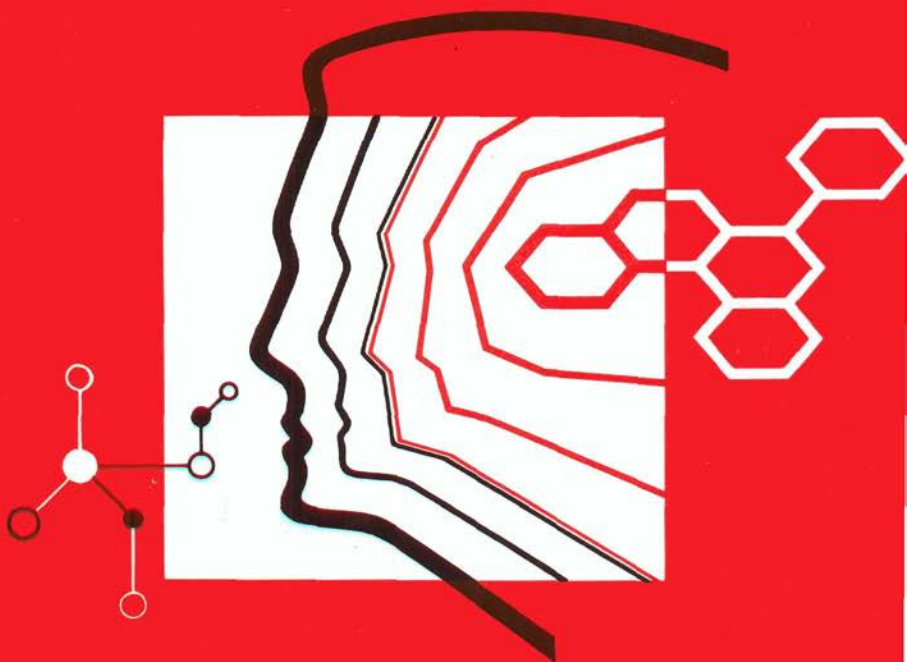
IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

Environmental Health Criteria 154

Acetonitrile



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[a] Out of print

continued inside back cover

Environmental Health Criteria 154

ACETONITRILE

First draft prepared by Dr K. Hashimoto (Kanazawa University, Japan), Dr K. Morimoto (National Institute of Hygienic Sciences, Japan) and Dr S. Dobson (Institute of Terrestrial Ecology, Monks Wood Experimental Station, United Kingdom)

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World Health Organization
Geneva, 1993

The **International Programme on Chemical Safety (IPCS)** is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by the IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

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CONTENTS

WHO TASK GROUP ON ENVIRONMENTAL HEALTH CRITERIA FOR ACETONITRILE

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NOTE TO READERS OF THE CRITERIA MONOGRAPHS

Every effort has been made to present information in the criteria monographs as accurately as possible without unduly delaying their publication. In the interest of all users of the Environmental Health Criteria monographs, readers are kindly requested to communicate any errors that may have occurred to the Director of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda.

* * *

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Case postale 356, 1219 Châtelaine, Geneva, Switzerland (Telephone No. 9799111).

* * *

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WHO TASK GROUP ON ENVIRONMENTAL HEALTH CRITERIA FOR ACETONITRILE

A WHO Task Group on Environmental Health Criteria for Acetonitrile met in Modena, Italy, from 24 to 28 November 1992. Mr Giorgio Baldini, the President of the Province of Modena, opened the meeting and greeted the participants on behalf of the Province of Modena. Dr B.H. Chen of the International Programme on Chemical Safety (IPCS) welcomed the participants on behalf of the Director, IPCS, and the three IPCS cooperating organizations (UNEP/ILO/WHO). The Task Group reviewed and revised the draft criteria monograph and made an evaluation of the risks for human health and the environment from exposure to acetonitrile.

The first draft of this monograph was prepared by Dr K. Hashimoto, Kanazawa University, Japan, Dr K. Morimoto, National Institute of Hygienic Sciences, Japan, and Dr S. Dobson, Institute of Terrestrial Ecology, Monks Wood Experimental Station, United Kingdom. The second draft was prepared by Dr K. Morimoto incorporating comments received following the circulation of the first draft to the IPCS Contact Points for Environmental Health Criteria monographs. Dr M. Lotti (Institute of Occupational Medicine, University of Padua, Italy) made a considerable contribution to the preparation of the final text.

Dr B.H. Chen and Dr P.G. Jenkins, both members of the IPCS Central Unit, were responsible for the overall scientific content and technical editing, respectively. The efforts of all who helped in the preparation and finalization of the document are gratefully acknowledged.

* * *

Financial support for this Task Group meeting was provided by the Province of Modena, Communes of Mirandola and Medolla, Local Hygiene Units N. 16 of Modena and N. 15 of Mirandola, Association of Business and Industries of the Province of Modena and ENICHEM (National Organization of Industrialization for Chemistry) in Italy.

ABBREVIATIONS

CLD	chemiluminescence nitrogen detector
GC	gas chromatography
HPLC	high performance liquid chromatography
NPD	nitrogen-phosphorus selective detector
TCD	thermal conductivity detection
TEA	thermal energy analyser

1. SUMMARY

1.1 Properties, uses and analytical methods

Acetonitrile (CH_3CN) is a by-product of acrylonitrile manufacture. It may also be formed by the combustion of wood and vegetation. It is a liquid with an ether-like odour. Acetonitrile is a volatile, highly polar solvent used to extract fatty acids and animal and vegetable oils. It is used in the petrochemical industry in extractive distillation based on its selective miscibility with organic compounds. It is used as a solvent for spinning synthetic fibres and in casting and moulding plastics. In laboratories, it is widely used in high-performance liquid chromatographic (HPLC) analysis and as a solvent for DNA synthesis and peptide sequencing.

The most widely used analytical technique for acetonitrile is gas chromatography.

1.2 Environmental levels and sources of human exposure

Very few data on acetonitrile levels in the environment are available. Worldwide, acetonitrile concentrations in air of 200 to 42 000 ng/m^3 have been reported. Slightly higher values were obtained for urban than rural air in one study. Single measurements before and after burning of bush and straw showed a 10-fold increase in acetonitrile air concentration.

Acetonitrile was not detected in 72 water samples from Japan but was found in 11 out of 60 aquatic sediment samples at concentrations between 0.02 and 0.54 mg/kg. Acetonitrile has not been detected in food.

Tobacco smoke contains acetonitrile and burning polyurethane foam releases acetonitrile and hydrogen cyanide.

Whilst production of acrylonitrile offers the greatest potential for exposure, this is carried out in a closed system. Practical uses of acetonitrile lead to greater exposure.

1.3 Environmental distribution and transformation

Acetonitrile volatilizes from water and would also volatilize from soil surfaces. It is readily biodegraded by several strains of

bacteria common in sewage sludge, natural waters and soil. Acclimatization of bacteria to acetonitrile or petroleum wastes increases the rate of degradation. Anaerobic degradation appears to be limited or absent.

Hydrolysis of acrylonitrile in water is extremely slow. There is no significant photodegradation in either water or the atmosphere. Reaction with ozone is slow as is reaction with singlet oxygen. The major mechanism for removal of acetonitrile from the troposphere is reaction with hydroxyl radicals; residence times have been estimated at between 20 and 200 days.

Acetonitrile does reach the stratosphere where it is characteristically associated in positive ion clusters in the upper regions.

1.4 Environmental effects

Acetonitrile has low toxicity to microorganisms (bacteria, cyanobacteria, green algae and protozoans) with thresholds at 500 mg/litre or more. Freshwater invertebrates and fish acute LC_{50}s are 700 mg/litre or more. Acute tests have been conducted under static conditions without analytical confirmation of concentrations. Similar results obtained from 24- and 96-h tests suggest volatilization of acetonitrile.

1.5 Absorption, distribution, biotransformation and elimination

Acetonitrile is readily absorbed from the gastrointestinal tract, through the skin and the lungs. All three routes of exposure have been reported to lead to systemic effects.

Postmortem examination of tissues from poisoned humans has revealed that acetonitrile distributes throughout the body. This is supported by animal studies in which acetonitrile distribution has been found to be fairly uniform throughout the body. There are no indications of accumulation in animal tissues following repeated administrations of acetonitrile.

There are substantial data to suggest that most of the systemic toxic effects of acetonitrile are mediated through its metabolism to cyanide, which is catalysed by the cytochrome P-450 monooxygenase system. Cyanide is subsequently conjugated with thiosulfate to form thiocyanate which is eliminated in the urine. Peak concentrations of cyanide in the blood of rats following administration of near lethal doses of acetonitrile approximate to

the concentrations observed following the administration of an LD_{50} dose of potassium cyanide. However, the peak concentration of cyanide after administration of acetonitrile is delayed by up to several hours as compared to other nitriles. Moreover, the more rapid rate at which cyanide is produced in the mouse appears to account for the much greater sensitivity of this species to the toxic effects of acetonitrile. Cyanide and thiocyanate have been identified in human tissues after exposure to acetonitrile. A portion of the acetonitrile dose is also eliminated unchanged in expired air and in urine.

1.6 Effects on laboratory mammals

Acetonitrile induces toxic effects similar to those observed in acute cyanide poisoning, although the onset of symptoms is somewhat delayed compared to inorganic cyanides or other saturated nitriles. The 8-h inhalation LC_{50} in male rats is 13 740 mg/m^3 (7500 ppm). The oral LD_{50} in the rat varies from 1.7 to 8.5 g/kg depending on the conditions of the experiment. Mice and guinea-pigs appear to be more sensitive, with an oral LD_{50} in the range of 0.2-0.4 g/kg. The main symptoms in animals appear to be prostration followed by seizures.

Dermal application of acetonitrile causes systemic toxicity in animals and has been implicated in the death of one child. The percutaneous LD_{50} in rabbits is 1.25 ml/kg.

Subchronic exposure of animals to acetonitrile produces effects similar to those seen after acute exposures.

Acetonitrile is not mutagenic in assays using *Salmonella typhimurium*, both with and without metabolic activation. It induces aneuploidy in a diploid yeast strain at very high concentrations. No animal studies on chronic or carcinogenic effects of acetonitrile have been reported.

1.7 Effects on humans

The levels causing toxicity in man are unknown but are probably in excess of 840 mg/m^3 (500 ppm) in air. Symptoms and signs of acute acetonitrile intoxication include chest pain, tightness in the chest, nausea, emesis, tachycardia, hypotension, short and shallow respiration, headache, restlessness, semiconsciousness, and seizures. Other non-specific symptoms may be due to the irritant effects of the compound. The systemic effects appear to be

largely attributable to the conversion of acetonitrile to cyanide. Blood cyanide and thiocyanate levels are elevated during acute intoxication. Two fatalities after exposure to acetonitrile vapour in the workplace and one fatal case of a child ingesting an acetonitrile-containing cosmetic have been reported. Elevated tissue cyanide concentrations were found in postmortem examination of these cases.

No epidemiological study of cancer incidence relating to acetonitrile exposure has been reported.

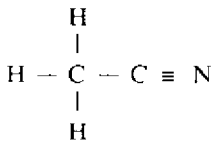
Acetonitrile can cause severe eye burns. Skin contact with liquid acetonitrile should be avoided. An employee's exposure to acetonitrile in any 8-h shift has been recommended in many countries not to exceed a time-weighted average of 70 mg/m^3 air (40 ppm).

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, AND ANALYTICAL METHODS

2.1 Identity

Chemical formula: CH_3CN

Chemical structure:



Relative molecular mass: 41.05

CAS chemical name: acetonitrile

CAS registry number: 75-05-8

Synonyms: cyanomethane, ethanenitrile, nitrile of acetic acid, methyl cyanide, ethyl nitrile, methanecarbonitrile

Specifications for commercial acetonitrile are given in Table 1. The principal organic impurity in commercial acetonitrile is propionitrile, although small amounts of allyl alcohol may also be present (Grayson, 1985).

2.2 Physical and chemical properties

2.2.1 Physical properties

Acetonitrile is a volatile, colourless liquid with a sweet, ether-like odour (Grayson, 1985). It is infinitely soluble in water and readily miscible with ethanol, ether, acetone, chloroform, carbon tetrachloride and ethylene chloride (Clayton & Clayton, 1982). It is immiscible with many saturated hydrocarbons (petroleum fractions) (Budavari, 1989).

Important physical constants and properties of acetonitrile are summarized in Table 2.

Table 1. Commercial acetonitrile specifications[a]

Specific gravity (at 20 °C)	0.783-0.787
Distillation range (°C)	
initial point, minimum	80.5
end point, maximum	82.5
Purity (minimum), % by weight	99.0
Acidity (as acetic acid, maximum % by weight)	0.05
Copper (maximum), ppm	0.5
Iron (maximum), ppm	0.5
Water (maximum), % by weight	0.3
Colour (maximum), Pt-Co	15

[a] From: Grayson (1985)

2.2.2 *Chemical properties*

Although acetonitrile is one of the most stable nitriles, it undergoes typical nitrile reactions and is used to produce many types of nitrogen-containing compounds. It can be trimerized to *S*-trimethyltriazine and has been telomerized with ethylene and copolymerized with alpha-epoxides (Grayson, 1985).

Acetonitrile produces hydrogen cyanide when heated to decomposition or when reacted with acids or oxidizing agents (Reynolds, 1982).

2.3 Conversion factors

1 ppm = 1.68 mg/m^3 (25 °C, 760 mmHg)

1 mg/m^3 = 0.595 ppm (25 °C, 760 mmHg) (Clayton & Clayton, 1982)

Table 2. Physical properties of acetonitrile

Properties	Value	Reference
Appearance	colourless liquid	Budavari (1989)
Odour	ether-like	Budavari (1989)
Boiling point	81.6 °C (760 mmHg)	Budavari (1989)
Freezing point	-45.7 °C	Grayson (1985)
	-44 to -41 °C	Verschueren (1983)
Specific gravity	0.78745 (15/4 °C)	Grayson (1985)
	0.7138 (30/4 °C)	Grayson (1985)
Vapour density	1.42 (air = 1)	Clayton & Clayton (1982)
Refractive index (N_D)	1.34604 (15 °C)	Clayton & Clayton (1982)
	1.33934 (30 °C)	Clayton & Clayton (1982)
Solubility in water	infinitely soluble	Clayton & Clayton (1982)
Vapour pressure		
at (15.5 °C)	7.32 kPa (54.9 mmHg)	US EPA (1984)
at (20.0 °C)	(74.0 mmHg)	Verschueren (1983)
at (30.0 °C)	(115.0 mmHg)	Verschueren (1983)
Water azeotrope	boiling point 76 °C	
	water content 16%	US EPA (1984)
Log P (octanol/water partition coefficient	-0.38	Leo et al. (1971)
	-0.34	Verschueren (1983)
Flash point	5.6 °C (open cup)	Reynolds (1982)
	12.8 °C (closed cup)	Reynolds (1982)
Ignition temperature	524 °C	Sax & Lewis (1989)
Explosive limits in air (% by volume)	lower 4.4	Grayson (1985)
	3.05	Prager (1985)
	upper 16.0	Grayson (1985)
	17.0	Prager (1985)

2.4 Analytical methods

2.4.1 Determination of acetonitrile in ambient air

2.4.1.1 Sampling methods

The use of absorption tubes to trap acetonitrile from ambient air with subsequent thermal or liquid desorption prior to gas chromatographic (GC) analysis has been reported in many references. The National Institute of Occupational Safety and Health (NIOSH, 1977, 1984) recommended the use of a glass tube (9 cm long and 6 mm internal diameter) containing two sections of 20-40 mesh activated (600 °C) coconut charcoal (front = 400 mg and back = 200 mg) separated by 3 mm section urethane foam and held in place with plugs of silanized glass wool. The tube is then flame-sealed at both ends until it is used for air sampling. Other sampling tubes containing different sorbents (i.e. porous polymer beads) have also been recommended (Campbell & Moore, 1979; Berg et al., 1980; Rigby, 1981; Kashihira, 1983; Kashihira et al., 1984; Wood, 1985; Cobb et al., 1986).

2.4.1.2 Measurement of acetonitrile in collected air samples

Several methods have been used to measure acetonitrile in environmental samples. Most of the reported methods are based on the use of GC.

a) *Gas chromatography*

GC is frequently used for determining acetonitrile using different kinds of detectors in conjunction with the charcoal or porous polymer beads sampling technique. A number of detectors have been recommended. Until recently, almost all of the published work involved the use of flame ionization detection (FID). However, it was found that FID did not respond to acetonitrile in a repeatable way even with the use of internal standards (Joshipura et al., 1983).

Attention has therefore turned to the use of thermal conductivity detection (TCD) (Joshipura et al., 1983) and to nitrogen-phosphorus selective detector, NPD (Cooper et al., 1986). Rounbehler et al. (1982) described a modification for the thermal energy analyser (TEA), a highly sensitive nitrosyl-specific GC chemiluminescence detector, which allows it to be used as a highly selective one in detecting nitrogen-containing compounds. They concluded that the modified TEA was as sensitive as the alkali-

bead flame ionization detection (AFID) but had a much higher selectivity toward nitrogen-containing compounds. Using the TEA, these investigators were not able to detect any acetonitrile in bacon or beer. Kashihira et al. (1984) used a chemiluminescence nitrogen detector GC (CLD-GC) method to measure acetonitrile and acrylonitrile in air. The method was able to detect as little as 20 ng of acetonitrile per injection.

Cooper et al. (1986) developed a very sensitive method of measuring nitrogen-containing hazardous pollutants in complex matrices by GC with NPD and were able to detect 1.5 pg acetonitrile.

Table 3 summarizes the different types of detectors used in GC analysis of acetonitrile along with the conditions employed and their corresponding detectability.

b) High-performance liquid chromatography (HPLC)

The use of HPLC to determine trace amount of acetonitrile in environmental samples has not been reported.

c) Microwave spectrometry

Kadaba et al. (1978) analysed toxic constituents including acetonitrile in tobacco smoke by microwave spectroscopy and were able to measure acetonitrile down to 2 ppm.

2.4.2 Monitoring methods for the determination of acetonitrile and its metabolites in biological materials

2.4.2.1 Acetonitrile in urine

Mckee et al. (1962) determined acetonitrile in urine samples obtained from 20 male nonsmokers and 40 male smokers by a modification of the method reported by Rhoades (1958, 1960) for the analysis of coffee volatiles. The modification permitted the stripping of urinary volatiles at 37 °C and at reduced pressure. The stripped volatiles were collected in a liquid nitrogen trap, vapourized, and analysed by GC with a thermal conductivity detector. The column, which was packed with 15% Carbowax 1500 and silicone oil 200 (ratio 2:1) on 40-60 mesh Chromosorb P, was operated at 40 °C. The carrier gas was helium at a pressure of 4 pounds per square inch. Acetonitrile concentrations as low as 2.9 μg/litre could be measured in urine using this method.

Table 3. Gas chromatographic conditions for acetonitrile determination

Packing	Conditions	Detection	Reported level of detectability	References
Porapak	250 x 0.25 cm, 160 °C injector 150 °C helium, 70 ml/min	FID	10 ppm in acrylonitrile	Thomson (1969)
Porapak Q	122 x 0.63 cm, 180 °C injector 270 °C nitrogen, 50 ml/min	FID	10 mg/m^3 in air (6 ppm)	NIOSH (1977)
Porapak Q	305 x 0.32 cm, 200 °C injector 200 °C nitrogen, 20 ml/min	FID	0.01 ppm in air	Campbell & Moore (1979)
0.1% SP 1000 on Carbopack C	200 x 0.19 cm, 35-235 °C injector 125 °C nitrogen, 21 ml/min	FID	0.07 ppm in air	Berg et al. (1980)
20% Carbowax 20 M	180 x 0.2 cm, 90-145 °C injector 120 °C	TEA	0.041 ppm	Rounbehler et al. (1982)

Table 3 (contd).

Packing	Conditions	Detection	Reported level of detectability	References
Chromosorb 103	90 x 0.3 cm, 85 °C injector 150 °C helium, 60 ml/min	CLD	1 ppb in air	Kashihira et al. (1984)
Porapak Q	508 x 0.32 cm, 170 °C injector 200 °C nitrogen, 30 ml/min	FID	0.2 ppm in air	Wood (1985)
20% SP-1200W/0.1% Carbowax 1500	305 x 0.32 cm, 180 °C injector 190 °C nitrogen, 30 ml/min or helium, 35 ml/min	NPD	1.5 ppb	Cooper et al. (1986)

FID = Flame ionization detection; CLD = Chemiluminescent nitrogen detection; NPD = Nitrogen-phosphorous detection; TEA = Thermal energy analyser

2.4.2.2 Acetonitrile in serum

Freeman & Hayes (1985a) determined serum acetonitrile concentrations in rats dosed orally with acetone, acetonitrile, and a mixture of acetone and acetonitrile by GC equipped with FID. The analysis was performed isothermally (150 °C) at a helium flow rate of 30 ml/min using a 2 mm x 1.22 m Chromosob 104 column (100/120 mesh) with a 15-cm precolumn. Propionitrile was added to the serum samples as an internal standard prior to injection, and the samples were injected directly into the column. Under the conditions of this study, the retention times of acetone, acetonitrile and propionitrile were 2.05, 3.65 and 6.20 min, respectively. The limit of detection was not reported. However, it was reported that the serum acetonitrile concentrations of animals in the control group were all below 1 mg/litre.

2.4.2.3 Acetonitrile metabolites in tissues and biological fluids

a) Cyanide

Since hydrogen cyanide is a reactive and volatile nucleophile, a variety of problems are encountered in its assay in biological materials due to tissue binding or diffusibility (Troup & Ballantyne, 1987). To reduce artefacts due to simple evaporative losses, cyanide should be extracted under alkaline conditions.

Amdur (1959) determined the cyanide level in the blood of 16 workers, who were accidentally exposed to acetonitrile, by the method of Feldstein & Klendshoj (1954), which uses a Conway microdiffusion approach (Conway, 1950). The sensitivity of this method is as low as 0.1 μg cyanide in a 1 ml sample. Willhite & Smith (1981) measured cyanide concentrations in the liver and brain of mice challenged by acetonitrile using the method of Bruce et al. (1955), which is capable of determining 0.05 μg cyanide in a 1 ml sample. Haguenoer et al. (1975a,b) determined free cyanide in the tissues and urine of rats using the pyridine–benzidine method described by Aldridge (1944); the sensitivity of this method was 0.7 μg hydrogen cyanide in a 1 ml sample. Ahmed & Farooqui (1982) determined the tissue and blood cyanide levels in rats by the Conway diffusion method described by Pettigrew & Fell (1973). Willhite (1983) determined tissue cyanide level in hamsters by the procedure of Bruce et al. (1955). A combination of the aeration procedure of Bruce et al. (1955) with the colorimetric method of Epstein (1947), which can determine 0.2 μg of cyanide in a 1 ml sample, has been used to determine the

cyanide level in brain (Tanii & Hashimoto, 1984a) and in liver microsomes of mice (Tanii & Hashimoto, 1984b). The aeration apparatus consists of three serial tubes containing 25 ml 20% NaOH, 5 ml 20% trichloroacetic acid and 0.5 ml 0.1 N NaOH. An aliquot of samples is added to the tube containing trichloroacetic acid, which is then aerated at a flow rate of 600 ml/min, passing from the tube containing 20% NaOH for 10 min toward the tube containing 0.1 N NaOH. An aliquot from the tube containing 0.1N NaOH is then removed, neutralized with acetic acid and subjected to analysis for cyanide. Under these conditions, the recovery of known amounts of cyanide is 97-100%. Freeman & Hayes (1985a) determined cyanide in the blood of rats by a microdiffusion method modified from Feldstein & Klendshoj (1954). Samples were analysed colorimetrically at 586 nm using pyridine-barbituric acid reagent as described by Blanke (1976). Cyanide concentrations as low as 0.1 mg/litre could be reproducibly detected by these methods. Zamecnik & Tam (1987) reported an improved GC method for cyanide analysis in blood with acetonitrile as an internal standard. GC with NPD was used with a 180 x 0.2 cm column packed with 100/120 mesh Porapak Q. Other conditions were: temperature, column 120 °C, detector 250 °C, and a helium gas flow rate of 20 ml/min. The blood samples containing cyanide were pipetted into disposable vials. Samples were then sealed and glacial acetic acid was injected into the vials. These were then vortexed and allowed to equilibrate for 30 min at room temperature. The head space was injected into the gas chromatograph. The typical retention times for the cyanide and acetonitrile peaks were 0.6 min and 2.5 min, respectively. The sensitivity for cyanide was 0.05 ppm. Three procedures for the determination of cyanide in biological fluids have been reported with full detail (Rieders & Valentour, 1975). The first procedure is qualitative, the second colorimetric (chloramine-T and barbituric acid and pyridine), and the third depends on GC using electron capture detection.

Table 4 summarizes the methods which have been used for cyanide analysis in biological samples.

b) Thiocyanate

Pozzani et al. (1959a) determined urinary thiocyanate levels in various animals by means of the colorimetric method of Chesley (1941). Using this method, 25-180 mg thiocyanate/litre urine could be measured with a ± 4% error. Silver et al. (1982) determined thiocyanate in the urine of rats dosed with acetonitrile.

Table 4. Analysis of cyanide in biological materials

Analytical methods			Application	
Principle	Detectability (μg/ml)	References	Biological materials	References
Conway diffusion method	0.1	Feldstein & Klendshoj (1954)	human blood	Amdur (1959)
	0.1	Pettigrew & Fell (1973)	rat tissues and blood	Ahmed & Farooqui (1982)
	0.1	Feldstein & Klendshoj (1954); Blanke (1976)	rat blood	Freeman & Hayes (1985a)
Benzidine and pyridine methods, colorimetry	0.1	Aldridge (1944)	rat tissues and urine	Haguenoer et al. (1975a,b)
Aeration procedure and colorimetry	0.2	Bruce et al. (1955); Epstein (1947)	mouse brain	Tanii & Hashimoto (1984a,b)
	0.05	Bruce et al. (1955)	mouse liver and brain	Willhite & Smith (1981)
	0.05	Bruce et al. (1955)	hamster tissues	Willhite (1983)
GC, nitrogen-phosphorus detector	0.05	-	blood	Zamecnik & Tam (1987)

Thiocyanate was first isolated from urine by separation on an ion exchange column (10 x 1 cm) of Amberlite CG-400 as described by Kanai & Hashimoto (1965) and then measured colorimetrically according to the method of Epstein (1947). Willhite (1983) determined the tissue thiocyanate levels in hamsters using the method described by Bruce et al. (1955).

Pereira et al. (1984) used the method of Contessa & Santi (1973) to determine thiocyanate levels in urine samples collected from rats treated with different nitriles. The method was able to detect thiocyanate concentrations as low as 100 μg in a 0.2 ml urine sample.

Table 5 summarizes the methods reported for analysis of thiocyanate in biological samples.

Table 5. Analysis of thiocyanate in biological materials

Analytical methods			Application	
Principle	Detectability (μg/ml)	References	Biological materials	References
Colorimetry	25	Chesley (1941)	animal urine	Pozzani (1959a)
	0.6	Bruce et al. (1955)	hamster tissues	Willhite (1983)
Ion exchange separation and colorimetry	0.5	Kanai & Hashimoto (1965); Epstein (1947)	rat urine	Silver et al. (1982)

3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

3.1 Natural occurrence

Acetonitrile may be formed by combustion of wood, straw and other vegetation. However, the rate of formation and the contribution to atmospheric acetonitrile has not been quantified (Becker & Ionescu, 1982).

3.2 Anthropogenic sources

3.2.1 Production levels and processes

Acetonitrile is a by-product of acrylonitrile synthesis. This process is known as the SOHIO (Standard Oil Company of Ohio) process and involves a high temperature catalytic reaction between propylene and ammonia. The SOHIO process is the principal route to both acrylonitrile and acetonitrile, produced in the ratio of 0.035 kg acetonitrile/kg acrylonitrile (Lowenheim & Moran, 1975).

Acetonitrile can be synthesized by several other routes. Good yields are obtained by dehydration of an acetic acid and ammonia mixture, acetamide or ammonium acetate.

$$CH_3COOH + NH_3 \rightarrow CH_3CN + 2H_2O$$
$$CH_3CONH_2 \rightarrow CH_3CN + H_2O$$
$$CH_3CO_2NH_4 \rightarrow CH_3CN + 2H_20$$

A 90% yield of acetonitrile is obtained by the reaction of ethanol and ammonia in the presence of catalyst such as Ag, Cu, MoO_3, and ZnS at moderate temperatures. Acetonitrile is also produced by the reaction of cyanogen chloride with methane, ketones, ethanol, alkylene epoxides, and paraffins or olefins.

The principal organic impurity in commercial acetonitrile is propionitrile, together with a small amount of allyl alcohol (US EPA, 1992).

Reported production of acetonitrile in the USA during the period 1980-83 (US EPA, 1985) was:

Year	Production (millions of kg)
1980	10.1
1981	9.5
1982	9.4
1983	11.4

3.2.2 Uses

Being a volatile highly polar solvent, acetonitrile finds its greatest use as an extracting fluid for fatty acids and animal and vegetable oils.

Acetonitrile has been widely used as an extractive distillation solvent in the petrochemical industry for separating olefin-diolefin mixtures and for C4-hydrocarbons. When acetonitrile is used in this way, recycling is effected by water dilution of the extract and condensate with subsequent phase separation, after which the acetonitrile is azeotroped from the aqueous phase.

Acetonitrile has been used as a solvent for polymer spinning and casting because of the combination of high solubility and desirable intermediate volatility. It is also used as a solvent for isolating components from crude products such as crude wool resin. Acetonitrile is used as a common laboratory solvent for recrystallizing various chemicals and is widely used as a solvent in HPLC analysis. Acetonitrile is also used in biotechnology research as a solvent in the synthesis of DNA and peptide sequencing (Borman, 1990).

Acetonitrile can be used to remove tars, phenols and colouring matter from petroleum hydrocarbons that are not soluble in acetonitrile.

Acetonitrile is also used as a starting material for the synthesis of many chemicals such as acetophenone, alpha-naphthyl acetic acid, thiamine and acetomidine (Hawley, 1971).

The use patterns of acetonitrile are summarized in Table 6.

Table 6. Main use patterns of acetonitrile[a]

Extraction of fatty acids and animal and vegetable oils
Extraction of unsaturated petroleum hydrocarbons
Solvent for polymer spinning and casting
Moulding of plastics
Removal of tars, phenols and colouring matter from petroleum hydrocarbons
Purification of wool resin
Recrystallization of steroids
Starting material for synthesis of chemicals
Solvent in DNA synthesis and peptide sequencing
Medium for promoting reactions
Solvent in non-aqueous titrations
Non-aqueous solvent for inorganic salts
High-pressure liquid chromatographic analysis
Catalyst and component of transition-metal complex catalysts
Extraction and refining of copper
Stabilizer for chlorinated solvents
Perfume manufacture
Pharmaceutical solvents

[a] From: Veatch et al. (1964); NIOSH (1978); Toxic Substances Control Act (1979); Smiley (1983); Borman (1990)

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION

4.1 Transport and distribution between media

4.1.1 Water

Hine & Mookerjee (1975) reported that the ratio of concentration in the water phase to the gas phase of a dilute aqueous solution of acetonitrile at equilibrium at 25 °C is 891:1. The inverse of this ratio (1.1×10^{-3}) is the unit-less Henry's Law constant. Conversion to units, using an RT value of 2.4×10^{-2}-m^3 atm/mol (where R is the gas constant and T is the temperature in K), yields a Henry's Law constant of 2.6×10^{-5}-m^3 atm/mol. This value of Henry's Law constant indicates that the volatilization of acetonitrile is probably significant for most environmental bodies of water (Lymann et al., 1982). The concentration of acetonitrile in river water decreased to 5% of the original level after 72 h in a study carried out under stable conditions (Chen et al., 1981).

4.2 Transformation

4.2.1 Biodegradation

4.2.1.1 Water and sewage sludge

Ludzack et al. (1958, 1959) measured the biodegradation of acetonitrile in Ohio River water and in aged sewage by measuring CO_2 production. Degradation in the river water occurred at a faster rate than in the sewage; the 12-day biological oxygen demand (BOD) was 40% in river water but only 20% in the sewage. Acclimatization of microorganisms was examined by reculturing, and the degradation was found to occur 5 times more rapidly using acclimatized microorganisms. The effect of temperature on biodegradation was also studied; degradation at 5 °C took 2.5-5 times longer than at 20 °C. Ludzack et al. (1961) examined the degradation of acetonitrile by activated sludge in a continuous feed test at 22-25 °C; 82-94% BOD was removed during 4 weeks of test operation. Anaerobic digestion does not appear to be an effective means of removing the compound from waste water (Ludzack et al., 1961).

Using the Japanese MITI (Ministry of International Trade and Industry) test, Sasaki (1978) reported that acetonitrile is "readily

biodegradable", meaning that oxygen consumption is > 30% in 2 weeks. Thom & Agg (1975) reported that acetonitrile should be degradable by biological sewage treatment with appropriate acclimatization. Mimura et al. (1969) isolated the bacterium *Corynebacterium nitrilophius* from activated sludge and found that this microorganism was capable of assimilating acetonitrile. Kelly et al. (1967) found virtually no degradation of acetonitrile using a nitrogenase from *Azotobacter chroococcum*.

Goud et al. (1985) isolated bacteria of several genera from various points in an effluent treatment plant at a petrochemical installation. *Azobacter* spp and, more particularly, *Pseudomonas* spp were able to degrade acetonitrile, added to the culture medium at 1% as sole carbon source. *Aeromonas* spp and *Bacillus* spp, however, were unable to degrade acetonitrile. The authors pointed out that many of the bacterial species tested are common in the environment, and that regular exposure to petrochemicals selects strains that are able to degrade such compounds.

Chapatwala et al. (1992) investigated mixed cultures of bacteria isolated from an area contaminated with organic cyanide and polychlorinated biphenyls and found that they readily utilized acetonitrile as sole carbon and nitrogen source. Nearly 70% of ^{14}C-labelled acetonitrile was recovered as CO_2, the remainder being incorporated into bacterial growth. The mixed culture lost its capacity to degrade biphenyl when repeatedly recultured with acetonitrile, indicating more ready degradation of the nitrile.

Ludzack et al. (1961) observed high levels of nitrates in effluents from activated sludge degrading acetonitrile. Firmin & Gray (1976) used a species of *Pseudomonas* capable of utilizing acetonitrile as sole carbon source to show that acetonitrile undergoes direct enzymatic hydrolysis. These authors postulated the following metabolic pathway based on their results with [2-^{14}C] acetonitrile: acetonitrile → acetamide → acetate → tricarboxylic acid cycle intermediates (citrate, succinate, fumarate, malate, glutamate, etc.).

4.2.1.2 Soil

DiGeronimo & Antoine (1976) isolated *Nocardia rhodochrus* LI100-21 from barnyard soil and demonstrated that the microorganism was capable of using acetonitrile as a source of carbon and nitrogen. A decrease in acetonitrile content within the culture medium was correlated with an increase in acetamide and

acetic acid levels; ammonia was also detected. Under the test conditions, the initial concentration of acetonitrile was reduced by 14% in 3 h and by 52% in 8 h. Crude cell-free extracts were also found to degrade acetonitrile by an enzymatic hydrolysis mechanism that was reported to be inducible. Kuwahara et al. (1980) found that *Aeromonas* species BN 7013 could be grown using acetonitrile as a nitrogen source; the microorganism was isolated from soil. Harper (1977) isolated a strain of the fungus *Fusarium solani* from soil and found that cell-free extracts, containing the nitrilase enzyme, were capable of hydrolysing acetonitrile enzymatically.

4.2.2 Abiotic degradation

4.2.2.1 Water

Brown et al. (1975) reported that the hydrolysis rate constant for acetonitrile in an aqueous solution of pH 10 is 1.195×10^{-8} M^{-1} sec^{-1}. Assuming a constant pH of 10, the half-life for this process would be > 18 000 years.

Anbar & Neta (1967) reported that the rate constant for the reaction of acetonitrile with hydroxyl radicals in aqueous solution at pH 9 and room temperature is 2.1×10^{6} M^{-1} sec^{-1}; assuming an environmental hydroxyl radical concentration at 10^{-17} M, a half-life of 1042 years can be calculated. Dorfman & Adams (1973) reported a similar hydroxyl radical rate constant of 3.5×10^{6} M^{-1} sec^{-1}.

The absorption maximum for acetonitrile in the UV range is < 160 nm (Silverstein & Bassler, 1967); therefore, the direct photolysis of acetonitrile in the aquatic environment is not expected to occur.

4.2.2.2 Air

Harris et al. (1981) found in laboratory studies that the rate of reaction of acetonitrile with ozone was relatively slow, the rate constant being $\leq 1.5 \times 10^{-19}$ cm^3 $molecule^{-1}$ sec^{-1}. Assuming a typical atmosphere concentration of 10^{12} ozone molecules/cm^3, a half-life of $\geq$ 54 days can be calculated from this rate constant.

The reaction rate constant between singlet oxygen and acetonitrile is reported to be 2.4×10^{-16} cm^3 $molecule^{-1}$ sec^{-1}

(Graedel, 1978); this predicts an atmospheric half-life of > 5000 years for acetonitrile.

Dimitriades & Joshi (1977) reported on the reactivity of acetonitrile as measured in an US EPA smog chamber with 22 blacklights, 7 sunlamps, 4 ppm acetonitrile and 0.2 ppm NOx. Acetonitrile was found to be unreactive with respect to ozone yield. The average rate of disappearance of acetonitrile was found to be 0.02% per hour, i.e. 100 times slower than that measured for propane. Kagiya et al. (1975) measured the photochemical decomposition rate of acetonitrile (300-2000 ppm) in air saturated with water in a reaction cell irradiated with a mercury lamp. No degradation was observed, however, when chlorine gas (2000 ppm) was added to the cell, the decomposition rate being 1.32% per second. Reaction between chlorine radicals and acetonitrile in the atmosphere is not thought to be significant in relation to hydroxyl radical reaction (Arijs et al., 1983).

The absorption maximum for acetonitrile in the UV range is < 160 nm (Silverstein & Bassler, 1967). Therefore, the direct photolysis of acetonitrile in the ambient atmosphere is not expected to occur.

The major mechanism for removal of acetonitrile from the troposphere is reaction with hydroxyl radicals. The rate constant for the gas-phase reaction of acetonitrile with hydroxyl radicals has been experimentally determined by Harris et al. (1981) to be 0.494×10^{-13} cm^3 $molecule^{-1}$ sec^{-1} at 24.2 °C; in the temperature range 298-424 °K (25-151 °C), the rate constant was described by the equation $k = 5.86 \times 10^{-13} \exp(-1500 \text{ cal mole}^{-1}/RT)$. From this rate constant data, Harris et al. (1981) calculated the tropospheric destruction rate of acetonitrile at 25 °C to be approximately 5×10^{-7} sec^{-1} for a mean concentration of 10^7 hydroxyl radicals/cm^3 in a moderately polluted troposphere; this rate yielded a tropospheric lifetime of approximately 20 days. In a more average atmosphere of 10^6 hydroxyl radicals/cm^3, the lifetime will be 10 times longer. Guesten et al. (1981) reported the rate constant for the reaction between hydroxyl radicals and acetonitrile in the gas phase to be approximately 0.2×10^{-13} cm^3 $molecule^{-1}$ sec^{-1} at room temperature, which agrees reasonably well with the findings of Harris et al. (1981). The Arrhenius activation energy of approximately 1500 cal $mole^{-1}$, as determined by Harris et al. (1981), indicates that the reaction proceeds largely or entirely by abstraction of a hydrogen atom.

Acetonitrile does reach the upper atmosphere. It is characteristically associated in positive ion clusters of the form $H^+(CH_3CN)_m (H_2O)_n$. These ions do not occur in the ionosphere but become important at 35 km altitude. At lower altitudes still (about 12 km), acetone ions become evident (Arijs et al., 1983; Huertas & Marenco, 1986).

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental levels

5.1.1 *Air*

Becker & Ionescu (1982) monitored air near to the ground in both urban and rural areas and detected acetonitrile at concentrations of 3360 to 11 960 $\mu g/m^3$ (2–7 ppb by volume) using GC/MS. There was some indication that results from city centre samples were higher than general rural samples; acetonitrile at concentrations of 7.4 ± 2.4 ppb was reported for the city centre in Wuppertal, Germany. Given the small number of samples, however, a comparison of the sites is difficult. A rural site was sampled in the air before and after burning of bush and grass by farm workers and results showed an increase in acetonitrile concentration from 4.0 to 34.9 ppb. This seems to be the only reported demonstration of non-anthropogenic sources of atmospheric acetonitrile. Acetonitrile has also been reported to be present in the upper stratosphere (Arijs et al., 1983). It was detected at concentrations of 210 to 42 000 ng/m^3 in the Environmental Survey of Chemicals in Japan (Office of Health Studies, Environment Agency, 1990).

In the USA, two samplings of air over a period of 24 h in a rural area gave daily mean levels of 0.048 ppb by volume. A single sampling of urban air was below the detection limit of the analytical method (US EPA, 1988).

5.1.2 *Water and bottom sediment*

Acetonitrile was not detected in water but was detected in bottom sediment in the Environmental Survey of Chemicals in Japan (Office of Health Studies, Environment Agency, 1990). The sampling was conducted in all 47 prefectures of Japan, but no information is available concerning the nature of the sampling sites. It is not known, therefore, whether the high ends of the ranges in air and aquatic sediment were associated with industrial production and release (Table 7).

5.1.3 *Food*

No report has been published showing contamination of food by acetonitrile.

Table 7. Environmental levels in Japan of acetonitrile in 1987[a]

	Concentration	Frequency of detection[b]	Detection limit
Water	not detected	0/72	3 μg/litre
Sediment	0.021 to 0.54 mg/kg	11/60	0.021 mg/kg
Air	210 to 42 000 ng/m^3	44/70	200 ng/m^3

[a] From: Office of Health Studies (1990)
[b] Number of detections/number of samples

5.1.4 Tobacco smoke

The absorption of acetonitrile from smoke has been confirmed by GC/MS analysis of a composite sample of the urine of 40 smokers (Mckee et al., 1962). The average acetonitrile level was 117.6 μg/litre urine, while the average level for 20 nonsmokers was 2.9 μg/litre urine.

5.1.5 Other sources of exposure

Nitrogen-containing products such as hydrogen cyanide, acetonitrile and acrylonitrile, and some other toxic gases have been detected from the thermal decomposition of flexible polyurethane foams (Woolley, 1972). The yield of hydrogen cyanide and acetonitrile, respectively, from 10 mg foam was 26.4 and 21.4 μg at 800 °C, where a volatile yellow smoke was produced, and 522 and 30.5 μg at 1000 °C, where the yellow smoke was decomposed.

5.2 Occupational exposure

Synthesis of acetonitrile is usually carried out in a closed system. Therefore, occupational exposure would only be accidental. NIOSH estimated that 23 000 workers may be exposed to acetonitrile in the USA. Since much of the acetonitrile produced has noncaptive uses, the general population may also be exposed (NIOSH, 1979).

The occupational exposure limit for acetonitrile in various countries is shown in Table 8.

Table 8. Occupational exposure limits for various countries[a]

Country	TWA		STEL	
	(ppm)	(mg/m^3)	(ppm)	(mg/m^3)
Australia	40	70	60	105
Belgium	40	67	60	101
Denmark	40	70	-	-
Finland	40	70	60	105
France	40	70	-	-
Germany	40	70	-	-
Hungary	-	50	-	100
Switzerland	40	70	80	140
United Kingdom	40	70	60	105
USA				
(ACGIH)	40	67	60	101
(NIOSH/OSHA)	-	70	-	10
USSR	-	-	-	10

[a] From: ILO (1991)

5.3 Acetonitrile in various solvent products

After a nationwide survey in Japan of organic solvent components in various solvent products, acetonitrile was not detected in either thinners (321 samples) or miscellaneous solvents (56 samples), but was detected in 1% of the degreasers (145 samples) (Inoue et al., 1983).

6. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

6.1 Absorption

6.1.1 Human studies

Acetonitrile is well absorbed by inhalation. There is little information on absorption of inhaled acetonitrile in humans.

Studies on smokers showed that 91 ± 4% of the acetonitrile inhaled in cigarette smoke was retained (Dalhamn et al., 1968a). A significant portion of this could have been retained in the mouth, as 74% of the acetonitrile was retained as a result of holding smoke in the mouth for 2 sec (Dalhamn et al., 1968b).

There are no absorption studies concerning dermal or oral exposure. However, human poisoning cases indicate that acetonitrile is well absorbed by both routes.

6.1.2 Experimental animal studies

6.1.2.1 Intake through inhalation

Although there is information that acetonitrile is easily absorbed from the lungs of animals exposed to acetonitrile vapour, no quantitative analytical data is available on the pulmonary absorption of acetonitrile.

6.1.2.2 Dermal absorption

Pozzani et al. (1959a) studied the skin penetration of undiluted or diluted acetonitrile under polyethylene sheeting in rabbits (the site of application was not reported). The dermal LD_{50} value was decreased when application was made as a 75% (by volume) aqueous solution, i.e. from 1.25 (0.84 to 1.85) ml/kg in the case of the undiluted compound to 0.5 (0.37 to 0.67) ml/kg in the case of the diluted aqueous solution. These LD_{50} values are similar or even lower than those obtained after oral administration in other animal species, indicating effective skin absorption of acetonitrile.

6.1.2.3 Intake via the gastrointestinal tract

Although there is information that acetonitrile is easily absorbed from the gastrointestinal tract, no quantitative analytical data are available.

6.2 Distribution

6.2.1 Human studies

A postmortem investigation on a man accidentally exposed to acetonitrile suggested that acetonitrile absorbed through inhalation or skin contact is distributed in the body as shown in Table 21 (section 8.1.1).

6.2.2 Experimental animal studies

Ahmed et al. (1992) studied by means of whole body autoradiography the distribution of radioactivity derived from 2-^{14}C-acetonitrile in the body of ICR mice at time points between 5 min and 48 h after administration of a single intravenous dose. Irreversible association of label was determined in co-precipitated protein and nucleic acids and extracted lipid. No attempt was made to distinguish between metabolically incorporated or adducted label. The highest concentrations of non-volatile radioactive compounds were generally found in the liver, kidney and the contents of the upper gastrointestinal tract. A significant fraction (40–50%) of the radioactivity found in liver at 24 and 48 h was bound to the macromolecular fractions of the tissues. The radioactivity contents of other organs were, in large part (40–50% of total), present in the lipid fraction of the tissue.

6.3 Biotransformation and elimination

6.3.1 Human studies

There is no specific human study describing acetonitrile biotransformation and elimination. However, accidental poisoning cases indicate that acetonitrile is biotransformed to cyanide and thiocyanate, which are then excreted from urine (see section 9).

6.3.2 Experimental animal studies and in vitro studies

6.3.2.1 Cyanide liberation from acetonitrile

The release of cyanide from acetonitrile and its subsequent metabolism to thiocyanate have been studied under a number of experimental conditions and in several animal species.

Biotransformation of acetonitrile to cyanide and thiocyanate has been demonstrated in a variety of *in vitro* preparations. Liver slices obtained from male golden hamsters show an increasing generation of cyanide and thiocyanate as the concentration of acetonitrile increases (Willhite, 1983). Release of cyanide from acetonitrile is also catalysed by liver microsomes of hamster in a concentration-dependent manner (Willhite, 1983). Production of cyanide from acetonitrile has been demonstrated in isolated hepatocytes from female SD rats; the K_m and V_{max} values (mean ± SD) were 3.4 ± 0.8 mM and 1.1 ± 0.1 nmol cyanide/10^6 cells per 10 min, respectively (Freeman & Hayes, 1987). The release of hydrogen cyanide from acetonitrile has also been demonstrated in mouse liver microsomes, both with and without NADPH (Ohkawa et al., 1972). The K_m and V_{max} values obtained from male ddY mouse microsomes were 4.19 mM and 14.3 ng cyanide formed in 15 min per mg protein, respectively (Tanii & Hashimoto, 1984a).

Dahl & Waruszewski (1989) studied the metabolism of acetonitrile to cyanide in rat nasal and liver tissues and found that the maximum rates of cyanide production from acetonitrile by nasal maxilloturbinate and ethmoturbinate microsomes and liver microsomes were 0, 0.9 ± 0.2 and 0.098 ± 0.008 nmol cyanide/mg protein per min, respectively.

In vivo metabolism of acetonitrile to cyanide and thiocyanate was first demonstrated by Pozzani et al. (1959a). Studies were conducted in rats, monkeys and dogs under a number of experimental conditions. Fifteen male and fifteen female rats were exposed to acetonitrile vapour (166, 330, and 655 ppm) 7 h/day, 5 days/week for 90 days. During the 5-day sampling period (inhalation days 59 to 63), thiocyanate concentrations in urine ranged from 27 to 79 and 29 to 60 mg/100 ml for the 166 and 330 ppm exposure groups, respectively. Thiocyanate was not completely eliminated between daily exposures, but was almost completely excreted during the 2.5-day rest period over weekends. The excretion of thiocyanate in the higher exposure group was not reported.

The concentrations of thiocyanate in the urine of three dogs exposed to 350 ppm acetonitrile in air increased from 69 to 252 mg/litre over the same 5-day inhalation period as described above for rats. Unlike the rats, dogs continued to eliminate thiocyanate beyond the 2.5-day rest period over the weekend. When three monkeys were exposed to 350 ppm acetonitrile in the same manner as the dogs, the urinary thiocyanate concentration ranged from 60 to 114 mg/litre. Thiocyanate was also excreted after the 2.5-day rest period.

Rhesus monkeys were injected intravenously either with acetonitrile (0.1 ml/kg) or with thiocyanate (1.55 ml/kg of a 10% solution in saline). The percentages of the dose excreted as thiocyanate were 12% and 55%, respectively. It seems therefore that more than 12% of the injected acetonitrile was converted into thiocyanate (Pozzani et al., 1959a).

After a single intraperitoneal administration of acetonitrile (780 mg/kg) in rats, all animals died in 3 to 12 h, and acetonitrile was found to be distributed in various organs (Dequidt & Haguenoer, 1972). The free cyanide varied from 170 μg/kg in the liver to 3.5 mg/kg in the spleen. Concentrations of combined cyanide in the liver, spleen, stomach and skin were 3.6, 13.5, 17.6 and 10.5 mg/kg tissue, respectively.

Haguenoer et al. (1975a,b) studied the pharmacokinetics of acetonitrile in male Wistar rats after a single intraperitoneal acetonitrile injection or inhalation exposure. Rats given 2340 or 1500 mg/kg died within 3 to 28 h after the intraperitoneal injection, but rats given 600 mg/kg survived with no apparent symptoms. After administration of 2340 mg/kg, concentrations of acetonitrile and free and combined cyanide in various organs ranged from 900 to 1700 mg/kg, 200 to 3500 μg/kg, and 3.5 to 17 mg/kg tissue, respectively. Mean total urinary acetonitrile and free and combined cyanide (essentially all thiocyanate) excreted during the 11 days following an intraperitoneal injection of 600 mg/kg were 28, 0.2 and 12 mg, respectively. These values were equivalent to 3, 0.035 and 2.3% of the acetonitrile dose, respectively. Urinary acetonitrile was detectable for 4 days after dosing, whereas free and combined cyanide were detectable until 11 days, at which time the animals were sacrificed. Rats inhaling 25 000 ppm died within 30 min from the beginning of exposure. The concentration of acetonitrile in muscle and kidney ranged from about 1.4 to 24 mg/kg, and that of free cyanide in liver and spleen from 0.3 to 4 mg/kg tissue. When three rats were exposed

to 2800 ppm (2 h/day for 3-5 days) the concentrations of acetonitrile and free cyanide in various tissues at the time of death were 1000-2900 mg/kg and 0.5-10 mg/kg tissue, respectively.

The liver and brain cyanide levels of male CD-1 mice (n = 9-10) that died 2.5 h after intraperitoneal administration of 175 mg acetonitrile/kg were found to be 47.8 ± 36.1 and 13.4 ± 4.8 μmol/kg, respectively (Willhite & Smith, 1981). Sprague-Dawley rats administered an oral LD_{50} of acetonitrile (2460 mg/kg) were found to have cyanide levels of 16 ± 6 mg/kg in liver, 102 ± 39 mg/kg in kidney and 28 ± 5 mg/kg in brain (Ahmed & Farrooqui, 1982).

Freeman & Hayes (1985a) found that the peak blood cyanide concentration (5.2 ± 0.5 mg/litre) was achieved 35 h after oral administration of 1470 mg/kg to female SD rats. Silver et al. (1982) reported that urinary thiocyanate excretion for a 24-h period following oral or intraperitoneal adminstration of acetonitrile (30.8 mg/kg) in SD rats was 11.8 ± 2.5 and 4.4 ± 0.5% of the dose, respectively. Inhalation studies on male and female Wistar rats exposed to 166 and 330 ppm (660 ppm was fatal) indicated that the amount of thiocyanate in urine was not proportional to the concentration of acetonitrile inhaled (Pozzani et al., 1959a).

Table 9 shows that acetonitrile is converted to cyanide at a slower rate than other nitriles. In fact, one hour after acetonitrile administration the blood level of cyanide was much lower than those after acute toxic doses of other nitriles. Peak concentrations of blood cyanide were found 7.5 h after acetonitrile dosing and were comparable to those of other nitriles measured one hour after dosing.

Brain cyanide concentration one hour after acetonitrile dosing was also lower than those after exposure to potassium cyanide (KCN) or other nitriles. Urinary excretion of thiocyanate after exposure to various nitriles indicated that for acetonitrile the percentage of the dose excreted was lower than for other nitriles, even though the absolute given amount of acetonitrile, based on its oral LD_{50} value, was much higher. These data, taken together, indicate that the toxicity of acetonitrile is lower than those of cyanide and other nitriles, as shown by oral LD_{50} values in Table 9. The reason for this is most probably the slower transformation of acetonitrile to cyanide and consequently the more efficient detoxification via thiocyanate excretion.

Table 9. Metabolism of nitriles to cyanide in relation to their lethal effects

Compound	Cyanide concentration (1 h after an oral LD_{50})		Urinary thiocyanate excretion (% dose/24 h)[d]	Oral LD_{50} (mg/kg body weight)[c]
	Blood (mg/litre)[a]	Brain (mg/kg)[c]		
Potassium cyanide	6.3	748 ± 200	not measured	10
Acetonitrile	0.3[b]	28 ± 5	11.8 ± 2.5	2460
Propionitrile	4.0	508 ± 84	65.1 ± 2.9	40
Butyronitrile	3.8	437 ± 106	64.9 ± 3.5	50
Malononitrile	6.5	649 ± 209	not measured	60
Isobutyronitrile	not measured	not measured	74.0 ± 2.6	160
Acrylonitrile	4.1	395-106	37.3 ± 1.9	90

[a] Estimated from: Ahmed & Farooqui (1982)

[b] 7.5 h after oral administration (1470 mg/kg body weight), the blood cyanide level was found to be 7.3 mg/litre (Estimated from: Freeman & Hayes, 1985a)

[c] Ahmed & Farooqui (1982) 1 h after oral LD_{50}

[d] Silver et al. (1982)

The relevance of acetonitrile pharmacokinetics is further illustrated by examining the relationship between symptoms produced by acetonitrile one hour after exposure and the amounts of cyanide, as well as the effect on cytochrome *c* oxidase in the brain (Table 10). Animals treated with acetonitrile were asymptomatic at this time, but animals treated with other nitriles or KCN at LD_{50} doses were symptomatic. In fact, the inhibition of brain cytochrome *c* oxidase paralleled brain cyanide concentrations. In the case of acetonitrile, the brain cyanide concentration was too low to affect cytochrome *c* oxidase activity and therefore to cause symptoms.

In conclusion, the data reported in Tables 9 and 10 indicate that the apparent lack of relationship, assessed shortly after dosing, between acetonitrile toxicity and cyanide production is due to the slow transformation of acetonitrile to cyanide.

There is sufficient evidence from all animal species studied that the toxicity of acetonitrile is due to cyanide. Interspecies variations, as shown in Tables 11 and 12, are probably related to the relative speed of cyanide formation from acetonitrile (data of Willhite & Smith, 1981 in mice versus the data of Ahmed & Farooqui, 1982 in rats).

6.3.2.2 *The oxidative pathway of acetonitrile metabolism*

Following the observation of acetonitrile metabolism to cyanide and thiocyanate by Pozzani et al. (1959a), many authors reported the same results in humans as well as in experimental animals both *in vitro* and *in vivo* (Amdur, 1959; Ohkawa et al., 1972; Willhite & Smith, 1981; Ahmed & Farooqui, 1982; Silver et al., 1982; Willhite, 1983; Pereira et al., 1984; Tanii & Hashimoto, 1984a,b, 1986; Freeman & Hayes, 1985a,b; Ahmed et al., 1992). They all suggested a metabolic pathway in which acetonitrile is biotransformed by cytochrome P-450 monooxygenase system initially to cyanohydrin, which then spontaneously decomposes to hydrogen cyanide and formaldehyde as shown in Fig. 1. Formaldehyde has not been identified in all of these studies, but this could be due to its high reactivity and rapid conversion into a simple metabolite (CO_2).

Acetone, an inducer of cytochrome P-450 isozyme LM3a (Koop & Casazza, 1985; Johannsen et al., 1986), has been demonstrated to stimulate the metabolism of acetonitrile to cyanide *in vivo* in rabbits (Freeman & Hayes, 1985a). In an *in vitro*

Table 10. Biochemical and clinical effects in Sprague-Dawley male rats dosed with cyanide and nitriles[a]

Compound	Brain cyanide concentration (mg/kg)	Brain cytochrome c oxidase activity (% of control)	CNS depression[b]	Convulsion[b]	Respiratory failure[b]
Control	0	100	no	no	no
Potassium cyanide	748 ± 200	29	4	4	4
Acetonitrile	28 ± 5	92	no	no	no
Propionitrile	508 ± 54	47	3	1	1
Butyronitrile	437 ± 106	41	2	1	1
Malononitrile	649 ± 209	73	3	3	2

[a] Measured 1 h after an LD_{50}; data from: Ahmed & Farooqui (1982)
[b] Physiological changes were graded on a scale of 1 (lowest) to 4 (highest)

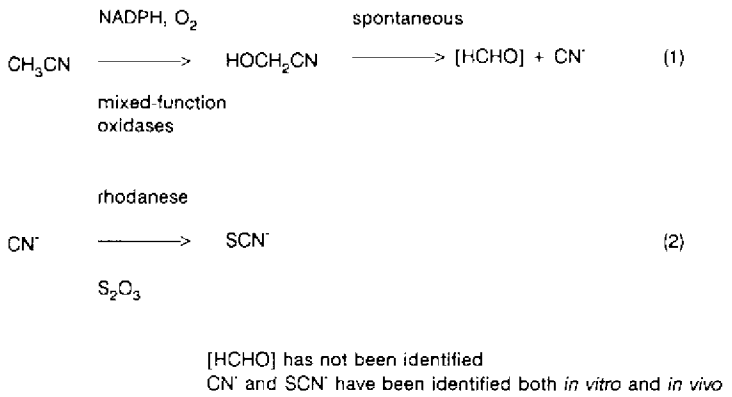


Fig. 1. Oxidation (1) and conjugation (2) reactions in acetonitrile metabolism

study, liver microsomes were isolated and pooled 24 h after pretreatment of female Sprague-Dawley rats with acetone. Microsomal metabolism of acetonitrile to cyanide was found to be NADPH-dependent and heat-inactivated tissue was unable to catalyse this reaction (Freeman & Hayes, 1985b). The metabolism of some nitriles, including acetonitrile to cyanide by mouse hepatic microsome system, has been shown to be NADPH-dependent and enhanced by pretreatment with ethanol (Tanni & Hashimoto, 1986). Ohkawa et al. (1972) found that the amount of hydrogen cyanide released in mouse liver microsomal preparations was increased greatly by the addition of NADPH. It is known that treatment of rats with cobalt-heme effectively depletes liver cytochrome P-450 concentrations (Drummond & Kappas, 1982). Freeman & Hayes (1987) demonstrated a marked decrease in acetonitrile metabolism in isolated hepatocytes prepared from rats pretreated subcutaneously with cobalt-heme (90 μmol/kg) 48 h before killing. However, the rate of acetonitrile biotransformation into cyanide by liver microsomal preparation obtained from cobalt-heme-treated rats was 13% of controls, while the total cytochrome P-450 content was reduced by only 41% compared to the controls.

Treatment of rats with inducers of P-450 IIE1, such as pyrazole, 4-methylpyrazole and ethanol, resulted in a 4- to 5-fold increase in cyanide production from acetonitrile by isolated microsomes (Feierman & Cederbaum, 1989). Phenobarbital

treatment had a small stimulatory effect, whereas 3-methylcholanthrene treatment decreased microsomal oxidation of acetonitrile. Cyanide production was inhibited by carbon monoxide, ethanol, 2-butanol, dimethyl sulfoxide (DMSO) and 4-methylpyrazole *in vitro*. Oxidation of acetonitrile to cyanide by microsomes from rats treated with pyrazole or 4-methylpyrazole was nearly completely inhibited by an antibody (IgG) against P-450 3a.

These results imply a role for P-450 in the oxidation of acetonitrile to cyanide and suggest that P-450 IIE1 may be the specific catalyst for this oxidation. Acetonitrile oxidation was not affected by hydroxyl radical scavengers or by desferrioxamine.

The results of human and animal studies indicate that cyanide formed *in vivo* is subsequently conjugated with thiosulfate to form thiocyanate, which is then eliminated in urine. This conjugation is catalysed by the enzyme rhodanese (thiosulfate cyanide sulfur transferase: EC 2.8.1.1) (Pozzani et al., 1959a; Takizaw & Nakayama, 1979; Silver et al., 1982; Willhite, 1983; Pereira et al., 1984).

Acetone inhibits acetonitrile metabolism when the two compounds are administered simultaneously. Blood cyanide concentrations were maximally elevated 9 to 15 h after female SD rats were dosed with acetonitrile alone at 1470 mg/kg. In rats dosed concomitantly with acetonitrile (1470 mg/kg) and acetone (1960 mg/kg), blood cyanide concentrations measured 0 to 24 h after dosing were much lower than those in rats given the same dose of acetonitrile alone. Blood cyanide levels, however, reached peak concentration 39 to 48 h after dosing with the two compounds and were 50% higher than those measured in rats treated with acetonitrile only (Freeman & Hayes, 1985a).

From these time courses of blood cyanide it was postulated that acetone has a biphasic effect on acetonitrile metabolism, causing an initial inhibition and a subsequent stimulation of cyanide generation from acetonitrile. Freeman & Hayes (1985b) also found that the *in vitro* metabolism of acetonitrile to cyanide by either hepatic microsomal preparations or by isolated liver cells (hepatocytes) from rats pretreated with acetone (2.5 ml/kg) was significantly increased (2 fold). However, when acetone was incubated with hepatocytes, it inhibited acetonitrile metabolism without affecting cell viability.

Ethanol has also been shown to affect the *in vitro* metabolism of some nitriles, including acetonitrile (Tanii & Hashimoto, 1986). A 1.8-fold increase in cyanide liberation from acetonitrile was observed in hepatic microsomes from male ddY mice pretreated with ethanol (4.0 g/kg) 13 h prior to the study.

Freeman & Hayes (1988) further investigated the metabolism of acetonitrile *in vitro* and the effects of acetone and other compounds. They suggested that the conversion of acetonitrile to cyanide is mediated by specific acetone-inducible isoforms of cytochrome P-450 and cytochrome P-450j (LM3a, LMeb). Acetone, dimethylsulfoxide and ethanol competitively inhibited this conversion. Aniline HCl has been shown to reduce acetonitrile metabolism.

6.4 Biological monitoring of acetonitrile uptake

Workers accidentally exposed to acetonitrile vapour showed increased serum cyanide and thiocyanate levels but the exposure concentrations were unknown (Amdur, 1959). In three human volunteers exposed at different times to concentrations of up to 160 ppm for 4 h (Pozzani, 1959a), no significant changes in urinary blood cyanide and thiocyanate levels were observed compared to those measured prior to exposure. In experimental animal studies using various routes of exposure, blood cyanide and thiocyanate levels showed increases but they were not proportional to the exposures (Pozzani, 1959a). It should be noted that there is a delay of several hours in the formation of cyanide following exposure to acetonitrile, and the timing of blood sampling is therefore critical.

From these data it is not possible to derive biological indices for exposure monitoring.

7. EFFECTS ON LABORATORY MAMMALS; *IN VITRO* TEST SYSTEMS

7.1 Acute toxicity

7.1.1 Single exposure

The LD_{50} values for acetonitrile in mammals are summarized in Table 11; they range between 175 and 5620 mg/kg body weight. The mouse and the guinea-pig seem to be the most sensitive species. No consistent effects of sex, administration route or vehicle were observed. An experiment using four different age groups of rats showed that new-born rats (24 to 48 h old, 5-8 g) are the most sensitive. Significant differences in LD_{50} values were found between 14-day-old and adult rats, but not between young adults (80-160 g body weight) and older adults (300-470 g body weight) (Kimura et al., 1971).

The acute inhalation toxicity of acetonitrile in various animal species is shown in Table 12. The LC_{50} values range between about 2700 ppm for a 1-h inhalation or 2300 ppm for a 2-h inhalation in mice and 16 000 ppm for a 4-h inhalation or 12 000 ppm for an 8-h inhalation in rats. Mice appear to be the most sensitive species to acetonitrile inhalation. In Nelson rats, the LC_{50} value for an 8-h inhalation was significantly lower in males (7551 ppm with 5975 to 9542 confidence interval) than in females (12 435 ppm with 11 036 to 14 011 confidence interval), while that for a 4-h inhalation was the same in both sexes (16 000 ppm with 13 070 to 19 636 confidence interval) (Pozzani et al., 1959a).

Pozzani et al. (1959b) studied the relationship between the observed and predicted LD_{50} of acetonitrile given in combination with other chemicals to rats exposed orally or by inhalation. Predictions were made using the method of Finney (1952). The mixture of acetonitrile and acetone seemed to show effects that were greater than additive. Results are summarized in Table 13.

7.1.2 Clinical observations

Signs and symptoms of acute acetonitrile intoxication are similar in different animal species. Verbrugge (1899) described signs of acute acetonitrile toxicity in rabbits. One to three hours after a subcutaneous acetonitrile injection of 90 to 150 mg/kg, rabbits showed rapid and irregular respiration, immobilization

Table 11. LD_{50} values of acetonitrile for various species and different routes of administration

Species (strain)	Sex	Observation period (days)	Route	LD_{50} (mg/kg or ml/kg body weight[b]	Vehicle	References
Mouse (Kunming)	male	-[a]	gavage	453 mg/kg	water	Chen et al. (1981)
Mouse		1	intraperitoneal	520.79 mg/kg		Yoshikawa (1968)
Mouse		-	intraperitoneal	0.25 ml/kg	saline	Pozzani et al. (1959a)
Mouse (NMRI)		7	intraperitoneal	400 mg/kg	water	Zeller et al. (1969)
Mouse (CD-1)	male	7	intraperitoneal	175 mg/kg	water	Willhite & Smith (1981)
Mouse (ddY)	male	7	oral	269 mg/kg	water	Tanii & Hashimoto (1984a)
Rat (Sherman)		-	oral	3800 mg/kg	-[a]	Smyth & Carpenter (1948)
Rat (Wistar) or albino	male	-	gavage	1.68 ml/kg	undiluted	Pozzani et al. (1959a)
Rat (Wistar) or albino	male	-	gavage	2460 mg/kg	water	Pozzani et al. (1959a)
Rat (Wistar) or albino	male	-	intravenous	1.68 ml/kg	undiluted	Pozzani et al. (1959a)
Rat (Wistar) or albino	female	-	gavage	2230 mg/kg	1% Tg[c]	Pozzani et al. (1959a)
Rat (Wistar) or albino	female	-	gavage	1730 mg/kg	corn oil	Pozzani et al. (1959a)
Rat (Wistar) or albino	female	-	gavage	8.56 ml/kg	undiluted	Pozzani et al. (1959a)
Rat (Wistar) or albino	female	-	intraperitoneal	7.96 ml/kg	undiluted	Pozzani et al. (1959a)
Rat (Wistar) or albino	female	-	intraperitoneal	5620 mg/kg	saline	Pozzani et al. (1959a)

Table 11 (contd).

Species (strain)	Sex	Observation period (days)	Route	LD_{50} (mg/kg or ml/kg body weight[b]	Vehicle	References
Rat (Wistar) or albino	female	-	intraperitoneal	0.85 ml/kg	undiluted	Pozzani et al. (1959a)
Rat (Wistar) or albino	female	-	intravenous	1.68 ml/kg	undiluted	Pozzani et al. (1959a)
Rat (SD)		-	oral	3200 mg/kg	water	Zeiler et al. (1969)
Rat (SD) 14-day old	male	-	oral	0.2 ml/kg	undiluted	Kimura et al. (1971)
Rat (SD) young adult	male	-	oral	3.9 ml/kg	undiluted	Kimura et al. (1971)
Rat (SD) older adult	male	-	oral	4.4 ml/kg	undiluted	Kimura et al. (1971)
Rat (SD)	female	3	oral	4050 mg/kg	undiluted	Freeman & Hayes (1985a)
Guinea-pig	male	-	gavage	0.177 ml/kg	undiluted	Pozzani et al. (1959a)
Rabbit		-	skin	5.0 ml/kg	undiluted	Smyth & Carpenter (1948)
Rabbit	male	-	skin	1.25 ml/kg	undiluted	Pozzani et al. (1959a)
Rabbit	male	-	skin	0.50 ml/kg	water	Pozzani et al. (1959a)

[a] - = not reported
[b] 1 ml acetonitrile = 783-787 mg at 20 °C
[c] Tg = Tergitol 7 in water

Table 12. Acute inhalation toxicity of acetonitrile[a]

Species (strain)	Sex	Concentration (ppm)	Exposure time (h)	Mortality measures[b]
Mouse (Kunming)		2300	2	LC_{50}
Mouse (Kunming)		5700	2	LC_{50}
Mouse (CD-1)	male	2700	1	LC_{50}
	male	5000	1	10/10
Rat (Nelson)	male	7551	8	LC_{50}
	female	12 435	8	LC_{50}
	male	16 000	4	LC_{50}
	female	16 000	4	LC_{50}
Rat (Wistar)		12 000	2	MLC
Guinea-pig	male + female	5655	4	LC_{50}
Guinea-pig		7400	2	MLC
Rabbit	male	2800	4	LC_{50}
Rabbit		4500	2	MLC
Dog	male	32 000	4	1/1
	male	16 000	4	3/3
	male	8000	4	0/1
	male	2000	4	0/2

[a] From: Willhite (1981), Pozzani et al. (1959a,b), Wang et al. (1964)
[b] MLC = minimum lethal concentration

and convulsions, and two out of seven animals died. Monkeys exposed to 2510 ppm acetonitrile vapour appeared normal after the first day of inhalation but showed poor coordination followed by prostration and laboured breathing during the second day. Death occurred a few hours later (Pozzani et al., 1959a). Mice exposed to concentrations of acetonitrile ranging from 500 to 5000 ppm (the LC_{50} for a 60-min exposure was 2693 ppm) displayed dyspnoea, tachypnoea, gasping, tremors, convulsions and corneal opacity 30–300 min after the beginning of the exposure. Exposure of mice to 5000 ppm acetonitrile for 60 min killed all the animals within 2 h. The syndrome of acute acetonitrile toxicity was indistinguishable from that observed after exposure to cyanide or other nitriles (Willhite, 1981; Willhite & Smith, 1981).

Table 13. Predicted and observed LC_{50} and LD_{50} values of acetonitrile in combination with other solvents in rat[a]

	4-h inhalation (g/m^3)		Oral (ml/kg)	
	PLC_{50}	OLC_{50}	PLD_{50}	OLD_{50}
Acetonitrile	-	26.9	-	8.27
Acetonitrile + n-hexane	45.6	74.1	-	-
Acetonitrile + acetone	39.7	14.6	9.99	2.75
Acetonitrile + ethyl acetate	32.4	51.4	9.40	14.1
Acetonitrile + carbon tetrachloride	31.5	45.5	4.35	6.77
Acetonitrile + toluene	22.3	44.4	8.68	3.73

[a] From: Pozzani et al. (1959b)
PLC_{50} or PLD_{50} = predicted LC_{50} or LD_{50}
OLC_{50} or OLD_{50} = observed LC_{50} or LD_{50}

In a study by Willhite (1983), pregnant hamsters were exposed to acetonitrile concentrations from 3800 to 8000 ppm for one hour. The number of hamsters showing tremors, hypersalivation, ataxia, hypothermia, lethargy and coma increased with increasing dose. Hamsters died about 3 h after exposure to 5000 ppm acetonitrile and within 90 min after exposure to 8000 ppm acetonitrile.

In a study by Johansen et al. (1986), all of five pregnant rats treated with acetonitrile at doses of 750 mg/kg or more per day by gavage on gestation days 6–15 died, whereas only three out of five animals treated with 375 mg/kg per day died. Four out of six rats treated with 275 mg/kg had reduced body weight at parturition, while two others died.

Ahmed & Farooqui (1982) measured cyanide levels one hour after administration of LD_{50} doses of several saturated and unsaturated nitriles to male SD rats. Few symptoms were noted with acetonitrile in this study because little cyanide was released within the first hour following treatment. The tissue concentrations of cyanide after lethal doses of propionitrile, butyronitrile

and malononitrile were very similar and approximately those observed with a lethal dose of KCN.

In female SD rats given an oral dose of acetonitrile (1770 mg/kg), acute toxic effects appeared after 30 h (Freeman & Hayes, 1985a).

7.1.2.1 Effect on skin

The skin irritation of acetonitrile in Sherman rats was reported by Smyth & Carpenter (1948) to be comparable to that of acetone, although no precise description of the technique used for testing skin irritation was provided.

7.1.2.2 Effect on the eyes

Eye injury caused by acetonitrile, reported by Smyth & Carpenter (1948), is of intermediate intensity and similar to that produced by acetone (Carpenter & Smyth, 1946). Corneal opacity has been observed after either inhalation or intraperitoneal administration of acetonitrile in male mice (Willhite, 1981; Willhite & Smith 1981). Pregnant hamsters exposed to 8000 ppm acetonitrile via inhalation for 60 min showed eye irritation (Willhite, 1983).

7.1.2.3 Effect on respiration

Animals exposed to acetonitrile via different routes of dosing always showed respiratory symptoms: rapid and irregular respiration after subcutaneous administration in rabbits (Verbrugge, 1899), laboured or difficult breathing after inhalation exposure in monkeys (Pozzani et al., 1959a) or rats (Haguenoer et al., 1975b), and intense dyspnoea after either inhalation or intraperitoneal administration in mice (Willhite, 1981; Willhite & Smith, 1981). Histopathological investigations of rat lungs after acetonitrile inhalation showed haemorrhage and congestion (Haguenoer et al., 1975b). After inhaling 660 ppm acetonitrile for 2 h, two monkeys showed focal areas of emphysema and atelectasis, with occasional proliferation of alveolar septa (Pozzani et al., 1959a).

7.1.2.4 Effect on adrenals

Szabo et al. (1982) studied structure-activity relationships of 56 chemicals, including acetonitrile, with respect to their potential for

causing adrenocortical necrosis in rats. The dose was selected on the basis of preliminary experiments and was aimed to lead to 70 to 100% mortality in 4 to 5 days. The compounds were given 3 times per day for 4 days, and surviving animals were sacrificed on the 5th day. Acetonitrile, along with 13 other compounds out of 56 test chemicals, did not show any adrenocorticolytic effect in rats.

7.1.2.5 Effect on the gastrointestinal tract

Rats that inhaled acetonitrile at a concentration of 2800 ppm (2 h/day for 2 days) showed temporary diarrhoea (Haguenoer et al., 1975b).

Acetonitrile did not produce duodenal ulcers in female SD rats after oral or subcutaneous administration 3 times per day for 4 days, the total dose being 432 mmol/kg (Szabo et al., 1982).

7.1.3 Biochemical changes and mechanisms of acetonitrile toxicity

7.1.3.1 Effect on cytochrome oxidase

An *in vitro* study carried out by Willhite & Smith (1981) showed that high concentrations of acetonitrile (up to 0.47 M) did not inhibit cytochrome *c* oxidase activity. Ahmed & Farooqui (1982) investigated the ability of acetonitrile and other nitriles to inhibit cytochrome *c* oxidase one hour after they were administered at the LD_{50} to male SD rats. There was no direct evidence for the inhibition of cytochrome oxidase after the administration of acetonitrile. However, very little increase in tissue or blood cyanide concentrations was observed one hour after dosing with acetonitrile. Symptoms had not occurred within this time period, and the evidence from other studies indicates that peak cyanide levels are achieved much later than one hour (in 9–15 h) (Freeman & Hayes, 1985a). The need to consider the different pharmacokinetic and metabolic factors involved in making such comparisons was emphasized by Willhite & Smith (1981).

7.1.3.2 Effect on glutathione

Levels of glutathione (GSH) in liver, kidney and brain were unaffected one hour after oral administration of acetonitrile (at the LD_{50} level) in male SD rats (Ahmed & Farooqui, 1982). Aitio & Bend (1979) studied the *in vitro* effect of 12 organic solvents,

including acetonitrile, on the activity of rat liver soluble glutathione S-transferase. They demonstrated that in the presence of 630 mM acetonitrile, the conjugation of styrene oxide, benzo[a]pyrene-4,5-oxide and 1,2-dichloro-4-nitrobenzene by GSH was reduced to 79.0 ± 5.2, 92.6 ± 3.0 and 59.2 ± 1.4%, respectively, of the control values.

7.1.4 Antidotes to acetonitrile

Multiple intraperitoneal administrations of 1 g sodium thiosulfate per kg at the rate of one injection every 100 min over a 10-h period or two intraperitoneal injections of 75 mg sodium nitrite per kg significantly reduced mortality in CD-1 mice exposed to 3800 or 5000 ppm acetonitrile by inhalation for 60 min (Willhite, 1981). Treatment of animals with thiosulfate at a dose rate of 1 g/kg every 100 min for an 8-h period was effective in providing significant protection against the lethal effect of an intraperitoneal injection of acetonitrile (575 mg/kg) in male CD-1 mice (Willhite & Smith, 1981). An intraperitoneal injection of sodium thiosulfate (300 mg/kg) 20 min prior to inhalation of 8000 ppm acetonitrile in pregnant hamsters abolished the overt signs of acetonitrile poisoning and reduced mortality from 3 out of 12 hamsters to zero (Willhite, 1983). Repeated intraperitoneal administrations (6 injections in 10 h) of sodium thiosulfate (1 g/kg), which started at the onset of acute toxicity about 30 h after oral administration of acetone (1960 mg/kg) and acetonitrile (1770 mg/kg) given simultaneously, provided significant protection against mortality in female SD rats (Freeman & Hayes, 1985a).

Two intraperitoneal injections of 75 mg sodium nitrite did not provide CD-1 mice with any significant protection against the lethal effect of acetonitrile (575 mg/kg) (Willhite & Smith, 1981).

7.2 Subchronic toxicity

7.2.1 Inhalation exposure

In a rat study, the body weight gain and organ weights of male and female rats which inhaled 166, 330 or 655 ppm acetonitrile (7 h/day, 5 days/week, for a total of 90 days) did not differ significantly from those of the controls (Pozzani et al., 1959a). Histopathological examination showed that of the 28 rats that inhaled 166 ppm, one had histiocyte clumps in the alveoli and another had atelectasis. Of 26 rats that inhaled 330 ppm, three

showed bronchitis, pneumonia, atelectasis and histiocyte clumps in the alveoli. After the inhalation of 655 ppm acetonitrile vapour, 10 out of 27 animals showed alveolar capillary congestion and/or focal oedema in the lung, often accompanied by bronchial inflammation, desquamation and hypersecretion. Tubular cloudy swelling of the kidneys in eight rats and swelling of the livers of seven rats were observed. These effects were statistically significant (lungs, $P < 0.001$; kidney, $P < 0.005$; liver, $P < 0.04$) compared with control animals. No lesions were found in the adrenals, pancreas, spleen, testes or trachea. Focal cerebral haemorrhage was observed in one of the five brains examined.

Wang et al. (1964) reported that there was no change of iodine levels in the thyroid of Wistar rats exposed to 80 or 400 mg acetonitrile/m^3 (4 h/day, 6 days/week) for 10 weeks. Degenerative changes in the epithelial cells of thyroid follicles were observed in rabbits exposed to 400 mg/m^3 (4 h/day, 6 days/week) for 16 weeks.

In an inhalation study (7 h/day) on four Rhesus monkeys, one female monkey was exposed to 2510 ppm, two females to 660 ppm and one male to 330 ppm (Pozzani et al., 1959a). The monkey exposed to 2510 ppm appeared normal during the first inhalation day but on the second day showed incoordination and laboured breathing and died a few hours later. In the two monkeys exposed to 600 ppm there was also incoordination from the second week. One monkey died on day 23 and the other on day 51. The monkey exposed to 330 ppm showed overextension reflexes and hyperexcitability towards the end of the 99-day inhalation period and was sacrificed then. At autopsy, the monkey exposed to 2510 ppm had engorgement of the dural capillaries, and the animals exposed to 660 and 330 ppm showed focal dural or subdural haemorrhage in the parietal and/or occipital tissues adjacent to the superior sagittal sinus. The monkey exposed to 2510 ppm had pleural effusion, and those exposed to 660 ppm had focal areas of emphysema and atelectasis with occasional proliferation of alveolar septa, and cloudy swelling of the proximal and convoluted tubules of the kidneys. The monkey exposed to 330 ppm had pneumonitis as shown by diffuse proliferation of alveolar septa, monocytic infiltration and pleural adhesions.

In another inhalation study (Pozzani et al., 1959a), three male Rhesus monkeys were exposed to 350 ppm acetonitrile (7 h/day, 5 days/week) for 91 days, and at the end of the study the animals were sacrificed. At autopsy, haemorrhages of the superior and

inferior sagittal sinuses were found in the brains of all three monkeys. Small discrete caseous nodules were seen in the lungs of two monkeys and one monkey had a pale liver. Histological investigations of the lung showed focal emphysema, diffuse proliferation of alveolar septa, and focal accumulations of pigment-bearing macrophages. In two of the monkeys there was cloudy swelling of the proximal tubules of the kidney.

One female and two male dogs inhaled 350 ppm acetonitrile (7 h/day, 5 days/week) for 91 days. The haematocrit and haemoglobin values of the three dogs were depressed by the fifth week of inhalation, but with the exception of one dog, there was a return to pre-inhalation values toward the end of the 91-day inhalation period. No significant deviation of the erythrocyte counts was seen in any dogs. Histopathological examination of these dogs showed some focal emphysema and proliferation of alveolar septa.

Roloff et al. (1985) exposed groups of male and female rats (strain unspecified) to acetonitrile vapour (0, 1038, 3104 and 10 485 mg/m^3) for one month (6 h/day, 5 days/week). Death and reduced body weight gains were observed at the highest exposure level. Respiratory and/or ocular irritation were noted in animals exposed to 3104 and 10 485 mg/m^3.

In a 13-week inhalation study of acetonitrile (100, 200 and 400 ppm) in 25 male mice and male rats, there were no effects on body weight or on testicular weight and sperm motility (Morrissey et al., 1988).

In a 13-week inhalation study on acetonitrile in mice and rats, ten mice (B6C3F$_1$) and ten rats (F-344/N) of each sex were exposed to acetonitrile vapour at 0, 100, 200, 400, 800 and 1600 ppm (6 h/day, excluding weekends and holidays) for 13 weeks (Battelle, Pacific Northwest Laboratories, 1986a,b). At 400 ppm one female mouse, at 800 ppm one male and four female mice, and at 1600 ppm ten female and ten male mice were found dead during the study. The majority of the mortality occurred after two weeks of exposure. Clinical signs observed were hypoactivity and a hunched rigid posture. Body weight gains were comparable to control values for all surviving mice. An increase in absolute and relative liver weight was attributed to acetonitrile exposure. The maximum tolerated concentration determined by this 13-week subchronic study was 200 ppm. Significant changes were observed in the liver and stomach of male mice exposed to 400 ppm of

acetonitrile and female mice exposed to 200 ppm or more. At 800 ppm one male rat and at 1600 ppm six male and three female rats were either moribund (and so sacrificed) or found dead during the study. The clinical signs observed were hypoactive, abnormal posture, ataxia, bloody crusts on nose and/or mouth and a rough haircoat. The moribund, sacrificed rats exhibited tonic/clonic convulsions. Reductions in body weight gain were observed in rats exposed to 1600 ppm. Minimum to mild lesions were found in the lungs and brain of some rats exposed to 800 ppm (Table 14).

In a 92-day study, reported as an abstract, acetonitrile was administered by inhalation to B6C3F$_1$ mice and Fischer-344 rats at concentrations of (25, 50, 100, 200 and 400 ppm) for a total of 65 days (Hazleton, 1990b). In mice, one male in each of the 50, 200 and 400 ppm groups died. There was an increase in body weight gain in all males exposed to 50, 100, 200 and 400 ppm acetonitrile and in the females of the 200 and 400 ppm groups. Body weight gain was decreased by comparison with controls in the 25, 50 and 100 ppm female groups. Liver/body weight ratio was increased in males at 400 ppm group and in females at 100, 200 and 400 ppm groups. Liver/brain weight ratio was increased in males at the 400 ppm and in female at 100 and 400 ppm groups. There was slight cytoplasmic vacuolization of hepatocytes in both males and females in the 200 and 400 ppm groups. Mean haematocrit and erythrocyte counts were marginally reduced in females at 200 and 400 ppm group. In females of the 200 and 400 ppm groups haematocrit, haemoglobin, red and white blood cell counts, and serum IgG were all depressed. In rats, one male in the 400 ppm group died during the study. There was slight cytoplasmic vacuolization of hepatocytes in females at 400 ppm. Marginal decreases in mean leucocyte counts were reported in males at 100 and 200 ppm and in both males and females at 400 ppm.

7.2.2 *Subcutaneous administration*

Marine et al. (1932a) gave daily subcutaneous injections of 0.1 ml acetonitrile to 4-month-old rabbits for 21 days. Two groups of four male rabbits developed pronounced (more than twice normal size) thyroid hyperplasia whereas one group of four females showed no effect. Allyl-benzyl and phenyl nitriles produced less pronounced hyperplasia or no effect on thyroids at up to 4 times the dose of acetonitrile. A further study (Marine et al., 1932b) suggested that young rabbits were more susceptible than adults and that the effect varied with the strain.

Table 14. Subchronic inhalation toxicity of acetonitrile in mice and rats

Species (strain)	Sex	Number of animals	Concentration (ppm)	Duration	Effects	References
Mice ($B6C3F_1$)	M, F	10, 10	100, 200, 400 800, 1600	6 h/day, 5 days/week, 13 weeks	changes in liver and stomach at > 400 ppm, hypoactivity, rigid posture; NOEL for males 200 ppm, for females 100 ppm	Battelle, Pacific Northwest Laboratories (1986a)
Mice ($B6C3F_1$)	M, F	10, 10	25, 50, 100, 200, 400	6 h/day, 65/92 days	increased body weight gain in male groups 50, 100, 200 and 400 ppm and female groups 200 and 400 ppm; liver/body weight ratio increased in 400 ppm males and 100, 200 and 400 ppm females; liver/brain weight ratio increased in 400 ppm males and 100 and 400 ppm females; minimal cytoplasmic vacuolization of hepatocytes in male and female 200 and 400 ppm groups; no effects on male reproductive system	Hazleton Laboratories (1990a)

Table 14 (contd).

Mice	M	25	100, 200, 400		no effect on reproductive system	Morrissey et al. (1988)
Rat (Carworth)	M, F	15, 15 15, 15 15, 15	166 330 655	7 h/day, 5 days/week, 90 days	bronchitis, pneumonia, atelectasis, alveolar congestion, kidney and liver changes	Pozzani et al. (1959a)
Rat (F-344)	M, F	10, 10	25, 50, 100, 200, 400	6 h/day, 65/92 days	minimal cytoplasmic vacuolization of hepatocytes in 400 ppm females, slightly decreased mean leucocyte counts in 100 and 200 ppm males and 400 ppm males and females	Hazleton (1990b)
Rat	M, F	not specified	1038, 3104, 10 485	6 h/day, 5 days/week, 1 month	eye/nose irritation, body weight loss, nervous system effects, mild anaemia at mid- and high-exposure levels	Roloff et al. (1985)
Rat (F-344/N)	M, F	10, 10	100, 200, 400, 800, 1600	6 h/day, 5 days/ week, 13 weeks	hypoactive, ataxia at > 800 ppm, body weight loss at > 1600 ppm	Battelle, Pacific Northwest Laboratories (1986b)

Table 14 (contd).

Species (strain)	Sex	Number of animals	Concentration (ppm)	Duration	Effects	References
Dog (Basenji)	M, F	2, 1	350	7 h/day, 5 days/ week, 91 days	body weight drop on day 3 and 5 decreased Hb	Pozzani et al. (1959a)
Monkey (Rhesus)	F	2	660	7 h/day, 23 days and 51 days	1 died on day 23 and 1 on day 51; brain haemorrhages, emphysema, atelectasis, cloudy swelling of renal convoluted tubes	Pozzani et al. (1959a)
Monkey (Rhesus)	M	3	350	7 h/day, 5 days/ week, 91 days	brain haemorrhages, focal emphysema, cloudy swelling of renal convoluted tubes	Pozzani et al. (1959a)
Monkey (Rhesus)	M	1	330	7 h/day, 5 days/ week, 99 days	chronic pneumonitis, "excitability"	Pozzani et al. (1959a)

7.3 Teratogenicity and embryotoxicity

In a study by Berteau et al. (1982), mated rats were administered daily aqueous solutions of acetonitrile by gavage (125, 190 and 275 mg/kg) on gestation days 6-19. Although maternal body weights were reduced and death occurred in the high-dose group, no other maternal effects were noted in any treated group. Embryotoxic effects, as shown by increases in early resorptions and postimplantation losses, were also noted in the high-dose group. However, no teratogenic responses were observed at any dose level.

When pregnant rabbits were given acetonitrile orally on gestation days 6-18 at dose levels of 0, 2, 15 and 30 mg/kg per day, animals given the highest dose showed anorexia and decreased body weight gain, and death occurred in 5 out of 25 rabbits at this level. Body weight gain was also reduced in animals receiving 15 mg/kg per day, but not at the lowest dose level. With respect to the fetuses of the treated animals, evidence of toxicity was only observed at the highest dose level. Therefore, acetonitrile is not considered to be toxic to fetuses at doses below those causing maternal toxicity (Argus Res Labs., 1984).

In a study by Willhite (1983), pregnant golden hamsters were exposed by inhalation for one hour to 0, 1800, 3800, 5000 or 8000 ppm acetonitrile on the 8th day of gestation. There was a significant and dose-dependent increase in the number of abnormal fetuses from animals exposed to the two highest dose levels.

Pregnant golden hamsters were exposed to a single gavage or a single intraperitoneal injection of 0, 100, 200, 300 or 400 mg/kg on the 8th day of gestation. Animals exposed intraperitoneally were killed on day 14 while those exposed orally were killed on day 15. An intraperitoneal injection of 200 to 400 mg/kg produced a significant increase in the average fetal body weight compared to controls. A single gavage dose of 300 to 400 mg/kg produced a significant increase in the number of malformed fetuses (particularly rib malformations) or resorptions. There was a significant decrease in the average fetal body weight, but not in maternal weight, at all dose levels. The same dose given by gavage seemed to show greater toxic and teratogenic effects than when given intraperitoneally (Willhite, 1983). The results of the teratologic studies are summarized in Table 15.

Table 15. Teratogenic effects of acetonitrile on Syrian golden hamster[a]

Route of administration	Dosage	Maternal effects	Fetal effects
Inhalation	1800 ppm, 60 min	none	none
Inhalation	3800 ppm, 60 min	dyspnoea, tremors, etc., death in one out of six hamsters after 3 h	none
Inhalation	5000 ppm, 60 min	irritation, dyspnoea, tremor, etc., death in one out of six hamsters after 5 h	6 out of 53 abnormal fetuses, exencephaly, encephalocoele, rib fusions
Inhalation	8000 ppm, 60 min	respiratory difficulty and ataxia in 4 out of 12 hamsters; death in 3 out of 4 hamsters after 1.5 h	29 out of 115 abnormal fetuses, exencephaly, encephalocoele, extrathoracie ectopia cordis, severe axial skeletal dysraphic disorders, reduced body weight
Intraperitoneal	100-400 mg/kg	none	encephalocoele, retrocession of maxilla, increase in average fetal body weight
Oral	100-400 mg/kg	none	increase in malformed fetuses (12 out of 65 at 300 mg/kg; 14 out of 76 at 400 mg/kg) and resorptions, decrease in body weight gain

[a] From: Willhite (1983)

When rats were orally administered acetonitrile, no changes in pregnancy rate, resorption of litters or perinatal toxicity in the offspring were found, even at doses of 300 and 500 mg/kg, which are toxic to the majority of females (Smith et al., 1987).

7.4 Mutagenicity

Table 16 summarizes the short-term genotoxicity testing of acetonitrile. Most of these tests have been performed using extremely high concentrations and therefore the interpretation of results is difficult.

7.4.1 Bacterial systems

Within a dose range up to 10 mg/plate, acetonitrile was not mutagenic toward Salmonella strains TA1535, TA1537, TA97, TA98 and TA100 either in the presence or the absence of the metabolic activation systems prepared from SD rats pretreated with Aroclor 1254. The test was performed in two different laboratories and showed good reproducibility (Mortelmans et al., 1986). Schlegelmilch et al. (1988) reported that acetonitrile does not show any mutagenicity activity in the Ames test (Salmonella/microsome assay) performed with strains TA98 and TA100.

7.4.2 Yeast assays

Acetonitrile has been found to induce aneuploidy, but not recombination or point mutations, in a diploid yeast strain D61.M (Zimmermann et al., 1985).

7.4.3 Drosophila melanogaster

FIX and ZESTE genetic test systems employing female *Drosophila melanogaster* were performed by Osgood et al. (1991a,b). Positive responses were obtained in these assays at acetonitrile concentrations of 0.2, 0.5, 2 and 5% (Osgood et al., 1991a). The Drosophila ZESTE system was used to monitor the induction of sex chromosome aneuploidy following inhalation exposure of adult females to acetonitrile. Acetonitrile was a highly effective aneuploidogen, inducing both chromosome loss and gain following short exposure to a concentration of 131 ppm (Osgood et al., 1991b).

Table 16. Short-term genotoxicity tests of acetonitrile

Assay	Concentration	Experimental conditions	Results	Reference
Salmonella TA100	3.8 µmol/plate	+S9	-	Maron et al. (1981)
Salmonella TA100, TA1535	2.4-24.4 µmol/plate	+S9	-	Mortelmans et al. (1986)
Salmonella TA98, TA100	0.27 ~ 1350 mM	-S9 +S9	- -	Schlegelmilch et al. (1988)
Sister chromatid exchange in CHO cells	3.9-121.8 mM 121.8 mM	+S9 -S9	- ±	Galloway et al. (1987)
Induction of aneuploidy in *Saccharomyces cerevisiae* (D61.M)	553-904 mM		+	Zimmermann et al. (1985)
Induction of aneuploidy in *Drosophila*	38-950 mM	FIX and ZESTE	+	Osgood et al. (1991a)
Aneuploidy in *Drosophila*	131 ppm	ZESTE system inhalation exposure (30, 50, 70 min)	+	Osgood et al. (1991b)
Micronucleus test in male NMRI-mice	60% of LD_{50}	24 h after intraperitoneal injection	±	Schlegelmilch et al. (1988)

7.4.4 Mammalian in vivo *assays*

Schlegelmilch et al. (1988) showed that a weak positive effect occurs with acetonitrile in the micronucleus assay 24 h after intraperitoneal injection of a dose equivalent to 60% of the LD_{50} value to four male and four female NMRI mice (13 weeks old).

7.4.5 Chromosome aberrations and sister chromatid exchange

Galloway et al. (1987) tested the ability of 108 chemicals, including acetonitrile, to induce chromosome aberration and sister chromatid exchange (SCE) in Chinese hamster ovary (CHO) cells both with and without a rat liver metabolic activation system. At 5000 mg acetonitrile/litre, there was a slight increase in SCE both with and without S9 activation, but chromosomal abberation tests yielded negative results.

7.5 Carcinogenicity

No data is available on the carcinogenicity of acetonitrile in experimental animals. It is noteworthy, however, that the US National Toxicology Program has long-term oncogenicity studies underway in mice and rats.

7.6 Cytotoxicity testing

Table 17 summarizes the cytotoxicity of acetonitrile. The cytotoxicity to 3T3-L1, BCL-D1 and human hepatoma Hep G 2 was very weak. The IC_{50} values in mouse neuroblastoma cells and in rat glioma cells, were 17.8 and > 20 mM, respectively.

Table 17. Cytotoxicity of acetonitrile

Cell type	Method	Harvest time	Results	Reference
Mouse 3T3-L1	FRAME Kenacid blue	after 72 h	IC_{50} = 562 mM	Clothier & Hulme (1987)
BCL-D1	dye binding	after 72 h	IC_{20} > 24 mM IC_{50} > 24 mM IC_{80} > 24 mM	Knox et al. (1986)
Human hepatoma Hep G2	cellular protection content	after 24 h	IC_{50} = 494 mM	Dierickx (1989)

8. EFFECTS ON HUMANS

8.1 Acute toxicity

8.1.1 Inhalation exposure

Grabois (1955) reported on 16 workers at a chemical plant accidentally poisoned with acetonitrile vapour during the brush painting of the inside walls of a storage tank with corrosion-resistant paint. One died after two days exposure, two were seriously ill and the remaining 13 workers were also affected. Amdur (1959) studied this incident further. The tank was of 22 730 litre capacity, approximately 6 m high, and 2.75 m at its greatest diameter. The paint contained 30-40% acetonitrile and the thinner contained 90-95% acetonitrile. Because of the viscosity of the paint, the tank was heated to 25 °C and thinned on the second day before application. Ventilation of the tank was stopped. Details of the fatal case (Case 1), and the two seriously ill cases (Cases 2 and 3) are as follows:

Case 1. A 23-year-old man was painting within the tank during day 2. He returned home without any symptoms but awoke shortly after midnight with malaise and chest pain. Nausea, vomiting and blood-spitting were followed by convulsions, and he was admitted to hospital in a coma at about 9:15 a.m. Respiration was shallow, irregular and infrequent and he died within one hour of admission. Post-mortem examination revealed cerebral, thyroid, liver, splenic and renal congestion, and a "peach pit" odour of all tissues. The blood and urine cyanide concentrations were 7960 and 2150 mg/litre, respectively. There was a trace of cyanide in the gastric fluid. Spleen, kidney and lung concentrations of cyanide were 3180, 2050 and 1280 mg/kg tissue, respectively. No cyanide was detected in the liver.

Case 2. A 35-year-old man painted for 3 h inside the tank. During the next day he began to feel ill and severe nausea and vomiting followed. He was admitted to hospital with a slow pulse rate (55 per min), severe hypotension and slow shallow respiration. He was treated with oxygen, intravenous fluids and whole blood, ascorbic acid, and sodium thiosulfate. Twelve hours after admission he recovered and he returned to work after ten days. The laboratory data are shown in Table 18.

Table 18. Laboratory data for case 2[a]

Approximate time after exposure	Blood cyanide (μg/litre)	Serum thiocyanate (mg/litre)
14 h	3060	ND
23 h	1930	ND
1 day	ND	160
2 days	2120	150
3 days	2180	ND
4 days	ND	120
5 days	1020	ND
27 days	ND	30
36 days	not detected	ND

[a] From: Arndur (1959); ND = not done

Case 3. A 28-year-old man painted outside and inside the tank. In the night he felt unwell and had diarrhoea, and by morning he felt nauseated and weak and he was sent to hospital at 12:30 in a semiconscious state with a pulse rate of 45 per min and a blood pressure of 100/50 mmHg. Respiration was shallow and intermittent, motor power was severely impaired, and deep tendon reflexes were not elicited. He was treated with oxygen, intravenous fluids and whole blood, ascorbic acid and sodium thiosulfate, and improved rapidly. He was in hospital for 10 days and returned to work after 20 days. The laboratory data are shown in Table 19.

The laboratory data for twelve other workmen are summarized in Table 20, together with those for three severe cases described above.

Dequidt et al. (1974) reported a fatal case of acute acetonitrile poisoning in a 19-year-old male laboratory worker. After handling acetonitrile for 2 days without problems, he poured an unknown amount of acetonitrile and boiling water on the floor to clean it. Four hours after work he complained of epigastric pain and nausea and vomited repeatedly. Next day he became comatose and had convulsions. On admission to hospital large amounts of cyanide,

Table 19. Laboratory data for case 3[a]

Approximate time after exposure	Blood cyanide (μg/litre)	Serum thiocyanate (mg/litre)
24 h	9700	150
2 days	10 880	230
3 days	8800	ND
4 days	ND	200
5 days	2960	ND
8 days	1400	ND
10 days	ND	100
20 days	35	ND
36 days	not detected	ND

[a] From: Amdur (1959); ND = not done

thiocyanate and acetonitrile were found in the blood and urine. Treatment with dicobalt ethylenediaminetetraacetic acid (EDTA) and hydroxycobalamine was ineffective and he died 6 days after the poisoning. Table 21 shows the results of clinical and postmortem examinations of cyanides in blood and tissues.

In a human volunteer study, Pozzani et al. (1959a) studied the acute inhalation toxicity of acetonitrile in three men between the age of 31 and 47. They first inhaled 40 ppm acetonitrile vapour for 4 h in a 7900-litre chamber. The two older subjects had no subjective response during or after the 4-h inhalation period. There was no appreciable increase in urinary thiocyanate and no detectable blood cyanide. The youngest subject experienced a slight tightness in the chest during the evening after inhalation. The following morning he also reported a cooling sensation, which persisted for about 24 h and was similar to that experienced when menthol was inhaled. There was only a slight increase in the urinary thiocyanate levels in this subject. All three subjects detected the odour of acetonitrile for the first 2 or 3 h, after which they experienced some olfactory fatigue.

The two older subjects then inhaled 80 ppm acetonitrile vapour for 4 h one week after the 40 ppm trial, with no symptoms. No

Table 20. Summary of clinical findings of acute acetonitrile intoxication in man[a]

Case No.	Age	Working condition	Symptoms and signs	Outcome	Blood cyanide highest value (μg/litre)	Serum thiocyanate highest value (mg/litre)
1	23	hand-brushing inside of tank for 12 h	chest pain, nausea, emesis, blood spitting, convulsions, shallow, irregular and infrequent respiration	death 14 h after work	7960	-
2	35	hand-brushing inside of tank for 3 h	lightheaded, weakness, nausea, emesis, tachycardia, pallor, shallow respiration, abdominal pain	returned to work after 11 days	3060	160
3	28	hand-brushing outside of tank for 12 h	semiconsciousness, slate gray colour, BP 100/50, shallow and intermittent respiration, impaired motor power, deep tendon reflexes absent, headache	returned to work after 18 days	10 880	230
4	28	hand-brushing inside of tank for 2.5 h	-	returned to work after 10 days	720	145

Table 20 (contd).

Case No.	Age	Working condition	Symptoms and signs	Outcome	Blood cyanide highest value (μg/litre)	Serum thiocyanate highest value (mg/litre)
5	20	not clear	nausea, headache, lassitude, hyper-ventilation	-	580	180
6	18	sand-blasted and mixed paint for 7 h	headache, weakness, tightness of chest and abdomen	recovered after 5 days	330	100
7	42	mixed paint	nausea, tiredness	returned to work within one week	ND	135
8	25	present in the work area for entire day	severe pain of chest and abdomen after 3 days, hepatomegaly	returned to work after two weeks	ND	60
9	24	mixed paint for 3 h	nausea, listlessness	-	ND	100
10-16	-	various	no complaint	-	ND	under 30

[a] From: Amdur (1959); ND = not detected

Table 21. Cyanides in blood, urine and tissues after acetonitrile intoxication[a]

Sample	Days after acetonitrile exposure	Free HCN[b]	Combined HCN[b]	Acetonitrile[b]
Blood	2	1120	3760	-
Blood	3	870	10 380	11760
Urine	4	4600	1050	311 000
Heart	6	trace	2420	6130
Lung	6	340	11 120	2870
Liver	6	123	2670	11 840
Spleen	6	440	3860	9340
Kidney	6	270	2620	13 550
Brain	6	220	2370	-
Pancreas	6	200	1090	trace
Bladder	6	trace	910	trace

[a] From: Dequidt et al. (1974)
[b] µg/litre for blood and urine, µg/kg for tissues

blood cyanide was detected in any of the samples taken after the inhalation period. The urinary thiocyanate value in one subject was higher immediately before inhalation than it was after. The values for the other subject were relatively constant.

The same two subjects inhaled 160 ppm acetonitrile vapour for 4 h, 9 days after the 80-ppm run. One subject reported a slight transitory flushing of the face 2 h after inhalation, and a slight feeling of bronchial tightness about 5 h later, which disappeared overnight. The blood cyanide and urinary thiocyanate levels of both subjects did not change significantly from pre-inhalation values.

8.1.2 *Dermal exposure*

Caravati & Litovitz (1988) reported two cases of paediatric accidental exposure to an acetonitrile-containing cosmetic. The exposure occurred both via the skin and by inhalation. Approximately 30 ml of a nail remover (SuperNail Nail Off) containing 98-100% acetonitrile spilled on a 2-year-old 12-kg previously healthy boy and his bed (the actual amount of contact

to the skin was not specified). No symptoms were noted immediately after the exposure. Eight hours later, the boy was moaning, poorly responsive, and had vomited. On arrival at the emergency department, he was lethargic and pale. Vital signs were as follows: temperature, 36.9 °C; pulse rate, 140/min; respirations 56/min; and blood pressure, 70/30 mmHg. The electrocardiogram revealed a sinus tachycardia. Therapy included oxygen by face mask, and an intraosseous line of 5% dextrose containing 0.2% potassium chloride and 20 mmol of sodium hydrogen carbonate. Although the diagnosis was known, nitrites and thiosulfate were not given due to the patient's prompt response to supportive care. Whole-blood cyanide levels were: 6 mg/litre 12 h after the exposure, 60–70 μmol/litre from 24 to 48 h and 15 μmol/litre after 60 h. The patient was discharged 3 days later in good condition.

8.1.3 Oral exposure

Caravati & Litovitz (1988) reported on a 16-month-old 11.8-kg previously well boy who ingested 15 to 30 ml of SuperNail Nail Off (1–2 g acetonitrile/kg body weight). The child vomited spontaneously about 20 min after the ingestion. Telephone assistance from the poison centre and paediatrician was sought, but the product was mistaken for an acetone-containing nail polish remover and toxicity was expected to be minimal. The child was put to bed. Later the mother noted that he was breathing heavily and noisily, but left him to sleep through the night. He was found dead in his crib the next morning, about 12 h after the ingestion. Postmortem examination showed moderately severe pulmonary oedema, a blood cyanide level of 119 (3.1 mg/litre), and brain cyanide level of 0.2 mg/kg.

Jaeger et al. (1977) reported a case of acute acetonitrile intoxication in a 26-year-old man who ingested 40 g of acetonitrile in a suicide attempt. After a 3-h latent period, he suffered from vomiting, convulsions, coma, acute respiratory insufficiency, severe metabolic acidosis, and two cardiac arrests. In addition to supportive treatment (oxygen, mechanical ventilation, correction of shock and acidosis), dicobalt EDTA, sodium nitrite, sodium thiosulfate and hydroxocobalamin were also administered. His clinical course was complicated but he fully recovered 3 months later.

Turchen et al. (1991) reported the case of a 39-year-old woman, who was found vomiting and confused 7 h after ingesting

59 ml of nail polish remover containing 99% acetonitrile (4 g/kg). About 12 h after ingestion, she developed severe metabolic acidosis, seizures and shallow respiration. Eight hours after ingestion she had a whole blood cyanide level of 3130 μg/litre. At 65 h the serum cyanide level was 10 mg/litre and thiocyanate was 120 mg/litre, whereas at 77 h they were 12 mg/litre and 30 mg/litre, respectively. She responded to the treatment with sodium nitrite and sodium thiosulfate. Although she had several relapses, each time she responded to sodium thiosulfate administration. On the fifth hospital day the cyanide level was 360 μg/litre and thiocyanate level 30 mg/litre and the patient was discharged on day six.

Geller et al. (1991) reported a case of acute acetonitrile poisoning of a 3-year-old 17.2-kg child who presented to the emergency department without any noticeable symptoms approximately 30 min after ingesting an estimated 15-30 ml of a nail tip and glue remover containing acetonitrile. The amount of ingested acetonitrile was estimated to be 0.7 to 1.4 g/kg. Gastric lavage was performed with 1 litre of saline containing 20 g of activated charcoal. Three hours and 45 min after ingestion, the cyanide blood level was 1.24 mg/litre and thiocyanate 11 mg/litre. Eleven hours after ingestion the child was alert, but 2 h later the patient suddenly vomited, was confused and developed seizures. A dose of 35 ml of a 25% solution of sodium thiosulfate was intravenously administered over 30 min. The patient recovered quickly and was discharged 42 h later.

Kurt et al. (1991) reported a case of a 15.8-kg 2-year-old girl who ingested 5-10 ml (0.25-0.5 mg/kg) of a nail glue containing 84% acetonitrile. Taken to the hospital, she was asymptomatic and discharged. However, she later became restless and started vomiting. Toxic clonic seizures also appeared about 14 h after ingestion. She was admitted to the hospital comatose with hyperpnoea and tachycardia. Gas analysis showed marked hypoxia and acidosis. She was treated with oxygen and amyl nitrite by inhalation. Activated charcoal was also administered. She made a rapid recovery and was discharged after 2 days.

Michaelis et al. (1991) reported a case of suicidal oral acetonitrile ingestion in a previously healthy 30-year-old man. He ingested about 5 ml (64 mg/kg) of acetonitrile (98%) and, 30 min later, about 1 ml of ammonia and vomited once. Five hours later he was brought to the hospital because of increasing malaise. On the way to the hospital he received 250 mg of *p*-dimethyl

aminophenol and 1 g of sodium thiosulfate. The patient exhibited livid skin colour and excitation. Gastric lavage with charcoal was performed 5.5 h after ingestion, and treatment with oxygen and sodium thiosulfate (3/g intravenous) was given over 30 min. He recovered quickly and was transferred to a psychiatric unit 30 h after ingestion. Peak serum acetonitrile and blood cyanide levels were 99.2 and 15.0 mg/litre. Half-lives were calculated for acetonitrile and cyanide and found to be 32 and 15 h, respectively.

Jones et al. (1992) reported two fatal cases of a married couple who ingested acetonitrile by mistake. They were found dead with traces of vomit. Acetonitrile levels were 0.8 g/litre in blood, 1.0 g/litre in urine and 1.3 g/litre in stomach contents. Blood inorganic cyanide levels were 4.5 mg/litre (male) and 2.4 mg/litre (female).

Table 22 summarizes the reports on human acetonitrile poisoning.

8.2 Chronic toxicity

No data are available.

8.3 Mutagenicity and carcinogenicity

No data are available concerning the mutagenicity and carcinogenicity of acetonitrile in humans.

8.4 Occupational exposure to cyanide

El Ghawabi et al. (1975) studied the effect of chronic cyanide exposure in the electroplating sections of three factories employing 9, 12 and 15 male workers and compared them with a control group. The concentrations of cyanides to which the workers were exposed at the three factories were 10.87, 6.85 and 8.25 ppm, respectively. The duration of exposure and the number of workers were: 5 years, 14; more than 5 years, 14; more than 10 years, 7; and more than 15 years, 1. The symptoms listed in order of frequency were headache, weakness, changes in taste and smell, irritation of the throat, vomiting, effort dyspnoea, lacrymation, abdominal colic, and praecordial pain. Disturbances of accommodation, salivation, and nervous instability were found in 8% of the exposed workers. Two workers suffering from psychotic episodes worked in the part of the factory where the concentration of cyanides was the highest. None of the 36 workers

Table 22. Summary of reports on human acetonitrile poisoning

Route of exposure	Number of cases	Estimated doses	Time of onset of symptoms after exposure	Major symptom	Outcome	Toxicological findings	References
Inhalation	16	unknown	several hours	nausea, vomiting, respiratory failure, hypotension	one dead, others recovered	cyanide and thiocyanate in blood and urine	Admur (1959)
Inhalation	1	unknown	4 h	epigastric pain, nausea, vomiting, convulsions	dead	cyanide, thiocyanate and acetonitrile in blood and urine	Dequidt et. al. (1974)
Dermal/ inhalation	1	approximately 30 ml	8 h	moaning, poor response, vomiting, lethargic	survived	cyanide in blood	Carvati & Litovitz (1988)
Oral	1	15-30 ml	several hours	heavy and noisy breathing	dead 12 h later	cyanide in blood and urine	Carvati & Litovitz (1988)
Oral	1	40 g	3 h	vomiting, convulsion, respiratory failure, coma	recovery after 3 months	not tested	Jaeger et al. (1977)

Table 22 (contd).

Route of exposure	Number of cases	Estimated doses	Time of onset of symptoms after exposure	Major symptom	Outcome	Toxicological findings	References
Oral	1	59 ml	12 h	seizures, shallow respiration	recovery after 5 days	cyanide in blood	Turchen et al. (1991)
Oral	1	15 to 30 ml	12 h	alert, frightened, vomit, confusion	recovery after 24 h	cyanide and thiocyanate in blood	Gelier et al. (1991)
Oral	1	5 to 10 ml	10–14 h	moaning, restless, vomiting, seizures	recovery after 2 days	-	Kurt et al. (1991)
Oral	1	5 ml and 1 ml ammonia	5 h	malaise	recovery after 30 h	acetonitrile and cyanide in blood	Michaelis et al. (1991)
Oral	2	unknown	unknown	vomiting	dead	acetonitrile and cyanide in blood and urine	Jones et al. (1992)

showed any clinical signs of hypo- or hyperthyroidism, but 20 (56%) had mild or moderate thyroid enlargement. However, there was no correlation between duration of exposure and the incidence of enlargement, or size of the thyroid. ^{131}I thyroid uptakes at 4 and 24 h were significantly higher than those in the controls ($P < 0.001$), while ^{131}PBI (protein bound iodine) was unchanged. There were increased haemoglobin and lymphocyte counts in all exposed workers, and punctate basophilia was reported in 28 workers. Cyanmethaemoglobin was found only in the blood of the exposed workers, all of whom were non-smokers. The concentration of thiocyanate in urine increased towards the middle of the working week and then became almost stationary during the last three days. The regression line between mean values of urinary thiocyanate in the second half of each working week over two successive months and the mean values of the concentration of cyanides in air was linear, being represented by the equation $M = 0.65C$ (M = thiocyanate in total amount of urine in 24 h per mg, and C = concentration of cyanide in air in ppm).

Blanc et al. (1985) studied acute and residual toxic reactions to cyanide in 36 former male workers, aged from 19 to 62 (with mean age of 33.5 ± 11.4 (SD) years), in a silver-reclaiming facility with exposure to high levels of cyanide. The median time since last employment at this facility was 10.5 months and the mean duration of employment was 11 ± 10.4 (SD) months (with a medium of 8.5 months). Mild abnormalities of vitamin B_{12} ($P < 0.001$), folate ($P < 0.001$) and T3 resin uptake ($P < 0.01$) were detected.

8.5 Chronic poisoning by cyanides

8.5.1 *Ingestion*

Epidemiological studies suggested a correlation between chronic cyanide ingestion from cassava and certain neurological disorders (Wilson, 1983; WHO, 1992).

9. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

9.1 Microorganisms

Collins & Knowles (1983) reported that the bacterium *Nocardia rhodochrous* was able to grow at an acetonitrile concentration of 1.03 g/litre, apparently using acetonitrile as both carbon and nitrogen sources.

Bringmann & Kuhn (1977a) calculated toxicity thresholds based on the first detectable inhibition of cell multiplication. For the bacterium *Pseudomonas putida* the threshold was 680 mg/litre acetonitrile and for the green alga *Scenedesmus quadricauda* it was 7300 mg/litre. Bringmann & Kuhn (1978) calculated a toxicity threshold for the cyanobacterium (blue-green alga) *Microcystis aeruginosa* of 520 mg/litre. For the protozoan *Entosiphon sulcatum* the threshold was 1810 mg/litre (Bringmann & Kuhn, 1980).

9.2 Aquatic organisms

The acute toxicity of acetonitrile to aquatic organisms is summarized in Table 23. Due to the volatility of acetonitrile care must be taken when interpreting the test results, especially those based on nominal concentrations.

Acute toxicity data for various fish and other freshwater species have been determined by a static bioassay to give an LC_{50}. Values range from 730 mg/litre for *Cyprinus carpio* after a 48-h exposure to 6500 mg/litre for *Daphnia pulex* after a 3-h exposure (Nishiuchi, 1981). According to Bringmann & Kuhn (1977b), the 24-h LC_{50} for *Daphnia magna* is more than 10 g/litre.

Table 23. Toxicity of acetonitrile to aquatic organisms

Organism	Size/age	Water conditions[a]	Temperature (°C)	Hardness (mg/litre)[b]	pH	Duration (h)	LC_{50} (mg/litre)[c]	References
Invertebrates								
Snail (*Helisoma trivolvis*)	juvenile	stat	19-21	130	6.5-8.5	96	> 100 n	Ewell et al. (1986)
Flatworm (*Dugesia tigrina*)	juvenile	stat	19-21	130	6.5-8.5	96	> 100 n	Ewell et al. (1986)
Segmented worm (*Lumbriculus variegatus*)	juvenile	stat	19-21	130	6.5-8.5	96	> 100 n	Ewell et al. (1986)
Water flea (*Daphnia pulex*)	juvenile juvenile	stat stat	19-21	130	6.5-8.5	3 96	6500 > 100 n	Ewell et al. (1986)
Water flea (*Daphnia magna*)	24 h	stat	20-22		7.6-7.7	24	> 10 000 n	Bringmann & Kuhn (1977b)
Sideswimmer (scud) (*Gammarus fasciatus*)	juvenile	stat	19-21	130	6.5-8.5	96	>100 n	Ewell et al. (1986)

Table 23 (contd).

Organism	Size/age	Water conditions[a]	Temperature (°C)	Hardness (mg/litre)[b]	pH	Duration (h)	LC_{50} (mg/litre)[c]	References
Pillbug (*Asellus intermedius*)	juvenile	stat	19-21	130	6.5-8.5	96	> 100 n	Ewell et al. (1986)
Fish								
Fathead minnow (*Pimephales promelas*)	1.5 g	stat	25	20	7.4	24	1050 n	Henderson et al. (1961)
	1.5 g	stat	25	20	7.4	48	1000 n	Henderson et al. (1961)
	1.5 g	stat	25	20	7.4	96	1000 n	Henderson et al. (1961)
	1.5 g	stat	25	380	8.2	24	1150 n	Henderson et al. (1961)
	1.5 g	stat	25	380	8.2	48	1050 n	Henderson et al. (1961)
	1.5 g	stat	25	380	8.2	96	1000 n	Henderson et al. (1961)
	juvenile	stat	19-21	130	6.5-8.5	96	> 100 n	Ewell et al. (1986)
Bluegill (*Lepomis macrohirus*)	2.0 g	stat	25	20	7.4	24 & 96	1850 n	Henderson et al. (1961)
Ctenopharyngodon (*C. idellus*)	5-7 g	stat	10-11		7.4	24	1950 n	Chen (1981)
						48	880 n	Chen (1981)

Table 23 (contd).

Organism	Size/age	Water conditions[a]	Temperature (°C)	Hardness (mg/litre)[b]	pH	Duration (h)	LC_{50} (mg/litre)[c]	References
Guppy (*Poecilia reticulata*)	0.1 g	stat	25	20	7.4	24 & 96	1650 n	Henderson et al. (1961)
Medaka (*Oryzias latipes*)	0.2 g	stat	25			24 & 48	> 1000 n	Tonogai et al. (1982)
Carp (*Cyprinus carpio*)	juvenile					48	730	Nishiuchi (1981)
Golden orfe (*Leuciscus idus melanotus*)						48	5850-7050	Juhnke & Ludemann (1978)

[a] stat = static conditions (water unchanged for the duration of the test)
[b] Hardness measured as mg $CaCO_3$/litre
[c] n = nominal concentration

10. EVALUATION OF HUMAN HEALTH RISKS AND EFFECTS ON THE ENVIRONMENT

10.1 Evaluation of human health risks

Acetonitrile is a colourless liquid with an ether-like odour. It is found as a natural product and is manufactured for a variety of uses. It is an excellent solvent for many inorganic and organic compounds, including polymers. It is used for various purposes including the separation of butadiene from other C_4 hydrocarbon, a solvent for spinning synthetic fibres, for casting and moulding plastics, for HPLC analysis, as a starting material for organic synthesis, and in products for removing artificial finger nails.

Acetonitrile has not been detected in water but has been in bottom sediment in the environment in Japan. It has also been detected in air at low concentrations in some urban and rural environments in Germany. It has not been detected in food. Acetonitrile is found in the stratosphere. Along with hydrogen cyanide, acrylonitrile and other toxic products, acetonitrile is produced from the thermal decomposition of polyurethane foams.

Acetonitrile is readily absorbed by all routes and rapidly distributed throughout the body. It is converted enzymatically to cyanide, which is in turn conjugated with thiosulfate, forming thiocyanate, and eliminated via the urine. Some acetonitrile is eliminated unchanged in the expired air and urine. Acetonitrile does not accumulate in the body.

Acute acetonitrile toxicity is due mainly to cyanide formation and the signs and symptoms are those of acute cyanide poisoning. The toxic effects of acetonitrile usually appear after a latent period (lasting several hours) following exposure.

In humans, ingestion of 1 to 2 g acetonitrile/kg causes death. Animal experiments indicate that inhalation of acetonitrile at concentrations of 8400 to 16 800 mg/m^3 (5000 to 10 000 ppm) for one hour is fatal. It is irritant to the eyes and respiratory tract.

There are no available data on the chronic toxicity of acetonitrile in experimental animals or humans.

High doses of acetonitrile are teratogenic and embryotoxic in rats and hamsters; maternal toxicity also occurs at these dose

levels. The mechanism for these effects is related to the production of cyanide.

Tables in sections 6 and 7 indicate the reasons for the differences in toxicity between acetonitrile, cyanide and other nitriles. These are based on the slow toxicokinetics of acetonitrile due to the slower rate of formation of free cyanide from acetonitrile compared with other nitriles. These differences account for the different time course of blood cyanide and thiocyanate levels and of thiocyanate excretion, as well as for the different LD_{50} values. It can also be predicted that any differences in toxicity across species are probably due to toxicokinetics. Administration of cyanide antidotes such as sodium nitrite and sodium thiosulfate are effective. Care needs to be taken in the use of sodium nitrite because of its toxicity.

Occupational exposure in the production of acetonitrile is low because of the enclosed processes. Poisoning has been associated with use and accidental exposure. A time-weighted average (TWA) occupational exposure limit of 67 mg/m^3 (40 ppm) is used in many countries.

10.2 Evaluation of effects on the environment

Acetonitrile has low toxicity to microorganisms and freshwater invertebrates and fish.

The most sensitive species is the common carp (*Cyprinus carpio*) with a 48-h LC_{50} of 730 mg/litre. Application of an uncertainly factor of 100, to take into account static tests and lack of analytical confirmation, yields a value of 7.3 mg/litre.

Acetonitrile is seldom present in the environment at measurable levels and has not been detected in water. The highest measured level in sediment was 0.54 mg/kg. It is, therefore, highly unlikely that acetonitrile poses any threat to organisms in the environment except locally after spills.

11. RECOMMENDATIONS FOR THE PROTECTION OF HUMAN HEALTH

a) Acetonitrile and mixtures containing it should be clearly labelled with a warning of the toxicity of acetonitrile.

b) Clinicians should be aware of the delayed onset of signs and symptoms following exposure to acetonitrile.

12. FURTHER RESEARCH

a) The measurement of acetonitrile levels in expired air and urine should be investigated as a method for the biological monitoring of occupationally exposed populations.

b) Comparative studies on the kinetics of cyanide formation from acetonitrile, as well as of conjugation to thiocyanate and its elimination, should be conducted.

c) The *in vitro* sensitivity of cytochrome *c* oxidase to cyanide in different species, including humans, should be investigated.

13. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

No previous evaluations by international bodies are available.

REFERENCES

Ahmed AE & Farooqui MYH (1982) Comparative toxicities of aliphatic nitriles. Toxicol Lett, **12**: 157-164.

Ahmed AE, Loh JP, Ghanayem B, & Hussein G (1992) Studies on the mechanism of acetonitrile toxicity: I. Whole body autoradiographic distribution and macromolecular interaction of 2^{14}C-acetonitrile in mice. Pharmacol Toxicol, **70**: 322-330.

Aitio A & Bend JR (1979) Inhibition of rat liver glutathione S-transferase activity by aprotic solvents. FEBS Lett, **101**(1): 187-190.

Aldridge WN (1944) A new method for the estimation of microquantities of cyanide and thiocyanate. Analyst, **69**: 262-265.

Amdur ML (1959) Accidental group exposure to acetonitrile - A clinical study. J Occup Med, **1**: 627-633.

Anbar M & Neta P (1967) A compilation of specific biomolecular rate constants for the reactions of hydrated electrons. Hydrogen atoms and hydroxyl radicals with inorganic and organic compounds in aqueous solution. Int J Appl Radiat Isot, **18**: 493-523.

Arijs E, Nevejans D, & Ingels J (1983) Positive ion composition measurements and acetonitrile in the upper stratosphere. Nature (Lond), **303**: 314-316.

Balls M & Horner SA (1985) The FRAME interlaboratory programme on *in vitro* cytotoxicology. Food Chem Toxicol, **23**: 209-213.

Battelle, Pacific Northwest Laboratories (1986a) Subchronic study report on acetonitrile inhalation in mice. Richland, Washington, Battelle, Pacific Northwest Laboratories (Prepared for the National Toxicology Program, Contract No. N01-ES-55073, 23111-10823).

Battelle, Pacific Northwest Laboratories (1986b) Subchronic study report on acetonitrile inhalation in rats. Richland, Washington, Battelle, Pacific Northwest Laboratories (Prepared for the National Toxicology Program, Contract No. N01-ES-55073, 23111-10823).

Becker KH & Ionescu A (1982) Acetonitrile in the lower troposphere. Geophys Res Lett, **9**(12): 1349-1351.

Berg S, Jacobsson S, & Nilsson B (1980) Evaluation of an evacuated glass sampler for the analysis of volatile organic compounds in ambient air. J Chromatogr Sci, **18**: 171-179.

Berteau PE, Levinskas GJ, & Rodwell DE (1982) Teratogenic evaluation of aliphatic nitriles in rats. Toxicologist, **2**: 118.

Blanc P, Hogan M, Mallin K, Hryhorczuk D, Hessel S, & Bernard B (1985) Cyanide intoxication among silver-reclaiming workers. J Am Med Assoc, **253**: 367-371.

Blanke RV (1976) Analysis of drugs and toxic substances. In: Tietz NW ed. Fundamentals of clinical chemistry. Philadelphia, Pennsylvania, W.B. Saunders Co., pp 1117-1118.

Borman S (1990) Acetonitrile shortage hurts research laboratories. Chem Eng News, **26 March**: 15.

Bringmann G & Kuhn R (1977a) [Threshold values for the harmful effect of water pollutants on bacteria (*Pseudomonas putida*) and green algae (*Scenedesmus quadricauda*) in the cell reproduction inhibition test.] Z Wasser Abwasser Forsch, **10**: 87-98 (in German).

Bringmann G & Kuhn R (1977b) [Results of damaging effect of water pollutants on Daphnia magna.] Z Wasser Abwasser Forsch, **10**: 161-166 (in German).

Bringmann G & Kuhn R (1978) [Threshold values for the harmful effect of water pollutants on blue algae (*Microcystis aeruginosa*) and green algae (*Scenedesmus quadricauda*) in the cell reproduction inhibition test.] Vom Wasser, **50**: 45-60 (in German).

Bringmann G & Kuhn R (1980) [Comparison of the toxicity thresholds of water pollutants to bacteria, algae, and protozoa in the cell multiplication inhibition test.] Water Res, **14**: 231-241 (in German).

Brown SL, Chan FY, Jones JL, Liu DH, & McCaleb KE (1975) Research program on hazard priority ranking of manufactured chemicals (chemicals 41-60). Menlo Park, California, SRI International, p 85 (NTIS PB-263163).

Bruce RB, Howard JW, & Hanzal RF (1955) Determination of cyanide, thiocyanate, and alpha-hydroxynitriles in plasma or serum. Anal Chem, **27**: 1346-1347.

Budavari S ed. (1989) The Merck index: an encyclopedia of chemicals, drugs, and biologicals, 11th ed. Rahway, New Jersey, Merck & Co., Inc., p 63.

Campbell DN & Moore RH (1979) The quantitative determination of acrylonitrile, acrolein, acetonitrile and acetone in workplace air. Am Ind Hyg Assoc J, **40**: 904-909.

Caravati EM & Litovitz T (1988) Pediatric cyanide intoxication and death from an acetonitrile-containing cosmetic. J Am Med Assoc, **260**: 3470-3473.

Carpenter CP & Smyth HF (1946) Chemical burns of the rabbit cornea. Am J Ophthalmol, **29**: 1363.

Chapatwala KD, Barn GRV, & Nawaz MS (1992) Degradation of acetonitrile and biphenyl compounds by a mixed microbial culture. Environ Toxicol Chem, **11**: 1145-1151.

Chen BH, Hong CJ, Zhu HG, Hu RF, & Xu GA (1981) [The establishment of maximum allowable concentration (MAC) of acetonitrile in surface water.] In: [Research on the MACs of environmental pollutants in surface waters.] Beijing, People's Medical Publishing House, pp 20-25 (in Chinese).

Chesley IC (1941) The determination of thiocyanate in biological fluids. J Biol Chem, **140**: 135-140.

Clayton GD & Clayton FE ed. (1982) Patty's industrial hygiene and toxicology: Volume 2C - Toxicology with cumulative index for Volume 2, 3rd ed. New York, Chichester, Brisbane, Toronto, John Wiley & Sons.

Clothier RH & Hulme LM (1987) Comparison of the *in vitro* cytotoxicities and acute *in vivo* toxicities of 59 chemicals. Mol Toxicol, 1: 571-577.

Cobb GP, Braman RS, & Hua KM (1986) Carbon hollow tubes as collectors in thermal desorption/gas chromatographic analysis of atmospheric organic compounds. Anal Chem, **58**: 2213-2217.

Collins PA & Knowles CJ (1983) The utilization of nitriles and amides by *Nocardia rhodochrous*. J Gen Microbiol, **129**: 711-718.

Contessa AR & Santi R (1973) Liberation of cyanide from succinonitrile. Biochem Pharmacol, **22**: 827-832.

Conway EJ (1950) Microdiffusion analysis and volumetric error. New York, Van Nostrand Reinhold Co.

Cooper SW, Jayanty RDM, Knoll JE, & Midgett MR (1986) Determination of selected nitrogen-containing hazardous pollutants in complex matrices by gas chromatography with a nitrogenphosphorus detector. J Chromatogr Sci, **24**: 204-209.

Dahl AR & Waruszewski BA (1989) Metabolism of organonitriles to cyanide by rat nasal tissue enzymes. Xenobiotica, **19**: 1201-1205.

Dalhamn T, Edfors ML, & Rylander R (1968a) Mouth absorption of various compounds in cigarette smoke. Arch Environ Health, **16**: 831-835.

Dalhamn T, Edfors ML, & Rylander R (1968b) Retention of cigarette smoke components in human lungs. Arch Environ Health, **17**: 746-748.

Dequidt J & Haguenoer JM (1972) Etude toxicologique expérimentale de l'acétonitrile chez le rat. Intoxication aiguë par voie intrapéritonéale. Bull Soc Pharm Lille, **4**: 149-154.

Dequidt J, Furon D, Wattel F, Haguenoer JM, Scherpereel P, Gosselein B, & Ginestet A (1974) Les intoxications par l'acétonitrile à propos d'un cas mortel. Eur J Toxicol, **7**: 91-97.

Dierickx PJ (1989) Cytotoxicity testing of 114 compounds by the determination of the protein content in HEP G2 cell cultures. Toxicol *in vitro*, **3**: 189-193.

DiGeronimo MJ & Antoine AD (1976) Metabolism of acetonitrile and propionitrile by *Nocardia rhodochrous* LL100-21. Appl Environ Microbiol, **31**(6): 900-906.

Dimitriades B & Joshi SB (1977) Application of reactivity criteria in oxidant-related emission control in the U.S.A. In: Dimitriades B ed. Proceedings of the International Conference on Photochemical Oxidant Pollution and Its Control. Research Triangle Park, North Carolina, US Environmental Protection Agency, pp 705-711 (EPA-600/3-77-001B).

Dorfman LM & Adams GE (1973) Reactivity of the hydroxyl radical in aqueous solution. Washington, DC, National Bureau of Standards, p 51 (NTIS/ COM-73-5-623).

Drummond GS & Kappas A (1982) The cytochrome P-450- depleted animal: An experimental model for *in vivo* studies in chemical biology. Proc Natl Acad Sci (USA), **79**: 2384-2388.

El-Ghawabi SH, Gaafar MA, El-Saharti AA, Ahmed SH, Malash KK, & Fares R (1975) Chronic cyanide exposure: a clinical, radioisotop, and laboratory study. Br J Ind Med, **32**: 215-219.

Epstein J (1947) Estimation of microquantities of cyanide. Anal Chem, **19**: 272-274.

Ewell WS, Gorsuch JW, Kringle RO, Robillard KA, & Spiegel RC (1986) Simultaneous evaluation of the acute effects of chemicals on seven aquatic species. Environ Toxicol Chem, **5**: 831-840.

Feierman DA & Cederbaum AI (1989) Role of cytochrome P-450 and catalase in the oxidation of acetonitrile to cyanide. Chem Res Toxicol, **2**: 359-366.

Feldstein M & Klendshoj NC (1954) The determination of cyanide in biologic fluids by microdiffusion analysis. J Lab Clin Med, **44**: 166-170.

Finney DJ (1952) In: Probit analysis. Cambridge, Cambridge University Press, p 131.

Firmin JI & Gray DO (1976) The biochemical pathway for the breakdown of methyl cyanide (acetonitrile) in bacteria. Biochem J, **158**(2): 223-229.

Freeman JJ & Hayes EP (1985a) Acetone potentiation of acute acetonitrile toxicity in rats. J Toxicol Environ Health, **15**: 609-622.

Freeman JJ & Hayes EP (1985b) Effects of acetone microsomal metabolism of acetonitrile to cyanide. Toxicologist, **5**: 246.

Freeman JJ & Hayes EP (1987) The metabolism of acetonitrile to cyanide by isolated rat hepatocytes. Fundam Appl Toxicol, **8**: 263-271.

Freeman JJ & Hayes EP (1988) Microsomal metabolism of acetonitrile to cyanide. Effects of acetone on and other compounds. Biochem Pharmacol, **37**: 1153-1159.

Galloway SM, Armstrong MJ, Reuben C, Colman S, Brown B, Cannon C, Bloom AD, Nakamura F, Ahmed M, Duk S, Rimpo J, Margolin BH, Resnick MA, Anderson B, & Zeiger E (1987) Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: Evaluations of 108 chemicals. Environ Mol Mutagen, **10**(Suppl): 1-175.

Geller RJ, Ekins BR, & Iknoian RC (1991) Cyanide toxicity from acetonitrile-containing false nail remover. Am J Emerg Med, **9**: 268-270.

Goud HD, Parekh LJ, & Ramakrishnan CV (1985) Bacterial profile of petrochemical industry effluents. Environ Pollut, **A39**: 27-37.

Grabois B (1955) Fatal exposure to methyl cyanide. NY State Dep Labor Div Ind Hyg Mon Rev, **34**: 1-8.

Graedel TE (1978) Chemical compounds in the atmosphere. New York, London, San Francisco, Academic Press.

Grayson M ed. (1985) [Kirk-Othmer concise encyclopedia of chemical technology.] Tokyo, Maruzen Co., pp 997-998 (Japanese translation).

Guesten H, Filby WG, & Schoof S (1981) Prediction of hydroxyl radical reaction rates with organic compounds in the gas phase. Atmos Environ, **15**: 1763-1765.

Haguenoer JM, Dequidt J, & Jacquemont MC (1975a) Intoxications experimentales par l'acétonitrile. 1ère note: Intoxications aiguës par voie intraperitoneale. Eur J Toxicol, **8**: 94-101.

Haguenoer JM, Dequidt J, & Jacquemont MC (1975b) Intoxications expérimentales par l'acétonitrile. 2ème note: Intoxications aiguës par voie pulmonaire. Eur J Toxicol, **8**: 102-106.

Harper DB (1977) Fungal degradation of aromatic nitriles. Enzymology of C-N cleavage by *Fusarium solani*. Biochem J, **167**(3): 685-692.

Harris GW, Kleindienst TE, & Pitts JN (1981) Rate constant for the reaction of OH radicals with CH_3CN, C_2H_5CN and CH_2=CH-CN in the temperature range 298-424K. Chem Phys Lett, **80**: 479-483.

Hawley GG ed. (1971) The condensed chemical dictionary, 8th ed. New York, Van Nostrand Reinhold Co.

Hazleton Laboratories America, Inc. (1990a) 90-Day inhalation subchronic toxicity study of acetonitrile in B6C3F$_1$ mice. Vienna, Virginia, Hazleton Laboratories America, Inc. (Prepared for the National Toxicology Program).

Hazleton Laboratories America, Inc. (1990b) 90-Day inhalation subchronic toxicity study of acetonitrile in Fischer 344 rats. Vienna, Virginia, Hazleton Laboratories America, Inc. (Prepared for the National Toxicology Program).

Henderson C, Pickering QH, & Lemke AE (1961) The effect of some organic cyanides (nitriles) on fish. Proceedings of the 15th Industrial Waste Conference. Eng Bull Purdue Univ. **XLV**(2): 120-130.

Hine J & Mookerjee PK (1975) The intrinsic hydrophilic character of organic compounds. Correlations in terms of structural contributions. J Org Chem, **40**: 292-298.

Huertas ML & Marenco A (1986) Positive ion clustering with acetonitrile. Atmos Environ, **20**(8): 1647-1649.

ILO (1991) Occupational exposure limits for airborne toxic substances, 3rd ed. Geneva, International Labour Office, pp 4-5.

Inoue T, Takeuchi Y, Hisanaga N, Ono Y, Iwata M, Ogata M, Saito K, Sakurai H, Hara I, Matsushita T, & Ikeda M (1983) A nationwide survey on organic solvent components in various solvent products: Part 1. Homogeneous products such as thinners, degreasers and reagents. Ind Health, **21**: 175-184.

Jaeger A, Tempe JD, Porte A, Stoeckel L, & Mantz JM (1977) Acute voluntary intoxication by acetonitrile (Abstracted). Acta Pharmacol Toxicol, **41**(Suppl II): 340.

Johannsen FR, Levinskas GJ, Berteau PE, & Rodwell DE (1986) Evaluation of the teratogenic potential of three aliphatic nitriles in the rat. Fundam Appl Toxicol, **7**: 33-40.

Jones AW, Löfgren A, & Eklund A (1992) Two fatalities from ingestion of acetonitrile: Limited specificity of analysis by headspace gas chromatography. J Anal Toxicol, **16**: 104-106.

Joshipura MH, Desai NC, Mehta YP, & Rana JB (1983) Determination of acetonitrile in mixtures by GC. J Chromatogr Sci., **21**: 85-86.

Juhnke I & Ludemann D (1978) [Results of the testing of 200 chemical compounds for acute toxicity for fish by the orfe test.] Z Wasser Abwasser Forsch, **11**: 161–164 (in German).

Kadaba PK, Bhagat PK, & Goldberger GN (1978) Application of microwave spectroscopy for simultaneous detection of toxic constituents in tobacco smoke. Bull Environ Contam Toxicol, **19**: 104–112.

Kagiya T, Takemoto K, & Uyama Y (1975) Promotional oxidation degradation method for air pollutant using artificial photochemical process. In: Proceedings of the 32nd Japan Chemical Society Springterm Annual Meeting. Tokyo, Japan Chemical Society (Paper 1036).

Kalyanaranam UP, Kalyanaraman K, & Cullinan SA (1983) Neuromyopathy of cyanide intoxication due to 'laetrile' (amygdalin). Cancer, **51**: 2126–2133.

Kanai R & Hashimoto K (1965) Determination of acrylonitrile, cyanide and thiocyanateinbiological materials. Ind Health, **3**: 47–52.

Kashihira N (1983) [Study on adsorption behavior of nitrogen compounds on porous polymer beads for air sampling.] Taiki Osen Gakkaishi, **18**: 425–431 (in Japanese).

Kashihira N, Makino K, Kirita K, & Watanabe Y (1984) [Determination of acetonitrile and acrylonitrile in air by gas chromatography with adsorptive enrichment and chemiluminescent nitrogen detector.] Bunseki Kagaku, **33**: 402–406 (in Japanese).

Kawalek JC & Andrews AW (1980) The effect of solvents on drug metabolism *in vitro*. Drug Metab Dispos, **8**: 380–384.

Kelly M, Postgate JR, & Richards RL (1967) Reduction of cyanide and isocyanide by nitrogenase of azotobacter chroococcum. Biochem J, **102**: 10–30.

Kimura ET, Ebert DM, & Dodge PW (1971) Acute toxicity and limits of solvent residue for sixteen organic solvents. Toxicol Appl Pharmacol, **19**: 699–704.

Knox P, Uphill OF, Fry JR, Benford DJ, & Balls M (1986) The FRAME multicentre project on *in vitro* cytotoxicology. Food Chem Toxicol, **24**: 457–463.

Koop DR & Casazza JP (1985) Identification of ethanol-inducible P-450 isozyme 3a as the acetone and acetol monooxygenase of rabbit microsomes. J Biol Chem, **260**: 13607–13612.

Kurt TL, Day LC, Reed WG, & Gandy W (1991) Cyanide poisoning from glue-on nail remover. Am J Emerg Med, **9**: 271–272.

Kuwahara M, Yanase H, Kikuchi Y, & Okuzumi K (1980) [Metabolism of succinonitrile in *Aeromonas sp.*] Hakko Kogaku, **58**: 441–448 (in Japanese).

Leo A, Hansch C, & Elkins D (1971) Partition coefficients and their uses. Chem Rev, **71**: 525–616.

Lowenheim F & Moran MK (1975) In: Faith, Keyes, and Clark's industrial chemicals, 4th ed. New York, Chichester, Brisbane, Toronto, John Wiley and Sons.

Ludzack FJ, Schaffer RB, Bloomhuff RN, & Ettinger MB (1958) Biochemical oxidation of some commercially important organic cyanides: I. River oxidation. Proceedings of the 13th Industrial Waste Conference. West Lafayette, Indiana, Purdue University, pp 297-312.

Ludzack FJ, Schaffer RB, Bloomhuff RN, & Ettinger MB (1959) Biochemical oxidation of some commercially important organic cyanides. Sew Ind Wastes, **31**: 33-44.

Ludzack FJ, Schaffer RB, & Bloomhuff RN (1961) Experimental treatment of organic cyanides by conventional processes. J Water Pollut Control Fed, **33**: 492-505.

Lymann WJ, Reehl WF, & Rosenblatt DH (1982) Handbook of chemical property estimation methods. New York, McGraw-Hill Co., pp 7/4, 15/15-15/17.

McKee HC, Rhoades JW, Campbell J, & Gross AL (1962) Acetonitrile in body fluids related to smoking. Public Health Rep, 77: 553-554.

Marine D, Baumann EJ, Spence AW, & Cipra A (1932a) Further studies on etiology of goiter with particular reference to the action of cyanides. Proc Soc Exp Biol Med, **29**: 772-775.

Marine D, Spence AW, & Cipra A (1932b) Production of goiter and exophthalmos in rabbits by administration of cyanide. Proc Soc Exp Biol Med, **29**: 822-823.

Maron D, Katzenellenbogen J, & Ames BN (1981) Compatibility of organic solvents with the salmonella/microsome test. Mutat Res, **88**: 343-350.

Michaelis HC, Clemens C, Kijewski H, Neurath H, & Eggert A (1991) Acetonitrile serum concentrations and cyanide blood levels in a case of suicidal oral acetonitrile ingestion. Clin Toxicol, **29**: 447-458.

Mimura A, Kawano T, & Yamaga K (1969) [Application of microorganisms to the petrochemical industry. I. Assimilation of nitriles by microorganisms.] J Ferment Technol, **47**: 631-638 (in Japanese).

Mori Y, Yamazaki H, Toyoshi K, Emi Y, Uchida K, Tsutsumi M, & Konishi Y (1985) Inhibitory effect of organic solvents on the mutagenicity of N-nitrosodialkylamines in Salmonella. Mutat Res, **142**: 153-158.

Morrissey RE, Schwetz BA, Lamb JC IV, Ross MD, Teague JL, & Morris RW (1988) Evaluation of rodent sperm, vaginal cytology, and reproductive organ weight data from National Toxicology Program 13-week studies. Fundam Appl Toxicol, **11**: 343-358.

Mortelmans K, Haworth S, Lawlor T, Speck W, Tainer B, & Zeiger E (1986) Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. Environ Mutagen, **8**(Suppl 7): 1-119.

NIOSH (1977) Acetonitrile. Analytical method No. S165. In: NIOSH manual of analytical methods, 2nd ed. Cincinnati, Ohio, National Institute of Occupational Safety and Health, vol 3, pp S165/1-S165/8 (DHEW-77-157-C).

NIOSH (1978) Criteria for a recommended standard... Occupational exposure to nitriles. Cincinnati, Ohio, National Institute of Occupational Safety and Health (DHEW-78-212).

NIOSH (1979) National occupational hazards survey: Updated projection data collected 1972-1974. Cincinnati, Ohio, National Institute of Occupational Safety and Health.

NIOSH (1984) Method No. 1606. In: NIOSH manual of analytical method, 3rd ed. Cincinnati, Ohio, National Institute of Occupational Safety and Health, pp 1606/1-1606/3 (DHHS 84-100).

Nishiuchi Y (1981) [Toxicity of pesticides to some aquatic animals. II. Toxicity of several solvents to carp and daphnids.] Seitai Kagaku, **4**: 45-47 (in Japanese).

Office of Health Studies, Department of Environmental Health, Environment Agency, Japan (1990) [Chemicals in the environment. The annual report of chemical assessment.] Tokyo, Environment Agency, pp 492-493 (Office of Health Studies Report Series) (in Japanese).

Ohkawa H, Ohkawa R, Yamamoto I, & Casida JE (1972) Enzymatic mechanisms and toxicological significance of hydrogen cyanide liberation from various organo-thiocyanates and organonitriles in mice and houseflies. Pestic Biochem Physiol, 2: 95-112.

Osgood C, Zimmering S, & Maison JM (1991a) Aneuploidy in Drosophila. II. Further validation of the FIX and ZESTE genetic test systems employing female *Drosophila melanogaster*. Mutat Res, **259**: 147-163.

Osgood C, Bloomfield M, & Zimmer-Ring S (1991b) Aneuploidy in Drosophila. IV. Inhalation studies on the induction of aneuploidy by nitriles. Mutat Res, **259**: 165-176.

Pereira MA, Lin LHC, & Mattox JK (1984) Haloacetonitrile excretion as thiocyanate and inhibition of dimethylnitrosamine demethylase: A proposed metabolic scheme. J Toxicol Environ Health, **13**: 633-641.

Pettigrew AR & Fell GS (1973) Microdiffusion method for estimation of cyanide in whole blood end its application to the study of conversion of cyanide to the thiocyanate. Clin Chem, **19**: 466-471.

Philbrick DJ, Hopkins JB, Hill DC, Alexander JC, & Thomson RG (1979) Effects of prolonged cyanide and thiocyanate feeding in rats. J Toxicol Environ Health, **5**: 579-592.

Pitt MJ (1982) A vapour hazard index for volatile chemicals. Chem Ind, **16**: 804-806.

Placak OR & Ruchhoft CC (1947) Studies of sewage purification. XVII. The utilization of organic substrates by activated sludge. Sew Works J, **19**: 423-440.

Pozzani UC, Carpenter CP, Palm PE, Weil CS, & Nair JH (1959a) An investigation of the mammalian toxicity of acetonitrile. J Occup Med, 1: 634-642.

Pozzani UC, Weil CS, & Carpenter CP (1959b) The toxicological basis of threshold limit values: 5. The experimental inhalation of vapor mixtures by rats, with notes upon the relationship between single dose inhalation and single dose oral data. Am Ind Hyg Assoc J, **20**: 364-369.

Prager JC (1989) Acetonitrile. Danger Prop Ind Mater Rep, **9**(6): 46-60.

Reynolds JEF ed. (1982) Martindale: The extra pharmacopoeia, 28th ed. London, The Pharmaceutical Press.

Rhoades JW (1958) Sampling method for analysis of coffee volatiles by gas chromatography. Food Res, **23**: 254-261.

Rhoades JW (1960) Analysis of the volatile constituents of coffee. Agric Food Chem, **8**: 136-141.

Rieders F & Valentour JC (1975) Cyanide. In: Sunshine I ed. Methodology for analytical toxicology. Cleveland, Ohio, CRC Press, Inc., pp 113-118.

Rigby LJ (1981) The collection and identification of toxic volatiles from plastics under thermal stress. Ann Occup Hyg, **24**: 331-345.

Roloff V, Short R, Ribelin W, & Dietrich M (1985) Comparison of subchronic inhalation toxicity of five aliphatic nitriles in rats. Toxicologist, **5**: 30.

Rounbehler DP, Bradley SJ, Challis BC, Fine DH, & Walker EA (1982) Trace determination of amines and other nitrogen containing compounds with a modified thermal energy analyzer. Chromatographia, **16**: 354-358.

Sasaki S (1978) The scientific aspects of the chemical substance control law in Japan. In: Hutzinger O, Von Letyoeld LH, & Zoeteman BCJ ed. Aquatic pollutants: Transformation and biological effects. Oxford, New York, Pergamon Press, pp 283-298.

Sax NI & Lewis RJ ed. (1989) Dangerous properties of industrial materials, 7th ed. New York, Van Nostrand Reinhold Co.

Schaar JC & Sackett PH (1983) Rapid determination of acrylonitrile in water and acetonitrile by high-performance liquid chromatography. J Chromatogr, **267**: 232-237.

Schlegelmilch R, Krug A, & Wolf HU (1988) Mutagenic activity of acetonitrile and fumaronitrile in three short term assays with special reference to autoinduction. J Appl Toxicol, **8**: 201-209.

Sehgal A, Osgood C, & Zimmering S (1990) Aneuploidy in Drosophila. III. Aneuploidogens inhibit *in vitro* assembly of taxol-purified Drosphilia microtubules. Environ Mol Mutagen, **16**: 217-224.

Silver EH, Kuttab SH, Hasan T, & Hassan H (1982) Structural considerations in the metabolism of nitriles to cyanide *in vivo*. Drug Metab Dispos, **10**: 495-498.

Silverstein RM & Bassler GC (1967) Spectrometric identification of organic compounds. New York, Chichester, Brisbane, Toronto, John Wiley and Sons, Inc., p 256.

Smiley RA (1983) Nitriles. In: Kirk-Othmer encyclopedia of chemical technology, 3rd ed. New York, Chichester, Brisbane, Toronto, John Wiley and Sons, Inc., vol 15, pp 888-909.

Smith ADM, Duckett S, & Waters AH (1963) Neuropathological changes in chronic cyanide intoxication. Nature (Lond), **200**: 179-181.

Smith MK, George EL, Zenick H, Manson JM, & Stober JA (1987) Developmental toxicity of halogenated acetonitriles: Drinking water by products of chlorine disinfection. Toxicology, **46**: 83-93.

Smyth HF & Carpenter CP (1948) Further experience with the range finding test in the industrial toxicology laboratory. J Ind Hyg Toxicol, **30**: 63-68.

Smyth HF Jr, Carpenter CP, Weil CS, Pozzani UC, & Striegel JA (1962) Range-finding toxicity data-VI. Am Ind Hyg Assoc J, **23**: 95-107.

Szabo S, Bailey KA, Boor PJ, & Jaeger RJ (1977) Acrylonitrile and tissue glutathione - differential effect of acute and chronic interactions. Biochem Biophys Res Commun, **79**: 32-37.

Szabo S, Reynolds ES, & Unger SH (1982) Structure-activity relations between alkyl nucleophilic chemicals causing duodenal ulcer and adrenocortical necrosis. J Pharmacol Exp Ther, **223**: 68-76.

Takizawa A & Nakayama E (1979) [Variation of urinary thiocyanate.] Rodo-Eisei, **20**: 56-59 (in Japanese).

Tanii H & Hashimoto K (1984a) Studies on the mechanism of acute toxicity of nitriles in mice. Arch Toxicol, **56**: 47-54.

Tanii H & Hashimoto K (1984b) Structure - toxicity relationship of aliphatic nitriles. Toxicol Lett, **22**: 267-272.

Tanii H & Hashimoto K (1986) Influence of ethanol on the *in vivo* and *in vitro* metabolism of nitriles in mice. Arch Toxicol, **58**: 171-176.

Thom NS & Agg AR (1975) The breakdown of synthetic organic compounds in biological processes. Proc R Soc (Lond), **B189**: 347-357.

Thomson TB (1969) The determination of acetonitrile and other trace impurities in acrylonitrile by gas chromatography. J Chromatogr, **39**: 500-501.

Tonogai Y & Ito Y (1984) Toxicity of organic nitrogen compounds on fish: Syncopic effect of aniline derivatives on fish. Seitai Kagaku, **7**: 17-26.

Tonogai Y, Ogawa S, Ito Y, & Iwaida M (1982) Actual survey on TLm (median tolerance limit) values of environmental pollutants, especially on amines, nitriles, aromatic nitrogen compounds and artificial dyes. J Toxicol Sci, **7**: 193-203.

Troup CM & Ballantyne B (1987) Analysis of cyanide in biological fluids and tissues. In: Ballantyne B & Marrs TC ed. Clinical and experimental toxicology of cyanide. Bristol, John Wrigth, pp 22-40.

Turchen SG, Manoguerra AS, & Whitney C (1991) Severe cyanide poisoning from the ingestion of acetonitrile-containing cosmetic. Am J Emerg Med, **9**: 264-267.

US EPA (1984) Environmental fate data base (Envirofate). Cincinnati, Ohio, US Environmental Protection Agency, chapter 8, file 3.

US EPA (1988) National ambient volatile organic compounds (VOCs) database update. Research Triangle Park, North Carolina, US Environmental Protection Agency, Atmospheric Sciences Research Laboratory (EPA/600/3-/88/010(a)).

US EPA (1992) Chemical hazard information profile on acetonitrile. Hazardous substances databank No. 42. Cincinnati, Ohio, US Environmental Protection Agency.

Veatch F, Idol JD, Jaworowski FS, & Szabo LS (1964) Acetonitrile: Time for review. Hydrocarb Process Pet Refin, **43**: 177–183.

Verbrugge R (1899) Toxicité des mononitriles gras et aromatiques et action antitoxique de l'hyposulfite de soude vis-à-vis de ces mononitriles. Arch Phamacodyn, **5**: 161–197.

Verschueren K (1983) Handbook of environmental data on organic chemicals, 2nd ed. New York, Van Nostrand Reinhold Co., pp 151–152.

Wang WY & Guo LJ (1984) [Toxicity study on acetonitrile.] In: [Data compilation on labour health and occupational diseases.] Beijing, Institute of Occupational Medicine, Chinese Academy of Preventive Medicine, pp 32–44 (in Chinese).

WHO (1992) IPCS poison information monograph: cyanides. Geneva, World Health Organization, International Programme on Chemical Safety (IPCS/INTOX/PIM.159).

Willhite CC (1981) Inhalation toxicology of acute exposure to aliphatic nitriles. Clin Toxicol, **18**: 991–1003.

Willhite CC (1983) Developmental toxicology of acetonitrile in the Syrian golden hamster. Teratology, **27**: 313–325.

Willhite CC & Smith RP (1981) The role of cyanide liberation in the acute toxicity of aliphatic nitriles. Toxicol Appl Pharmacol, **59**: 589–602.

Wilson J (1983) Cyanide in human disease: a review of clinical and laboratory evidence. Fundam Appl Toxicol, **3**: 397–399.

Wood M (1985) The use of the Perkin Elmer passive sampler and ATD 50 automatic thermal desorber in the measurement of atmospheric concentrations of organic nitriles. Ann Occup Hyg, **29**: 399–413.

Woolley WD (1972) Nitrogen-containing products from thermal decomposition of flexible polyurethane foams. Br Polym J, **4**: 27–43.

Yoshikawa H (1968) Toxicity of nitrile compounds. I. Aliphatic nitriles. Kagaku Seibutsugaku, **77**: 1–4.

Zamecnik J & Tam J (1987) Cyanide in blood by gas chromatography with NP detector and acetonitrile as internal standard. Application on air accident fire victims. J Anal Toxicol, **11**: 47–48.

Zeller VH, Hofmann HT, Thiess AM, & Hey W (1969) [Toxicity of nitriles.] Zent. bl Arbeitsmed Arbeitsschutz, **19**: 225–238 (in German).

Zimmermann FK, Mayer VW, Scheel I, & Rensnick MA (1985) Acetone, methyl ethyl ketone, ethyl acetate, acetonitrile and other polar aprotic solvents are strong inducers of aneuploidy in Saccharomyces. Mutat Res, **149**: 339–351.

RESUME

1. Propriétés, usages et méthodes d'analyse

L'acétonitrile (CH_3CN) est un sous-produit de la fabrication de l'acrylonitrile. Il peut également se former lors de la combustion du bois et de la végétation. C'est un liquide d'odeur éthérée. L'acétonitrile est un solvant volatil, extrêmement polaire, que l'on utilise pour extraire les acides gras ainsi que les huiles animales et végétales. On l'emploie également dans l'industrie pétrochimique pour la distillation extractive, du fait qu'il présente une miscibilité sélective aux composés organiques. On l'utilise également comme solvant pour le filage des fibres synthétiques et dans le formage et le moulage des plastiques. Au laboratoire, on l'utilise largement en chromatographie liquide à haute performance (CLHP) ainsi que comme solvant pour la synthèse de l'ADN et le séquençage des peptides.

La technique d'analyse la plus largement utilisée pour l'acétonitrile est la chromatographie en phase gazeuse.

2. Concentrations dans l'environnement et sources d'exposition humaine

On ne dispose que de très peu de données sur les concentrations d'acétonitrile dans l'environnement. Dans l'ensemble du monde, on fait état de concentrations atmosphériques allant de 200 à 42 000 ng/m^3. Une étude donne des concentrations atmosphériques un peu plus élevées en milieu urbain qu'en milieu rural. Une mesure effectuée avant et après la combustion de broussailles et de paille a montré que la concentration atmosphérique d'acétonitrile était multipliée par dix.

On n'a pas décelé d'acétonitrile dans 72 échantillons d'eau au Japon, mais on en a trouvé dans 11 échantillons de sédiments aquatiques sur 60 à des concentrations allant de 0,02 à 0,54 mg/kg. On n'a pas trouvé d'acétonitrile dans les denrées alimentaires.

La fumée de tabac contient de l'acétonitrile et la combustion de la mousse de polyuréthanne libère de l'acétonitrile et du cyanure d'hydrogène.

C'est la production d'acrylonitrile qui présente les plus grands risques d'exposition mais elle s'effectue en enceinte fermée.

L'utilisation pratique de l'acétonitrile peut conduire à une exposition plus importante.

3. Distribution et transformation dans l'environnement

L'acétonitrile s'évapore à partir de l'eau et peut également le faire à partir de la surface du sol. Il est facilement décomposé par plusieurs souches de bactéries communément présentes dans les boues d'égouts, les eaux naturelles et le sol. L'acclimatation des bactéries à l'acétonitrile ou aux déchets de pétrole augmente la vitesse de décomposition. La décomposition anaérobie paraît limitée, voire absente.

L'hydrolyse de l'acrylonitrile est extrêmement lente. Il n'y a pas de photodécomposition sensible dans l'eau ou l'atmosphère. La réaction avec l'ozone est lente, de même qu'avec l'oxygène singulet. Le principal mécanisme d'élimination de l'acétonitrile de la troposphère consiste dans sa réaction avec les radicaux hydroxyles; la durée estimative de séjour est de 20 à 200 jours.

L'acétonitrile gagne la stratosphère où il se caractérise par son association aux amas d'ions positifs situés dans les régions élevées.

4. Effets sur l'environnement

L'acétonitrile est peu toxique pour les microorganismes (bactéries, cyanobactéries, algues bleues et protozoaires) avec un seuil de toxicité de l'ordre de 500 mg/litre ou davantage. Les valeurs de la CL_{50} dans le cas d'une intoxication aiguë sont de l'ordre de 700 mg/litre ou davantage pour les invertébrés et les poissons d'eau douce. Des tests de toxicité aiguë ont été effectués dans des conditions statiques sans confirmation analytique des concentrations. Les résultats analogues obtenus à l'issue de tests de 24 et 96 heures donnent à penser qu'il y a volatilisation de l'acétonitrile.

5. Absorption, distribution, biotransformation et élimination

L'absorption de l'acétonitrile s'effectue facilement par la voie digestive, percutanée et plumonaire. Ces trois voies d'exposition entraînent toutes des effets généraux.

L'examen nécropsique de tissus provenant de personnes intoxiquées montre que l'acétonitrile se répartit dans l'ensemble de l'organisme. Cette constatation est corroborée par l'étude sur

l'animal qui montre également que la distribution de l'acétonitrile est relativement uniforme dans l'ensemble de l'organisme. Rien n'indique que l'administration réitérée d'acétonitrile n'entraîne une accumulation dans les tissus chez l'animal.

On possède une quantité substantielle de données selon lesquelles la majeure partie des effets toxiques généraux de l'acétonitrile seraient dus à sa métabolisation en cyanure, métabolisation qui est catalysée par le système des monooxygénases du cytochrome P-450. La conjugaison du cyanure avec le thiosulfate conduit à la formation de thiocyanate qui est ensuite éliminé dans l'urine. Les concentrations maximales de cyanure dans le sang de rats après administration de doses quasi-mortelles d'acétonitrile correspondent sensiblement à celles que l'on observe après l'administration d'une dose de cyanure de potassium correspondant à la DL_{50}. Toutefois, après administration d'acétonitrile, le pic de concentration du cyanure apparaît avec un retard pouvant atteindre plusieurs heures, par comparaison avec les autres nitriles. En outre, la vitesse de formation plus élevée du cyanure chez la souris explique la sensibilité beaucoup plus forte de cette espèce aux effets toxiques de l'acétonitrile. On a reconnu la présence de cyanure et de thiocyanate dans des tissus humains après exposition à l'acétonitrile. Une partie de la dose d'acétonitrile est également éliminée telle quelle dans l'air expiré et dans les urines.

6. Effets sur les mammifères de laboratoire

L'acétonitrile produit des effets toxiques analogues à ceux que l'on observe en cas d'intoxication aiguë par le cyanure, encore que l'apparition des symptômes soit un peu plus tardive que dans le cas des cyanures minéraux ou d'autres nitriles saturés. La CL_{50} par inhalation à 8 heures pour le rat mâle est de 13 740 mg/m^3 (7500 ppm). La DL_{50} par voie orale chez le rat va de 1,7 à 8,5 g/kg selon les conditions de l'expérience. Les souris et les cobayes se révèlent plus sensibles, avec une DL_{50} par voie orale de qui est de l'ordre de 0,2-0,4 g/kg. Chez l'animal, les principaux symptômes consistent en une prostration suivie de crises convulsives.

L'application cutanée d'acétonitrile entraîne une intoxication générale chez l'animal et on lui a attribué la mort d'un enfant. Chez le lapin, la DL_{50} par voie percutanée est de 1,25 mg/kg.

L'exposition subchronique d'animaux de laboratoire à l'acétonitrile produit des effets analogues à ceux que l'on observe après une intoxication aiguë.

D'après les épreuves effectuées sur *Salmonella typhimurium*, l'acétonitrile n'est pas mutagène, qu'il y ait ou non activation métabolique. A très forte concentration, l'acétonitrile a provoqué une aneuploïdie chez une souche de levure diploïde. Il n'a pas été fait état d'études sur l'animal qui concernent les effets chroniques ou cancérogènes de l'acétonitrile.

7. Effets sur l'homme

On ne connaît pas les concentrations toxiques pour l'homme mais il est probable qu'elles sont supérieures à 840 mg/m^3 (500 ppm) d'air. Les symptômes d'une intoxication aiguë par l'acétonitrile consistent en douleurs et sensation de constriction au niveau du thorax, nausées, vomissements, agitation, état semi-comateux et convulsions. D'autres symptômes non spécifiques peuvent s'expliquer par l'effet irritant du composé. Les effets généraux sont, semble-t-il, en grande partie attribuables à la transformation de l'acétonitrile en cyanure. D'ailleurs, une intoxication aiguë provoque une élévation des taux sanguins de cyanure et de thiocyanate. On a signalé deux accidents mortels dus à l'exposition à des vapeurs d'acétonitrile sur le lieu de travail ainsi que la mort d'un enfant qui avait avalé un produit cosmétique contenant de l'acétonitrile. L'examen nécropsique de ces victimes a révélé la présence de fortes concentrations de cyanure dans les tissus.

On ne dispose d'aucune étude épidémiologique sur l'incidence de cancers qui seraient liés à une exposition à l'acétonitrile.

L'acétonitrile peut provoquer de graves brûlures oculaires. Il convient d'éviter tout contact de la peau avec le composé. Dans de nombreux pays, il est recommandé que l'exposition des travailleurs ne dépasse pas 70 mg/m^3 d'air (40 ppm) en moyenne pondérée par rapport au temps au cours d'un poste de travail de 8 heures.

RESUMEN

1. Propiedades, usos y métodos analíticos

El acetonitrilo (CH_3CN) es un subproducto de la fabricación del acrilonitrilo. También puede formarse por combustión de madera y de vegetación. Es un líquido de olor semejante al del éter. El acetonitrilo es un disolvente volátil de alta polaridad utilizado para la extracción de ácidos grasos y de aceites animales y vegetales. Se emplea en la industria petroquímica en la destilación extractiva debido a su miscibilidad selectiva con compuestos orgánicos. Se utiliza como disolvente para el hilado de fibras sintéticas y en la fusión y el moldeado de plásticos. Está muy difundido su empleo en laboratorio en los análisis por cromatografía líquida de alto rendimiento (HPLC) y como disolvente para la síntesis de ADN y la secuenciación de péptidos.

La técnica analítica más ampliamente utilizada para el acetonitrilo es la cromatografía de gases.

2. Niveles ambientales y fuentes de exposición humana

Hay muy pocos datos disponibles sobre los niveles de acetonitrilo en el medio ambiente. A escala mundial se han notificado concentraciones de acetonitrilo en el aire que oscilaban entre 200 y 42 000 ng/m^3. En un estudio se detectaron en el aire de zonas urbanas valores algo más elevados que en el de zonas rurales. Mediciones separadas efectuadas antes y después de la quema de arbustos y paja mostraron una decuplicación de la concentración de acetonitrilo en el aire.

No se ha detectado la presencia de acetonitrilo en 72 muestras de agua del Japón, pero sí en 11 de 60 muestras de sedimentos acuáticos, en concentraciones que oscilaban entre 0,02 y 0,54 mg/kg. Tampoco se ha encontrado acetonitrilo en los alimentos.

El humo de tabaco contiene acetonitrilo y la espuma de poliuretano al quemarse libera acetonitrilo y cianuro de hidrógeno.

Si bien la producción de acrilonitrilo conlleva el máximo riesgo de exposición, ésta se efectúa en un sistema cerrado. Los usos prácticos del acetonitrilo entrañan una exposición mayor.

3. Distribución y transformación en el medio ambiente

El acetonitrilo presente en el agua se volatiliza, como también se volatilizaría el que se hallase presente en la capa superficial del suelo. Se biodegrada fácilmente por acción de varias cepas de bacterias comunes en el fango de alcantarillas, en las aguas naturales y en el suelo. La aclimatación de las bacterias al acetonitrilo o a los desechos de petróleo incrementa la tasa de degradación. La degradación anaeróbica parece ser limitada o inexistente.

La hidrólisis del acrilonitrilo en el agua es extremadamente lenta. No hay fotodegradación significativa en el agua ni en la atmósfera. La reacción con el ozono es lenta, como también lo es la reacción con el oxígeno singlete. El principal mecanismo para eliminar el acetonitrilo de la troposfera es la reacción con radicales hidroxilo; los tiempos de residencia se han estimado entre 20 y 200 días.

El acetonitrilo llega hasta la estratosfera, en cuyas regiones superiores está asociado característicamente en aglomerados de iones positivos.

4. Efectos ambientales

El acetonitrilo es poco tóxico para los microorganismos (bacterias, cianobacterias, algas verdes y protozoarios) con umbrales de 500 mg/litre o más. Las CL_{50} agudas para invertebrados y peces de agua dulce son de 700 mg/litre o más. Se han hecho pruebas de toxicidad aguda en condiciones estáticas sin confirmación analítica de las concentraciones. Algunos resultados semejantes de otras pruebas, obtenidos después de 24 y 96 horas, parecen indicar una volatilización del acetonitrilo.

5. Absorción, distribución, biotransformación y eliminación

El acetonitrilo se absorbe fácilmente en el tracto gastrointestinal y a través de la piel y de los pulmones. Se ha informado de que la exposición por estas tres vías tiene efectos sistémicos.

El examen de tejidos en la autopsia de personas envenenadas ha mostrado que el acetonitrilo se distribuye por todo el cuerpo. Esta observación está corroborada por estudios realizados en animales, en los cuales se ha encontrado que el acetonitrilo se distribuye bastante uniformemente en todo el cuerpo. No hay indicaciones

bastante uniformemente en todo el cuerpo. No hay indicaciones de acumulación en los tejidos animales después de administraciones repetidas de acetonitrilo.

Hay datos sustanciales que hacen pensar que el acetonitrilo tiene efectos tóxicos sistémicos a través de su transformación metabólica en cianuro, catalizada por el sistema de la citocromo-P-450-monooxigenasa. El cianuro se conjuga posteriormente con el tiosulfato para formar tiocianato, que se elimina por la orina. Las concentraciones máximas de cianuro en la sangre de ratas después de la administración de dosis casi letales de acetonitrilo se aproximan a las concentraciones observadas después de la administración de una DL_{50} de cianuro de potasio. Sin embargo, la concentración máxima de cianuro después de la administración de acetonitrilo se alcanza con un retraso de hasta varias horas en comparación con otros nitrilos. Por otra parte, la mayor rapidez con la cual se produce el cianuro en el ratón parece explicar la sensibilidad mucho mayor de esta especie a los efectos tóxicos del acetonitrilo. Se ha detectado la presencia de cianuro y de tiocianato en tejidos humanos después de la exposición al acetonitrilo. Parte de la dosis de acetonitrilo también se elimina sin modificaciones a través del aire que se exhala y de la orina.

6. Efectos en mamíferos de laboratorio

El acetonitrilo produce efectos tóxicos similares a los observados en el envenenamiento agudo con cianuro, aunque los síntomas comienzan a manifestarse con algún retraso en comparación con los producidos por cianuros inorgánicos u otros nitrilos saturados. La CL_{50} en machos de rata sometidos a inhalación durante 8 horas es de 13 740 mg/m^3 (7500 ppm). La DL_{50} por vía oral en la rata oscila entre 1,7 y 8,5 g/kg, según las condiciones del experimento. Los ratones y los cobayos parecen ser más sensibles, con una DL_{50} por vía oral de 0,2 a 0,4 g/kg. Los síntomas principales en los animales parecen ser la postración seguida de convulsiones.

La aplicación dérmica de acetonitrilo tiene efectos tóxicos sistémicos en animales y ha sido un factor causal de defunción en un niño. La DL_{50} percutánea en conejos es de 1,25 ml/kg.

La exposición subcrónica de animales al acetonitrilo produce efectos similares a los observados después de la exposición aguda.

realizados con *Salmonella typhimurium*, con y sin activación metabólica. En concentraciones muy altas produce aneuploidía en una estirpe diploide de levaduras. No se tiene noticia de estudios sobre los efectos crónicos o carcinogénicos del acetonitrilo en animales.

7. Efectos en el hombre

Se desconocen los niveles tóxicos en el hombre, pero probablemente rebasen los 840 mg/m^3 (500 ppm) en el aire. Los síntomas y signos de la intoxicación aguda con acetonitrilo comprenden dolor torácico, sensación de opresión en el pecho, náuseas, vómitos, taquicardia, hipotensión, respiración corta y poco profunda, dolor de cabeza, agitación, semiinconsciencia y convulsiones. Otros síntomas no específicos tal vez obedezcan a los efectos irritantes del compuesto. Los efectos sistémicos parecen atribuibles en gran medida a la conversión del acetonitrilo en cianuro. Los niveles de cianuro y de tiocianato en la sangre son elevados durante la intoxicación aguda. Se han comunicado dos defunciones posteriores a la exposición a vapores de acetonitrilo en el lugar de trabajo y la defunción de un niño que había ingerido un cosmético que contenía acetonitrilo. Se encontraron concentraciones elevadas de cianuro en la autopsia de esas personas.

No se han notificado estudios epidemiológicos sobre la incidencia de cáncer relacionada con la exposición al acetonitrilo.

El acetonitrilo puede causar quemaduras graves en los ojos. Debe evitarse el contacto de la piel con el acetonitrilo líquido. En muchos países se ha recomendado que la exposición de los empleados al acetonitrilo en un turno de 8 horas no rebase un promedio, ponderado en función del tiempo, de 70 mg/m^3 de aire (40 ppm).

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