hepatocytes (29).

One worker died of acute hepatitis after one working day of exposure to 2-nitropropane at an estimated concentration of 1800 mg/m^3 (490 ppm) (53).

Rabbits exposed to 750 mg 2-nitropropane/m^3 (207 ppm) demonstrated elevated ornithine carbamoyltransferase levels after 1 and 3 months of exposure, but not after six months. Alanine aminotransferase levels in rats were elevated after 10 days, 1 month and 6 months under similar exposure conditions, indicating liver cell damage (41).

A single intraperitoneal injection (50 mg/kg) of 2-nitropropane given to rats induced lipid accumulation, centrilobular necrosis, degranulation of rough endoplasmic reticulum, proliferation of smooth endoplasmic reticulum and mitochondrial abnormalities in the liver 24 hours after the treatment. The activity of serum alanine aminotrasferase was concomitantly increased. The morphological and enzymatic changes suggested peroxidative cellular damage (67).

The exposure of cats, rats, rabbits and guinea pigs for one hour to 8600 mg 2-nitropropane/m^3 (2352 ppm) caused hepatocellular damage. No pathological changes were seen in rats, rabbits or guinea pigs following repeated exposure (seven hours a day, five days a week over a period of approximately six months) to 1170 mg/m^3 (328 ppm), but cats showed severe liver damage. Cats showed slight, reversible changes after exposure to concentrations as low as 300 mg/m^3 (83 ppm) (63).

Focal areas of hepatic cellular nodules were noted in 3 of 250 control rats and in 13 of 249 rats exposed for 22 months to 90 mg/m^3 (25 ppm) 2-nitropropane. The cells in the nodular areas were generally hypertrophied, but nuclei were normal. Other microscopic observations included focal cytoplasmic vacuolization of hepatocytes and liver congestion. Serum chemistry values (ALAT, OCT, thyroxine, and triiodothyronine uptake) were unchanged (20,21).

3.4. Kidney

Data were found only for **nitromethane** and **2-nitropropane**.

Nitromethane

No human data were found.

Very high, lethal doses (1.5 g/kg per os) to dogs caused kidney damage with swollen glomeruli and tubules, edema in capsular spaces, marked fatty changes and hyaline casts in collecting tubules; smaller doses (0,125 and 0,25 g/kg) had no observable effect on the kidneys (66).

2-Nitropropane

Necrosis in renal tubules was observed in two fatal cases of acute 2-nitropropane intoxication (The concentrations are unknown and the exact duration of the exposures is not given in the case reports.) (29).

Slight to moderate toxic degeneration of kidneys (not specified in detail) was seen in cats which died after 17 days of exposure to 1190 mg 2-nitropropane/m^3 (328 ppm), 7 h/day 5 days/week (63).

3.5. Blood

Nitromethane

No human data were found.

Nitromethane is a weak inducer of methemoglobinemia in rats; a single inhalation period of 6 hours at 33,000 mg/m^3 (3000 ppm) produced 0 - 0.1% methemoglobin, and 15 daily six-hour exposures at 1250 mg/m^3 (500 ppm) produced 0 - 0.25% (9).

Tetranitromethane

Methemoglobinemia was detected in workers suffering tetranitromethane poisoning caused by the vapors from melted trinitrotoluene, TNT (38). Since TNT is a known inducer of methemoglobinemia the role of tetranitromethane is not clear.

Tetranitromethane forms methemoglobin if administered orally to rats (83-205 mg/kg) and mice (262-511 mg/kg) (single doses). Acute methemoglobinemia is problably one of the toxic mechanisms involved in death following this route of entry. It was speculated that nitrogen dioxide was liberated from the molecule and converted to nitrate, which is subsequently converted to nitrite by the intestinal bacteria. Neither inhalation nor intravenous exposure increased methemoglobin levels in animals given doses slightly over the LD_{50} (rats 12.6 mg/kg: mice 63.1 mg/kg) or LC_{50} (rats 140 mg/m^3 (17.5 ppm), mice 440 mg/m^3 (54.4 ppm), 4 hours). The animals died of pulmonary damage) (36).

Nitroethane

No human data were found.

Nitroethane is a weak inducer of methemoglobinemia, although its potency is higher than that of nitromethane. A lethal intraperitoneal dose of 1.6 g/kg given to rats induced a methemoglobin level of 0.59%, and 14 daily doses of 0.11 g/kg a level of 1.5%. A six hour inhalation exposure to 40,000 mg/m^3 (13,000 ppm) raised the methemoglobin concentration to 2.84% (11).

Elevated methemoglobin levels with cyanosis, increased reticulocytes and Heinz bodies in peripheral blood, and associated splenic extramedullary hematopoesis were observed in rats after a 13-week inhalation exposure of 3100 mg/m^3 (1000 ppm). Less pronounced increase in methemoglobin was seen at 1100 mg/m^3 (350 ppm) and the increase was minimal at 310 mg/m^3 (100 ppm) (23).

1-Nitropropane

No human data were found.

1-Nitropropane induces methemoglobinemia in rats, but is less effective than 2-nitropropane. The percentage of methemoglobin after a 5-hour exposure to 47,000 mg/m^3 (13,000 ppm) was 8.5% and after an 8-hour exposure to 9,100 mg/m^3 (2500 ppm) was 4.1% No methemoglobin was detected after an 11 hour exposure to 4050 mg/m^3 (1100 ppm) (10).

2-Nitropropane

Methemoglobinemia has not been observed in human subjects in fatal cases of 2-nitropropane poisoning (29). Workers who used 2-nitropropane in solvent extraction (personal time-weighted average concentrations generally below 90 mg/m^3 (25 ppm), with occasional higher peaks) did not show any hematologic changes (7).

Single lethal intraperitoneal injections given to rats (1.1 g/kg or 1.7 g/kg) elevated the methemoglobin levels to 78 and 89% respectively. When injections (0.11 g/kg) of 2-nitropropane were given daily for 7 days, the methemoglobin level was elevated to 4.3% ten hours after the last injection. Four hours of inhalation exposure at 54,100 mg/m^3 (14,700 ppm) induced a methemoglobin content of 84%, but only 0.2 - 8.65% was detected after an 8-hour exposure to 2800 mg/m^3 (760 ppm) (9).

In a long-term study, female rats were exposed by inhalation to vapors of 2-nitropropane at 90 mg/m^3 (25 ppm), for 7 h/day, 5 days/week, over a period of 22 months. There was no elevation of nitrite in the blood. Other hematologic parameters (hemoglobin concentration, packed cell volume, erythrocyte

count, leukocyte count, and prothrombin time) were unchanged (20).

3.6. Gastrointestinal tract

Nitromethane, Tetranitromethane, Nitroethane and 1-Nitropropane.
No data were found.

2-Nitropropane
Several workers who were exposed to 2-nitropropane at 75 - 160 mg/m^3 (20 - 45 ppm) complained of nausea, vomiting, diarrhea and anorexia. They felt well the following morning but the symptoms recurred during exposure. The substitution of methyl ethyl ketone for 2-nitropropane in the solvent mixture relieved the symptoms (59).

In a fatal 2-nitropropane intoxication, a worker who was exposed for several hours to an estimated concentration of 1800 mg/m^3 (490 ppm) experienced vomiting and diarrhea (53).

Hemorrhage from the gastrointestinal tract has been reported in some fatal inhalation intoxications (29, 53).

3.7. Heart and blood vessels

No data were found.

3.8. The central nervous system

Nitromethane
The odor threshold is 88 mg/m^3 (3.5 ppm) (2).

Tetranitromethane
Prolonged exposure affects the central nervous system. The symptoms include regular headaches, fatigue and drowsiness (26).

Nitroethane
The odor threshold is 6.5 mg/m^3 (2.1 ppm) (2).

1-Nitropropane
The odor threshold is 40 mg/m^3 (11 ppm) (2).

2-Nitropropane
The odor threshold of 2-nitropropane was reported to be 260 mg/m^3 (70 ppm) (2), but a more recent study gives a much lower value of about 18 mg/m^3 (5 ppm) (8).

Men who worked for varying lengths of time in an area where 2-nitropropane concentrations were 75 to 160 mg/m^3 (20 to 45 ppm) had severe occipital headaches which came on gradually and progressed during the workday. They were symptom-free on days when they did not work (59).

Brain edema and a necrotic area in the corpus striatum were described in a fatal case of 2-nitropropane poisoning resulting from painting inside a tank with a paint containing 2-nitropropane, methyl ethyl ketone, cellosolve acetate (the exact chemical name is not given) and toluene. The exposure concentration is not known (29).

Increased activity of acetylcholine esterase, probably due to disarrangement of synaptosomal membranes, was detected in brain homogenates and isolated synaptosomes from rats which were given a single intraperitoneal dose (50 mg/kg) of 2-nitropropane (67).

Pathologic changes in rats, cats, rabbits and guinea pigs exposed to 8600 mg/m^3 (2352 ppm) included selective disintegration of brain neurons (63).

3.9. The peripheral nervous system

No data were found.

3.10. Reproductive organs

No data were found.

3.11. Fetus

Data were found only concerning 2-nitropropane.

2-Nitropropane
No human data were found.

Intraperitoneal 2-nitropropane injections (170 mg/kg) given to rats on days 1-15 of gestation induced delayed fetal development, but no teratogenic effects were found (27).

4. ALLERGY

No reports on allergic response to nitroalkane exposure were found.

5. GENOTOXIC EFFECTS

5.1. Mutagenicity

Nitromethane
Nitromethane has not shown mutagenicity in tests with Salmonella TA 98, TA 100 or TA 1535 (6,34,42).

Tetranitromethane
Tetranitromethane was mutagenic in Escherichia coli WP2 and Salmonella typhimurium TA 100 both with and without metabolic activation, but not in Salmonella typhimurium TA 98 (34).

Nitroethane
The reports on the mutagenic activity of nitroethane are conflicting. Hite and Skeggs (30) found it inactive in the Ames' test with Salmonella tester strains TA1537, TA92, TA98, and TA100, and Kawai et al (34) found it inactive in the strains TA98 and TA100, while another group found it to be mutagenic (the latter results are given in a meeting abstract without exact specification of the experimental conditions) (42).

Nitroethane has given negative results in the micronucleus test (30).

1-Nitropropane
1-Nitropropane yielded marginal mutagenicity in Salmonella strains TA98 and TA100 (24,60). The mutagenicity was increased in the presence of hamster microsomes (60). Another study has found 1-nitropropane inactive for strains TA1537, TA92, TA98 and TA100 (30).

In a micronucleus test 1-nitropropane was inactive (37).

2-Nitropropane
2-Nitropropane has been found to be mutagenic in Ames' tests with Salmonella strains TA92, TA98, TA100 and TA1535. Mutagenicity is highest in strain TA100. Microsomal activation of 2-nitropropane is not necessary, although the number of revertants is increased in the presence of microsomes (24,30,42,60)

2-Nitropropane has given negative results in the micronucleus test (30,37).

The ability of 2-nitropropane to modify DNA has been demonstrated by incubating DNA and 2-nitropropane at 56° for 18 h (60).

5.2. Chromosomal aberrations

Nitromethane, Tetranitromethane and 1-Nitropropane
No data are available.

Nitroethane
Mice exposed to 3100 mg nitroethane/m^3 (1000 ppm) showed multinucleated spermatids in the testes, an effect indicating chromosomal damage (23).

2-Nitropropane
In an in vitro test with human lymphocytes, sister chromatid exchanges were induced with 7.5 mM 2-nitropropane and metabolic activation (4).

6. CARCINOGENICITY

Nitromethane
No human data were found.

Nitromethane was not carcinogenic to rats and rabbits in a 6-month inhalation experiment with exposures of 250 and 1860 mg/m^3 (98 and 745 ppm) (41). Owing to its short duration the study cannot be regarded as an actual carcinogenicity study.

Tetranitromethane

When rats were exposed to 16 or 40 mg tetranitromethane/m^3 (2 or 5 ppm) and mice to 4 or 8 mg/m^3 (0.5 or 1 ppm) 6 h/day, 5 days/week for 2 years, both species showed a high frequency of lung cancer (62).

Nitroethane

No human data were found.

Rats of both sexes that were exposed to 610 mg/m^3 (200 ppm) 7 h/day 5 days/week for two years showed no significant non-neoplastic or neoplastic pathology when compared to control animals (22a).

1-Nitropropane

No human data were found.

Peroral, daily doses (5 times a week) of 1-nitropropane did not cause significant increases of tumors at dosage levels of 30 mg per rat per day or lower during a 52-week experiment (25). Nor was there any increased cancer frequency in rats given 89 mg/kg (1 mmol/kg) orally 3 times/week for 16 weeks and thereafter once a week for 10 weeks (16).

A 21.5-month (7 h/day, 5 days/week) inhalation exposure of rats to vapors of 1-nitropropane at 360 mg/m^3 (100 ppm) did not cause hepatocarcinomas or any histopathologic effects in other organs (22).

2-Nitropropane

In the U.S. the Occupational Safety and Health Administration and the National Institute for Occupational Safety and Health (50) have summarized an unpublished retrospective epidemiological study of mortality in 1481 workers employed in the manufacture of 2-nitropropane. There was no evident increase of risk for all sites combined. Seven deaths from sarcomatous cancer were observed: four of the sarcomas were classified histologically as lymphatic cancer; only one case of lymphatic cancer was expected on the basis of US mortality rates. No excess mortality from hepatic cancer was observed. The summary states that the study had only a 35% probability of

detecting a five-fold excess of mortality from liver cancer, since the period of follow-up was generally short and the data on exposure were inadequate.

Peroral doses of 89 mg/kg (1 mmol/kg) given to rats 3 times/week for 16 weeks caused benign and malign tumors in all the rats (16). Multiple hepatocellular carcinomas were present in the livers of all ten rats exposed to 750 mg/m^3 (207 ppm) nitropropane for 6 months. Numerous neoplastic nodules were also seen in the livers of all these rats. Ten control rats and ten rats exposed for 6 months to 100 mg/m^3 (27 ppm) did not show any carcinomas or neoplastic nodules. The hepatocellular carcinomas exhibited a variety of histologic characteristics, and in many cases the normal hepatic parenchyma was destroyed. No increase in tumors was observed in rabbits exposed to the same concentrations or in rats exposed to 100 mg/m^3 (27 ppm) (41).

2-Nitropropane did not induce hepatocarcinomas or any other tumors in rats exposed to 90 mg/m^3 (25 ppm) for 22 months (7 h/day, 5 days/week); no other exposure concentrations were used in this study (20).

7. INDICATORS OF EXPOSURE

7.1. Air concentrations

Nitromethane

Nitromethane is trapped in a tube containing Chromosorb 106, desorbed with ethyl acetate and quantified with a gas chromatograph equipped with an alkali flame ionization detector (GC/FID) (49).

Tetranitromethane

In the NIOSH recommended method, tetranitromethane is collected in impingers containing ethyl acetate. The solution is analyzed with a GC/FID. The method is applicable for air concentrations in the range 70 - 11.5 mg/m^3 (49).

Nitroethane

Nitroethane is trapped in XAD-2 tubes, desorbed with ethyl acetate and quantified with GC/FID (49).

1-Nitropropane

The methods used to measure 2-nitropropane can be employed.

2-Nitropropane

2-Nitropropane can be trapped with ethanol (5), XAD-7 tubes (desorption with ether) (40) or Chromosorb 106 (desorption with ethyl acetate) (19), and analyzed with gas chromatography.

7.2. Biological indicators

No biological tests for of nitroalkane exposure have been published.

8. EXPOSURE-EFFECT AND EXPOSURE-RESPONSE RELATIONSHIPS

8.1. Effects of single exposures (LD_{50} determinations)

The nitroalkanes have the following LD_{50} values (54):

Nitromethane:

Oral	rat	1210 mg/kg
Intraperitoneal	mouse	110 mg/kg

Tetranitromethane:

Oral	rat	120 mg/kg
Oral	mouse	375 mg/kg
Intraperitoneal	mouse	53 mg/kg
Intravenous	rat	12.6 mg/kg
Intravenous	mouse	63.1 mg/kg
Inhalation	rat	145 mg/m^3 (18 ppm) /4h
Inhalation	mouse	430 mg/m^3 (54 ppm) /4h

Nitroethane:

Intraperitoneal	mouse	310 mg/kg

1-Nitropropane:

Oral	rat	455 mg/kg

Intraperitoneal	mouse	250 mg/kg
Inhalation	rat	11300 mg/m^3 (3100 ppm) /8h

2-Nitropropane:

Intraperitoneal	mouse	75 mg/kg
Inhalation	rat	1450 mg/m^3 (400 ppm) /6h

8.2. Acute effects

Nitromethane

Human data are lacking.

After dogs were given a lethal dose of 1.5 g/kg (more than the LD_{50}), their livers showed central congestion and areas of hepatic edema as well as focal periportal and midzonal necroses. After a dose of 1.0 g/kg, the liver had midzonal necroses; after 0.5 g/kg fatty changes were seen in periportal and midzonal areas, with areas of hemorrhage. A dose of 0.125 g/kg produced mild fatty changes, with a few lymphocytes in the portal areas. The dose of 1.5 g/kg also damaged kidneys: swollen glomeruli and tubules, edema in capsular spaces, marked fatty changes and hyaline casts in collecting tubules were noted. Smaller doses (0.125 and 0.25 g/kg) had no observable effect on the kidneys (66).

Tetranitromethane

The irritating property of tetranitromethane has been reported to constitute a serious industrial nuisance and to limit the efficiency of workers who have to handle trinitrotoluene from which tetranitromethane has not been removed (52,57).

Tetranitromethane reacts with skin surfaces, forming pigmented areas. Contact with eyes can cause conjunctival inflammation, ulceration, and in more severe cases pupillary changes and paralysis of the eye muscles, as well as severe burns (1). The formation of methemoglobin has been reported in exposed workers, but they were simultaneuosly exposed also to trinitrotoluene, a known inducer of methemoglobinemia (38).

Cats exposed to tetranitromethane vapors from crude trinitrotoluene developed pulmonary edema (1-3 days, 24 to 72

mg/m^3 (3-9 ppm)). Only mild irritation of the respiratory tract (not specified in detail) was seen at 0.8 to 3.2 mg/m^3 (0.1-0.4 ppm) (57).

Methemoglobinemia developed in rats which were dosed orally with tetranitromethane (83 - 205 mg/kg) (36).

Nitroethane

No human data are available.

A lethal dose (15,400 mg/m^3 (5000 ppm) for 3 hours) caused liver damage in rabbits (43). Methemoglobin is formed in rats given nitroethane. However, even a lethal intraperitoneal dose (1.6 g/kg) induced very low methemoglobin levels (11).

1-Nitropropane

Human volunteers showed conjunctival irritation after exposure to 1-nitropropane concentrations higher than 360 mg/m^3 (100 ppm) (58).

Methemoglobin levels of 8.5% and 4.1% have been reported in rats exposed to 1-nitropropane at 48,000 mg/m^3 (13000 ppm) for 5 h and to 9200 mg/m^3 (2500 ppm) for 8 h, respectively (10).

2-Nitropropane

Several cases of fatal 2-nitropropane intoxication due to occupational exposure have been reported (28, 29, 53). Theoretically calculated concentrations in two cases were 62,000 mg/m^3 (17,000 ppm), the exposure time 6 to 16 hours in broken shifts, the longest over a 3-day period (29); and in the other case 1800 mg/m^3 for 6 hours (53). The cause of death was severe liver damage. Methemoglobinemia was not detected in these fatal poisonings.

Lipid accumulation and centrilobular necrosis were observed in the livers of rats after a single intraperitoneal dose of 50 mg/kg (67).

Single lethal intraperitoneal injections given to rats (1.1 - 1.6 g/kg) have elevated the methemoglobin levels to 78 - 89%. Inhalation of 54000 mg/m^3 (14700 ppm) for 4 hours induced 84%

methemoglobin, while inhalation of 2800 mg/m^3 (760 ppm) for 8 hours resulted in only 0.2 - 8.65% methemoglobin (9).

8.3. Effects of long-term exposure

Nitromethane

No human data are available.

An 8-week exposure to 1860 mg nitromethane/m^3 (745 ppm) decreased the body weight gain, increased thyroid weight and decreased serum thyroxin levels in rats and rabbits. No exposure-related gross or microscopic alterations were seen in any tissues at 1860 mg/m^3 (745 ppm) or 245 mg/m^3 (98 ppm) (41).

Tetranitromethane

Workers handling trinitrotoluene (TNT) that was contaminated by tetranitromethane (a byproduct of the synthesis) suffered severe lung edema and methemoglobinemia. Tetranitromethane had evaporated from the melted TNT. Two of the three reported cases were fatal. The exposure levels were unknown. The workers had been exposed for more than two weeks (38).

According to Hager (26), the chronic signs and symptoms among workers exposed to tetranitromethane include headache, fatigue and bronchial disturbances. Prolonged exposure affects the central nervous system and heart.

The 2-week inhalation exposures of rats to tetranitromethane at the concentrations of 30, 40 and 60 mg/m^3 (3.5, 5 and 7.5 ppm) induced histopathologic changes in a dose-related way. The changes were attributable to irritation of epithelium in the tracheobronchial tree and the alveoli. Lung edema was the most severe primary lesion and correlated closely with mortality. Secondary lesions were pneumonia and structural changes in lung architecture. Lesions seen in other organs (liver, heart, and kidneys) were associated with altered hemodynamics due to advanced disease in the lungs. The comparison of the dose-response relationships between tetranitromethane and nitrogen dioxide exposures indicated a difference in the mode of action of these two compounds (36).

Nitroethane

No human data were found.

Exposure of rats to 3100 mg/m^3 (1000 ppm) of nitroethane for 13 weeks (6 h/d, 5d/wk) resulted in decreased body weight gain, elevated methemoglobin levels with cyanosis, increased reticulocytes and Heinz bodies in peripheral blood and associated splenic extramedullary hematopoiesis. Other major effects included degenerative and inflammatory changes in the olfactory nasal epithelium, hepatocellular vacuolization, decreased cytoplasmic granularity of renal cortical epithelium and ductal epithelial cells of salivary glands. Rats exposed to 1100 mg/m^3 (350 ppm) showed similar but less severe changes in methemoglobin levels, spleen, nasal turbinates and salivary glands. Minimal changes in methemoglobin, spleen and salivary glands were observed in rats exposed to 310 mg/m^3 (100 ppm). There were no effects in rats of exposure to 610 mg/m^3 (200 ppm) on hematology nor were there any biologically significant effects on clinical chemistry or on organ weights (22a). Mice exposed to 3100 mg/m^3 (1000 ppm) showed increased methemoglobin, evidence of toxicity in the salivary glands, liver and olfactory nasal epithelium, and multinucleated spermatids in the testes. These changes were, however, less severe than in rats. Less extensive toxicity was observed in mice exposed to 1100 mg/m^3 (350 ppm) and only methemoglobin levels, liver, salivary glands and nasal turbinates were affected. Mice exposed to 310 mg/m^3 (100 ppm) showed minimal changes in the nasal turbinates and transient effects on salivary gland epithelium only. The concentration of 310 mg/m^3 (100 ppm) was judged to be a minimal effect level in the study (23).

1-Nitropropane

No human data were found.

A long-term inhalation exposure of rats (250 males and 250 females) to vapors of 1-nitropropane at 360 mg/m^3 (100 ppm) for 21.5 months did not induce hepatocarcinomas nor any histopathologic effects in other organs (22). No other concentrations were tested.

2-Nitropropane

Two men who had worked for a year in an area where the concentration of 2-nitropropane varied between 35 and 90 mg/m^3 (10 and 25 ppm) showed no ill effects; their exposure did not exceed 4 h a day or three days a week. Six men who worked for varying lengths in an area where 2-nitropropane concentrations were 75 and 160 mg/m^3 (20 to 45 ppm) showed some adverse effects. Those who had worked for the longest time and who had had the most intimate exposure experienced anorexia and nausea after several hours of work, followed by vomiting and diarrhea later in the day. Although too sick to eat in the evening, they would feel well the following morning. The cycle repeated in this fashion. The other workers in this group did not suffer nausea or vomiting, but had severe occipital headaches which came on gradually and progressed during the workday. All six workers noted increased symptoms when the weather was damp and reported that they were symptom-free on days when they did not work (59).

The health state of the workers in a process where 2-nitropropane was used in solvent extraction was examined without any findings of adverse effects of 2-nitropropane exposure. The work area levels sometimesd exceeded 90 mg/m^3 (25 ppm), while the personal time-weighted average levels were generally below 90 mg/m^3 (25 ppm). The 18 workers were examined for pulmonary, hepatic, renal, hematopoietic, integumentary and cardiovascular effects. The majority of these employees had served the company for 16 to 35 years. (7).

All ten rats exposed to 750 mg/m^3 (207 ppm) for 6 months developed multiple hepatocellular carcinomas and numerous neoplastic nodules in the livers, but livers of rats exposed to 100 mg/m^3 for the same time showed the same histological picture as control rats. All exposed rats developed lung edema and dark hemorrhagic foci in all parts of the lungs, but to a lesser extent at the lower dose (41).

Focal areas of hepatic cellular nodules were noted in 3/250 control rats and in 13/249 rats exposed to 90 mg/^{3} (25 ppm) for 22 months. The cells in the nodular areas were generally

hypertrophied, but nuclei were normal. Other microscopic observations included focal cytoplasmic vacuolization of hepatocytes and liver congestion (20,21).

According to the IARC, there is "sufficient evidence" for 2-nitro-propane to be classified as carcinogenic to rats (32).

9. RESEARCH NEEDS

Modern toxicological studies and observations on the effects of nitroalkanes on human are scanty. Only 2-nitropropane has been studied on a more extensive basis. Explanations of the biochemical mechanisms underlying its acute and chronic effects are still based on hypotheses.

The metabolism of nitroalkanes in humans is largely unknown.

Carcinogenicity testing of nitromethane, nitroethane, tetra-nitromethane and 1-nitropropane is not sufficient.

Test results on the mutagenicity of nitroalkanes, with the exception of 2-nitropropane, are conflicting.

10. DISCUSSION AND EVALUATION

In animal experiments, nitroalkanes produce irritation symptoms in the eye conjunctiva and in the mucous membranes of the nose and throat. This has been reported for animals exposed to high air concentrations of tetranitromethane, nitroethane and 1-nitropropane. There is no information on 2-nitropropane. Tetranitromethane holds an exceptional position, with reports of slight irritation symptoms at relatively low air concentrations.

The apprehension that the nitroalkanes would be strongly irritative to skin does not correspond with the results of animal experiments. Direct application for several consecutive days to the abdominal skin of rabbits caused no reaction for nitromethane, nitroethane, 1-nitropropane or 2-nitropropane. Tetranitromethane caused yellow coloring of the fur but no other reactions in a long-term inhalation experiment with rats.

Table 1. Survey of some important results from chronic exposure of rats to some nitroalkanes.

Substance	Toxicity LC_{50} mg/m³	Toxicity LD_{50}	Exposure Dose mg/m³	Exposure Time	Lungs	Liver	Kidney	Blood	Cancer	Ref
Nitro-methane		1270 po								54
			1860	6h/d, 5d/w 6 months	No changes	0	0	0	0	41
			1250	6h/d, 2w				0.25% MetHb		12
Tetra-nitro-methane	140 (4h)	130 po								36
			265	6.5h	65% died during exp, lung edema	0	0	0	0	65 31
			60	contin.	some died, lung edema					
			50	6h/d, 5d/w	58% mortality, lung edema (secondary infection); no lung damage in survivors	0	0	0	0	31
			40	6h/d, 5d/w 2 years	cancer				lung cancer	62
			28	contin. 2w	some mortality with lung edema					36
			16	6h/d, 5d/w 2 years	cancer				lung cancer	62

Table 1. cont.

Substance	Toxicity LC_{50_3} mg/m³	Toxicity LD_{50} mg/kg	Exposure Dose mg/m³	Time	Lungs	Liver	Kidney	Blood	Cancer	Ref
Nitro-ethane			3,100	6h/d,5d/w 13w		Vacuoles in hepa-tocytes	Slight reaction in tubuli	Methemoglobin, cyanosis,reticulo-cytosis, Heinz' bodies, extra-medullary erythropoiesis	0	23
			1,100	6h/d,5d/w 13w				Methemoglobin, extramedullary erythropoiesis	0	23
			610	7h/d,5d/w 2 years	0	0	0	0	0	22a
			310	6h/d,5d/w 13w				Insignificant methemoglobin	0	23
1-Nitro-propane	11,300 (8h)	455 po								54
			47,000	5h				8.5% metHb		10
			9,100	8h				4.1% metHb		10
			4,000	11h				0% metHb		10
			360	7h/d,5d/w 21.5 months	0	0 no trans-aminase increase	0 function tests normal		0	22

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Table 1. Cont.

Substance	Toxicity LC_{50_3} mg/m³	Toxicity LD_{50} mg/kg	Exposure Dose mg/m³	Time	Lungs	Liver	Kidney	Blood	Cancer	Ref
2-Nitro-propane	>5,500 (4h)									63
	1,460 (6h)									41
			15,000	1-3h	Lung edema	Liver damage				63
			2,800	8h				0.2-8.65% MetHb		9
			1,170	7h/d,5d/w 6 months	0	0	0		0	63
			750	7h/d, 5d/w	Petechiae, increased fluid con-tent	Focal necrosis, hepatocyte pro-liferation. All animals multiple hepatocyte cancer.			Liver cancer	41
			360	7h/d,5d/w 6 months		Focal necrosis, Cancer			Liver cancer	
			297	7h/d,5d/w several months	0	0	0	0	0	63
			100	7h/d,5d/w 6 months		0	0	0	0	41
			90	7h/d,5d/w 22 months		0	0	0	0	20, 21

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There is no information of direct application of this substance.

In animals exposed to sufficiently high air concentrations, all the substances cause irritation in respiratory organs and lung edema. The most irritative substance is tetranitromethane. The effect of chronic exposure is the most interesting. A survey of experiments with rats is given in table 1. The table indicates that tetranitromethane holds a special position, with lung edema and death of the animals exposed to 28 mg/m^3. Different animal species show significant differences in sensitivity, and there are also significant differences between animals in a group of the same species. The most sensitive is the cat, which reacts to considerably lower concentrations than other animals. Dogs, monkeys, guinea pigs and rats are less sensitive.

At sufficiently high exposure levels, all the substances cause more or less pronounced liver injuries. In long-term exposure experiments no changes in liver are seen at exposure levels which do not give lung injuries. Exceptions are 2-nitropropane, where severe liver injuries can appear without lung injuries and nitroethane, which at subchronic exposures causes liver and kidney reaction without lung effects.

With acute exposures to high air concentrations, tubulus injuries have been found in the kidneys - but only at concentrations causing liver and lung injuries. Kidney injuries are less conspicuous than injuries in liver or lungs.

There has been much discussion of methemoglobin formation and its relevance for the outcome in cases of severe poisoning. The results of the animal experiments show that methemoglobin formation after exposure to nitroalkanes varies greatly with animal species and path of administration. The most extensive methemoglobin formation results from oral administration. In inhalation experiments with rats, exposure to high concentrations of nitromethane causes insignificant methemoglobin formation, 1-nitropropane causes transformation of approximately 8% of the blood hemoglobin and 2-nitropropane in lethal

doses causes 84% methemoglobin. Tetranitromethane in air concentrations which cause lung injuries produces 11% methemoglobin in the cat. In chronic exposure experiments with nitroethane slight methemoglobin formation has been noted in rats, even in animals with no lung injuries. The variation in methemoglobin formation is thus large, but not of any essential significance in the chronic exposure experiments.

In cancer experiments it has been noted that exposure to 2-nitropropane can result in focal liver necrosis and thereafter proliferation of hepatocytes and cancer formation. Cancer has not been noted at exposure levels which do not cause liver necroses. In experiments with 1-nitropropane and nitroethane, no increase of cancer frequency has been shown. Tetranitromethane has caused lung cancer in rats and mice. For nitromethane, only a short-term experiment with negative response is available.

In the existing information about the effect of exposure on human subjects the following is found:

During **tetranitromethane** exposure in industrial environments, in reaction to relatively low but unknown concentrations or initially during exposure to higher concentrations, headache, feeling of dizziness, smarting pain in the eyes and flood of tears, smarting pain and feeling of rawness in the throat, pressure over the chest and hacking cough arise. Acute exposure to high concentrations causes breathing difficulties and a convulsive cough. In lethal poisonings lung edema has been noted. From animal experiments with chronic exposure it can be mentioned that serious lung injuries arise at air concentrations as low as 25 mg/m^3. At higher concentrations dose-related lung injuries and lung edema in some animals appeared. Air concentrations of 1-3 mg/m^3 caused only slight, non-specific irritation in the respiratory organs. A discussion of hygienic standard should be based upon the subjective symptoms in humans together with the findings from animal experiments, in which even low air concentrations can cause serious lung injuries. If the lungs are protected, apparently

the other organs as well are protected against injuries.

For **1-nitropropane**, in laboratory experiments with 15-min. exposure of humans, the majority experienced irritation in the eyes at 550 mg/m^3 and in the nose and throat at somewhat higher concentrations. The opinion was that 360 mg/m^3 was the maximum tolerable exposure. The animal experiments do not show any other effects than eye irritation at lower exposure levels. Chronic exposures at approximately this level have not been shown to have injurious effects. Therefore, the subjective discomfort is the effect which should be considered in the discussion of a threshold exposure limit.

Persons exposed to **2-nitropropane** at air concentrations of 90-150 mg/m^3 in industrial environments have described headache, nausea, loss of appetite, vomiting and diarrhea. The discomforts regressed quickly when exposure was broken off. Cases of poisoning due to exposure to higher air concentrations start with similar symptoms during or shortly after the exposure. The picture was later dominated by symptoms of liver injury. Serious liver damage and necrosis were established at autopsy of fatal cases. The animal experiments confirm that the liver is a critical organ. Furthermore, chronic exposure to 2-nitropropane in concentrations which cause liver necrosis will in the long run lead to development of liver cancer in 10 out of 10 rats. Lower exposure levels have not been shown to cause liver cancer. Rabbits exposed to levels that cause cancer in rats developed neither liver necrosis nor cancer. An epidemiologic study of industrially exposed persons gave a result which might indicate a carcinogenic effect. However, the study is limited in extent as well as observation time. To sum up, the discussion about a threshold exposure limit should be based on the risks of liver injury and cancer.

For **nitromethane** and **nitroethane**, there is only information from animal experiments. The acute as well as the chronic exposure experiments indicate that toxicity is relatively low. Very high exposure levels of **nitromethane** produce irritation effects in the respiratory organs and edema in the lungs.

According to the authors chronic exposure to 1860 mg/m^3 does not cause any changes in the lungs which can be assigned to the exposure (41). The methemoglobin formation is insignificant. In old experiments irritation of the respiratory organs was noted during inhalation of very high concentrations of **nitroethane.** The chronic exposure experiments mention no effects on parenchymatous organs at an exposure level of 364 mg/m^3. Subchronic exposure to 1075 mg/m^3 causes methemoglobin formation, increased blood formation, and extramedullar erythropoiesis, but at 307 mg/m^3 the methemoglobin formation was minimal. There is no need to take this into consideration in discussion of a threshold exposure limit. As only results from animal experiments are at hand and even those are scanty, the basis would be insufficient for establishing a threshold exposure limit. These substances are probably less toxic than 1-nitropropane, to which they can be compared.

11. SUMMARY

A.Zitting: Nitroalkanes. Nordic Expert Group for Documentation of Occupational Exposure Limits.

A survey and evaluation of literature relevant for discussion of exposure limits for the most commonly used nitroalkanes is given.

Nitromethane and nitroethane: There are only animal experiments available, which are an insufficient basis for establishing exposure limit values.

Tetranitromethane: The discussion ought to be based on irritation, particularly in the airways. Severe lung damage and cancer have been observed in animal experiments at relatively low air concentrations.

1-Nitropropane: Discomfort and irritation ought to be considered.

2-Nitropropane: The discussion of exposure limits ought to be based on risk of liver damage and cancer.

Key words: nitromethane, tetranitromethane, nitroethane, 1-nitropropane, 2-nitropropane, toxicology, occupational exposure limits.

A Swedish version is available in Arbete och Hälsa 1988:29.

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APPENDIX I. Occupational exposure limits for airborne nitroalkanes

Country	Nitromethane		Tetranitromethane		Nitroethane		1-Nitropropane		2-Nitropropane			Year	Note	Ref
	mg/m^3	ppm	mg/m^3	ppm	mg/m^3	ppm	mg/m^3	ppm	mg/m^3	ppm	note			
BRD	250	100	8	1	310	100	90	25			C	1987		5
Denmark	250	100	8	1	310	100	54	15	36	10		1988		2
Finland	250	100	8	1	310	100	90	25	18	5		1987		10
	375	150	24	3	465	150	150	40	150	40			15 min	
France	250	100	8	1	310	100	90	25	-		C	1987		11
Iceland	250	100	8	1	310	100	90	25	90	25		1978		8
The Netherlands	250	100	8	1	310	100	90	25	90	25		1986		7
Norway	250	100	8	1	310	100	90	25	90	25	C	1984		1
Soviet Union	30		0,3		30		30		30			1978	g	6
Great Britain	250	100							36	10		1987		4
	375	150							72	20			10 min	
Sweden									35	10	T,C	1988		3
USA (ACGIH)	250	100	8	1	310	100	90	25	35	10	T,C	1987-88		9

g=gas T=ceiling C=cancer

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