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The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals

118. Cyanoacrylates

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National Institute for Working Life

National Institute for Working Life

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Preface

The Nordic Council is an intergovernmental collaborative body for the five countries, Denmark, Finland, Iceland, Norway and Sweden. One of the committees, the Nordic Senior Executive Committee for Occupational Environmental Matters, initiated a project in order to produce criteria documents to be used by the regulatory authorities in the Nordic countries as a scientific basis for the setting of national occupational exposure limits.

The management of the project is given to an expert group. At present the Nordic Expert Group consists of the following members:

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

For each document an author is appointed by the Expert Group and the national member acts as a referent. The author searches for literature in different databases such as Toxline, Medline, Cancerlit and Nioshtic. Information from other sources such as WHO, NIOSH and the Dutch Expert Committee is also used as are handbooks such as Patty's Industrial Hygiene and Toxicology. Evaluation is made of all relevant scientific original literature found. In exceptional cases information from documents difficult to access are used. The draft document is discussed within the Expert Group and is finally accepted as the Group's document.

Editorial work is performed by the Group's Scientific Secretary, Brita Beije / Gregory Moore, at the National Institute for Working Life in Sweden.

Only literature judged as reliable and relevant for the discussion is referred to in this document. Concentrations in air are given in mg/m^3 and in biological media in mol/l. In case they are otherwise given in the original papers they are if possible recalculated and the original values are given within brackets.

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

The evaluation of the literature and the drafting of this document on Cyanoacrylates was made by Dr Johan Montelius, National Institute for Working Life, Solna, Sweden. The final version was accepted by the Nordic Expert Group May 22, 1995 as its document.

Brita Beije/Gregory Moore
Scientific Secretary

Per Lundberg
Chairman

Contents

1. Introduction

Cyanoacrylates were first synthesized by Ardis in 1949 (7) but it was not until the early fifties Coover and co-workers, at the laboratories of the Tennessee Eastman Company, by chance discovered their unique adhesive properties. When investigating a series of polymers derived from 1,1-disubstituted ethylenes, a drop of highly purified ethyl 2-cyanoacrylate was placed between the glass prisms in a refractometer in order to measure the refractive index. After the measurement they where unable to separate the prisms and within a few hours, the full implication of this accident was apparent and a new typ of adhesives discovered (32, 33, 34).

In 1958 the cyanoacrylate adhesive Eastman 910® (methyl 2-cyanoacrylate) was first introduced as a commercial product, soon followed by other formulations and higher homologues. The alkyl 2-cyanoacrylate form strong bonds between a variety of materials: rubber, different metals, glass, wood, plastics, leather, cork, nylon, ceramics, porcelain etc. The adhesives quickely found a widespread use in many industrial applications, especially the methyl and ethyl derivatives. Later, they were also marketed for household use under the product names such as Krazy Glue®, Super Glue®, Miracle Glue®, Loctite®, Nail Glue®, or Instant Magic® (34, 47).

In addition, the 2-cyanoacrylates, especially the n-butyl and isobutyl derivatives, have been extensively tested and used as a medical adhesive in several surgical specialities. Their ability to polymerize on moist surfaces and thereby glue skin and mucous membranes and because they biodegrade make them suited for this purpose (32).

2. Chemistry and Properties

2.1 Chemical and physical data

Methyl 2-Cyanoacrylate (2, 24, 34, 62, 67, 106, 120, 152, 169)

CAS No.:	137-05-3
Synonyms/Trade names:	Mecrylate; 2-propenoic acid, 2-cyano-, methyl ester; methyl 2-cyano-2-propeonate; 2-cyanoacrylic acid methyl ester; methyl α-cyanoacrylate; Eastman 910®; Cyanolit 102®; Mecrilat; Krazy Glue®
Formula:	$C_5H_5NO_2$
Structure:	$CH_2=C(C\equiv N)CO\text{-}OCH_3$
Molecular weight:	111.10

Vapour pressure:	0.33 kPa at 48 °C (27) <0.27 kPa at 25 °C (34) 0.026 kPa at 10 °C (169) 0.011 kPa at 0 °C (169) 0.004 kPa at -10 °C (169)
Refractive index (n_D^{25}):	1.443
Specific gravity (d_4^{27}):	1.104
Melting point:	2.5 °C
Flash point:	78 °C
Autoignition temperature:	468 °C
Boiling point:	47-49 °C at 0.24 kPa
Conversion factor:	1 ppm = 4.53 mg/m^3 1 mg/m^3 = 0.22 ppm
Viscosity (Brookfield):	2.20 cP at 25 °C
Heat of polymerisation:	42.5 ± 0.8 kJ/mole (in water)
General description:	Methyl 2-Cyanoacrylate is a colourless, thin liquid with a sharp smell and an odour threshold of between 1 and 5 ppm. It is soluble or partly soluble in methyl ethyl ketone, toluene, N,N-dimethyl formamide, acetone, and nitromethane.

Ethyl 2-Cyanoacrylate (34, 67, 91, 152)

CAS No.:	7085-85-0
Synonyms/Trade names:	Ethyl cyanoacrylate; Ethyl 2-cyano-2-propenoate; 2-Propenoic acid, 2-cyano-, ethyl ester; Aron Alpha®; Cyanolite 201®; Mediglue®; Cyacrine®; Krazy Glue®
Formula:	$C_6H_7NO_2$
Structure:	CH_2=C(C≡N)CO-OCH_2CH_3
Molecular weight:	125.12
Vapour pressure:	<0.27 kPa at 25 °C
Refractive index (n_D^{20}):	1.4391
Density (20 °C):	1.040 g/cc
Flash point:	82 °C
Autoignition temperature:	468 °C
Boiling point:	54-56 °C at 0.35-0.40 kPa
Conversion factor:	1 ppm = 5.12 mg/m^3 1 mg/m^3 = 0.20 ppm
Viscosity (Brookfield):	1.86 cP at 25 °C
General description:	Clear, colourless liquid with an irritating odour.

n-Butyl 2-Cyanoacrylate (34, 62, 91)

CAS No.:	6606-65-1
Synonyms/Trade name:	2-Propenoic acid, 2-cyano-, butyl ester; Enbucrilate®; Histoacryl®; Histoacryl® Blue; Nexacryl®
Formula:	$C_8H_{11}NO_2$
Structure:	CH_2=C(C≡N)CO-O$(CH_2)_3CH_3$
Molecular weight:	153.18
Vapour pressure:	<0.27 kPa at 25 °C
Refractive index (n_D^{20}):	1.4424
Density (20 °C):	0.989 g/cc
Melting point:	-15 °C
Flash point:	85 °C
Boiling point:	68 °C at 0.24 kPa
Conversion factor:	1 ppm = 6.26 mg/m^3 1 mg/m^3 = 0.16 ppm
Viscosity (Brookfield):	2.07 cP at 25 °C
General description:	n-Butyl 2-Cyanoacrylate is a colourless, thin liquid with a sharp smell.

Isobutyl 2-Cyanoacrylate (23, 34)

CAS No.:	1069-55-2
Synonyms/Trade name:	2-Propenoic acid, 2-cyano-, isobutyl ester; 2-Cyano-2-propenoic acid 2-methylpropyl ester; 2-cyanoacrylic acid isobutyl ester; Bucrylate; Bucrilate; IBC; IBCA
Formula:	$C_8H_{11}NO_2$
Structure:	CH_2=C(C≡N)CO-O$CH_2CH(CH_3)_2$
Molecular weight:	153.18
Vapour pressure:	<0.27 kPa at 25 °C
Boiling point:	71-73 °C at 0.25-0.29 kPa
Conversion factor:	1 ppm = 6.26 mg/m^3 1 mg/m^3 = 0.16 ppm
Refractive index (n_D^{25}):	1.4352
Density at 20 °C:	0.9954
Viscosity (Brookfield):	2.02 cP at 25 °C
General description:	Clear, colourless liquid.

Table 1. Some other cyanoacrylates (91, 158).

Name	CAS No.	Molecular weight	Boiling point (°C/kPa)
n-Propyl 2-CA[1]	6606-66-2	139	80/0.80
Isopropyl 2-CA*	10586-17-1	139	
n-Amyl 2-CA	6701-15-1	167	113/0.72
iso-Amyl 2-CA	19475-26-4	167	
n-Hexyl 2-CA	3578-06-1	181	90/0.21
n-Heptyl 2-CA	6701-16-2	195	125/0.16
n-Octyl 2-CA	6701-17-3	209	117/0.24
n-Decyl 2-CA	3578-07-2	237	
2-Propenyl 2-CA*	7324-02-9		
Ethoxyethyl 2-CA*	21982-43-4		
2,2,2-Trifluoromethyl 2-CA*	23023-91-8		
2-Methoxyethyl 2-CA*	27816-23-5		
2-Propenoic acid, 2-cyano-3,3-diphenyl-, 2-ethylhexyl ester*	6197-30-4		
Ethanaminium, 2-((2-cyano-3-(4-(diethylamino)phenyl)-1-oxo-2-propenyl)oxy)-N,N,N-trimethyl-, chloride*	64992-16-1		

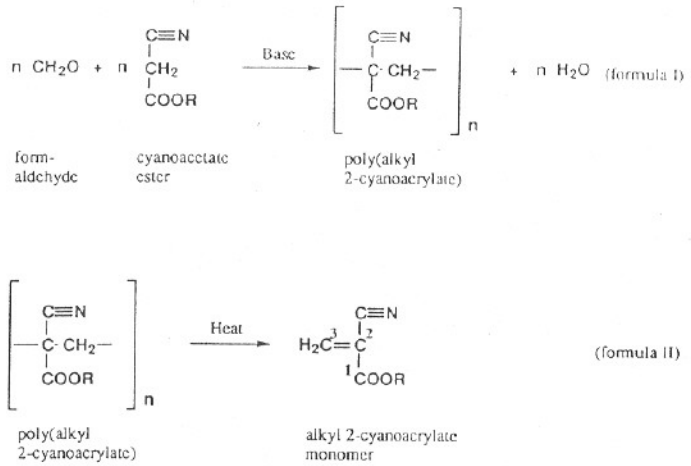
[1]2-CA, 2-cyanoacrylate

*In addition to methyl, ethyl, n-butyl, and isobutyl 2-cyanoacrylate, these 7 cyanoacrylates have been added by the US Environmental Protection Agency (EPA) to the Testing Priority List (158) (see Section 15).

Chemical and physical data for some cyanoacrylate polymers and additional data for cyanoacrylate monomers are available in refs. 34, 91, 101.

2.2 Synthesis

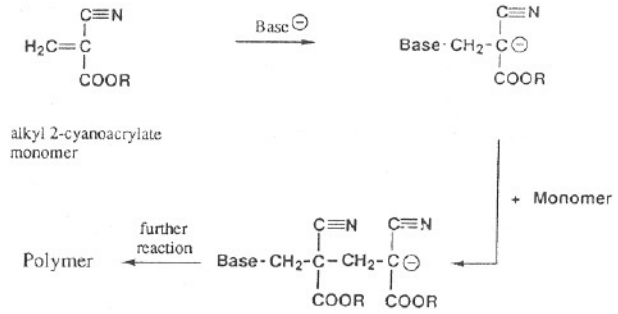
Alkyl 2-cyanoacrylatemonomers are usually synthesized in a two-step reaction. The first step is a base-catalysed polymerization reaction involving the condensation of formaldehyde and cyanoacetate esterified with an alcohol resulting in the formation of a poly(alkyl 2-cyanoacrylate) (33, 34, see formula I).



The structure of the side chain (R) defines the different alkyl 2-cyanoacrylates and is dependent on the alcohol that has been used. For instance, methanol gives methyl 2-cyanoacrylate, ethanol gives ethyl 2-cyanoacrylate, etc. (see Section 2.1). Depolymerisation occurs in a second step by heating of this material yielding the alkyl 2-cyanoacrylate monomer (see formula II). Purification of the crude monomer by redistillation is necessary since impurities inhibit polymerisation.

2.3 Polymerization and bonding

The bonding action of cyanoacrylates is generally believed to be a result of an anionic polymerisation that is highly exothermic and rapid occuring within seconds or minutes even at room temperature. Heat, excessive pressure, addition of solvents, or special catalysts are not required for this reaction to occur since weak bases such as water and alcohols or nucleofilic groups on proteins, e.g. amine or hydroxyl groups, already present on the adherent surfaces initiate the polymerisation. Their effects on the polymerisation is maximized by spreading the adhesive monomer into a very thin film. The proposed anionic mechanism of polymerisation (33) is shown in formula III, where Base⁻ represents the initiating base, an electron donor. The reaction starts by a nucleophilic attack on the ß-carbon (carbon 3) of the cyanoacrylate monomer with the formation of a stable carbanion that attacks another monomer. Propagation occurs by adding additional monomers to the initially formed dimer and continues until most of the monomers are consumed. The polymerisation is terminated by acid and certain acidic sub-



(formula II)

stances can thus be used as stabilizers (see Section 2.5). Although inhibiting polymerisation during storage, this effect is overcome when the adhesive is spread out into a thin film between the two surfaces to be cemented (33, 34).

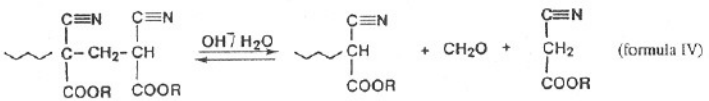
The cyanoacrylates function as adhesives by molecular attraction with smooth dense surfaces as well as mechanical adhesion caused by grip action or interlocking of the set adhesive in the surface irregularities, cavities, or pores of a rough surface. In addition, if a nucleophilic group on a protein initiates the polymerisation reaction, a covalent bond to the adhesive is formed which would add to the bonding strength in living tissues (33, 89). The short-chain cyanoacrylates form bonds with a higher tensile strength with different non-biological materials compared to the longer-chain homologues (90), e.g. on aluminium surfaces the methyl and ethyl homologues form bonds at least twice as strong as the butyl homologue. This makes them better suited for industrial and household use than the higher homologues. However, on proteinaceous substrates there is no simple relationship between alkyl side-chain length and bond strength and the higher homologues have approximately the bond strength of the methyl homologue (90, 170, 171). This is explained by the better wetting and spreading characteristics of the higher homologues on proteinaceous substrates (89, 90). For a homologue series of cyanoacrylates ranging from methyl up to octyl, the time for polymerisation in water is increased from 10 seconds for the short-chain to 5 minutes for the long-chain homologues (30, 89). For tissues and protein containing solutions, e.g. blood, the rate of polymerisation were directly opposite, with the higher homologues polymerising instantaneously or within seconds (30, 89, 102). This phenomenon has again been attributed to the poor wetting and spreading characteristics on proteinaceous substrates for the short-chain homologues (89, 90). Polymerisation rates can be affected by different surface activators such as organic amines (152) or by additives (see Section 2.5).

2.4 Degradation

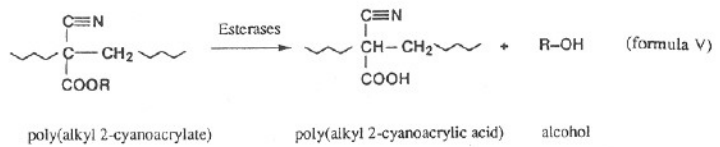
The initial step in the degradation of the polymer has been shown to occur chemically or be enzymatically mediated.

The chemical mechanism of degradation of poly alkyl cyanoacrylates in aqueous solutions have been suggested to involve an initial attack by hydroxyl ions leading to a reverse Knoevenagel reaction (89, 91). The cleavage of the carbon-to-carbon backbone of the polymer results in the degradation products formaldehyde and ultimately an alkyl cyanoacetate (26, 89, 91, 156, 161), see formula IV, in a process that is reversible. The degradation is enhanced by alkaline solutions and/or by heating. The mechanism of degradation is essentially the same for all poly alkyl cyanoacrylates, but the rate of degradation differs and depends on the nature of the alkyl side chain. Generally the degradation rate increases as the length of the side-chain decreases (89, 91, 111) but it is also dependent on the polymer surface, particle size, polymer molecular weight, and molecular weight distribution (156, 161). Degradation rates measured in vitro in organ cultures proceed in the same order with respect to the length of the side-chain (61).

Esterase catalysed degradation of the polymer has been suggested to occur in vivo (62, 87, 165). The poly(alkyl 2-cyanoacrylate) is enzymatically split into poly cyanoacrylic acid and the corresponding alcohol (see formula V). It has been shown that the degradation of poly(isobutyl cyanoacrylate) nanoparticles in a buffer solution containing rat liver microsomes proceeds mainly by hydrolysis of the ester bond with very little formation of formaldehyde (87). Although enzymatic cleavage of the ester bond represents a primary degradation pathway, a slower chemical hydrolysis of the ester also occurs.



(formula IV)



(formula V)

Cyanoacrylates are degradable in vivo, their rate of degradation being a function of the length of the side-chain, i.e. increasing the length of the side-chain decreases the degradation rate (89, 170, 171). A combination of the two degradation pathways (formula IV and V) would result in the formation of formaldehyde, alcohol and soluble low molecular weight acidic substances, e.g. cyanoacetate. Both mechanisms probably occur in vivo and the relative contribution of each pathway to the degradation of the cyanoacrylate polymer is dependent on the physiological environment, the nature of the side-chain, and the length and structure of the polymer (165) (for further details see Sections 6 and 7). Heating of cyanoacrylates (1 g) to about 400 °C resulted in the liberation of small amounts of hydrogen cyanide (59). Further details are not given.

2.5 Additives in adhesive formulations

Although pure cyanoacrylates are highly efficient adhesives in many industrial applications and for domestic use, it is desirable to regulate or change their physical properties. Several different additives have been included to improve their performance (34).

To stabilize against anionic and free-radical polymerisation and increasing curing-times and extending the shelf-life of the adhesive certain substances can be added such as sulphur dioxide, hydroquinone, catechol, metaphosphoric acid, phosphorus pentoxide, antimony oxide, picric acid, maleic anhydride, maleic acid, iron (III) chloride, nitric oxide, hydrogen fluoride, alkyl sulphates, mercaptans, alkyl sulfides, alkyl sulphones, alkyl sulphoxides, alkyl sulphites, 3-sulpholenes, sultones, and sulphur trioxide. Materials added to control and change the viscosity of the adhesive include polymethacrylates, polyacrylates, poly(vinyl acetates), poly(alkyl 2-cyanoacrylates), cellulose organic esters, and poly(lactic acid). Other physical properties of cyanoacrylate adhesives can be altered by combining two or more cyanoacrylate esters or by adding other monomers like methylene-malonitriles, allyl acrylate and alkyl acrylate, vinyl aromatic hydrocarbons, and diallyl, bis(2-methylallyl), and di-2-butenyl phthalates. The impact resistance of cured cyanoacrylate bonds can be improved by the addition of plasticisers, e.g. aliphatic monocarboxylic acids, dialkyl esters of aliphatic dicarboxylic acids, trialkyl phosphates, triaryl phosphates, dialkyl alkyl phosphonates, and alkyl phthalates. The otherwise colourless cyanoacrylates may be coloured by the addition of selected dyes, generally from the anthraquinone class (34). As an example, the composition of a cyanoacrylate glue is given in Table 2.

When cyanoacrylates are used as a medical adhesive additives should be as few as possible (18). Usually the adhesive consists of the pure monomer and some inhibitor, e.g. p-methoxyphenol, SO_2 (62, 136). Histoacryl as it is currently sold in Sweden, consists of n-butyl 2-cyanoacrylate, a blue colour (personal communication, Johan Vejde, Cyanamid Nordiska AB and (Ref. 11), probably 0.1% 1-hydroxy 4-(p-toluidine)-antrachion [sic] (49) (should probably be -anthraquinone)), and possibly some inhibitor. For medical use, the common

Table 2. Composition of a cyanoacrylate glue. Data are taken from Ref. 47.

Percentage	Ingredient
90.6	Ethyl 2-cyanoacrylate
9.0	Polymethylmethacrylate
0.4	Hydroquinone
Trace	Organic sulphonic acid

Plasticisers and thickening agents may be added

industrial and consumer grades of cyanoacrylate adhesives should be avoided because different harmful additives may be present; for instance methyl methacrylate is sometimes added to cyanoacrylate preparations to improve handling characteristics and mechanical properties. The clinical use of Eastman 910 adhesive has been banned in the United States for use in patients because of the carcinogenic properties of the methyl-acrylate group of the adhesive (146).

3. Occurrence, Production and Use

Because of their unique properties and ability to bind many different materials and to join dissimilar materials, the cyanoacrylates have found a widespread use as adhesives in many different industrial applications. Methyl and ethyl cyanoacrylates are the principal monomers used for the industrial market. There are very small differences in bonding performance between these two derivatives, although methyl cyanoacrylate generally gives stronger bonds. In certain applications on some substrates and with appropriate additives, one cyanoacrylate may be preferred to the other. Table 3 shows examples of some applications and substrates used in different industries.

Besides industrial, household, and medical use, cyanoacrylates are also used to develop fingerprints by many police forces. The item to be investigated for fingerprints is exposed to the vapour of cyanoacrylate. It polymerise selectively on the fingerprint ridges which become visible. To improve the print, it may be stained (68, 76).

In Sweden, cyanoacrylates are not produced but imported. Table 4 summarizes the types, approximate amounts, and main applications of cyanoacrylates imported to Sweden in 1993 (personal communication from Ulf Rick, Swedish National Chemicals Inspectorate). It can be seen from Table 4 that ethyl cyanoacrylate in different adhesive formulations for use in various industrial applications is quantitatively the highest.

In Norway, 2,000 kg of ethyl 2-cyanoacrylate was imported in 1994 (personal communication from Petter Kristensen, National institute of Occupational Health, Norway) and approximately 8,000 kg of ethyl 2-cyanoacrylate and less than 500 kg of methyl 2-cyanoacrylate are imported to Denmark each year (personal communication from Adolf Schaich Fries, National Institute of Occupational Health, Denmark).

Table 3. Examples of some industrial applications for cyanoacrylates. Data are taken from Ref. 152.

Industry	Applications and Substrates
Aircraft	Neoprene rubber gaskets
Appliance	Components for clothes-dryer lint switch: flexible rubber cap to acrylonitrile-butadiene-styrene (ABS) plastic housing. Automatic washing machine components: rubber boot to ceramic disk
Automotive	Flexible polyvinyl chloride (PVC) trim strips. Regulator switch Alternator components: nylon to nylon. Horn assemblies. Warning buzzer for doors: moulded nylon parts
Bicycle	Rubber grips to metal handlebars for bicycles and tricycles
Cosmetic	Eye-shadow applicator: sponges bonded to propionate and polystyrene handles. Lipstick case: plastic to metal
Electric	Regulator switch cover to switch assembly
Electronic	Components to circuit board. Magnetic amplifier: iron ferrite magnet to plastic coil
Machinery	Nitrile-rubber O-ring to brass collar. Rubber gasket to metal end cap.
Medical	Syringe: latex rubber to vinyl tube. Rubber stopper to douche bag. Blood analysis equipment: nylon to stainless steel, nylon to PVC tubing
Office equipment	Rubber stamps: fabric impregnated with neoprene rubber bonded to itself
Phonographic	Needle assembly: ABS plastic to zinc
Photographic	Film squeegee: neoprene rubber to ABS plastic
Shoe	Tennis shoe: rubber label to rubber shoe heel

Different cyanoacrylates, especially the n-butyl and isobutyl cyanoacrylates, have been extensively used and tested as a medical adhesive in many different surgical specialities. However, lack of approval from the US FDA has limited their clinical use, at least in the United States (32). In Sweden, Histoacryl (n-butyl 2-cyanoacrylate) is registered by the Medical Products Agency as a sterile single use medical device for the closure of skin wounds (personal communication, Siv Asplund Peiro, Swedish Medical Products Agency). Approximately 2,500 boxes of Histoacryl® blue (manufactured by B. Braun) tissue adhesive, each box containing 5 ampoules of 0.5 g, is sold in Sweden each year (personal communication, Johan Vejde, Cyanamid Nordiska AB).

Table 4. Type, amount, and applications of cyanoacrylates imported into Sweden in 1993 (personal communication, Ulf Rick, Swedish National Chemicals Inspectorate).

Type of Cyanoacrylate	Approximate Amount Imported (kg)	Application(s)
Methyl 2-CA[1]	500	Mainly instant glue for house-hold use.
Ethyl 2-CA	6,000	Ethyl 2-cyanoacrylate is imported in 73 different adhesive products. Most of them are manufactured by Loctite (Ireland). Its main use is in various industrial applications but it is also used as instant glue for house-hold use.
n-Butyl 2-CA	<100	As medical adhesive. Possible other unknown uses.
Methoxyethyl 2-CA	<100	Unknown use.
Ethoxyethyl 2-CA	<100	Unknown use.

[1]2-CA = 2-cyanoacrylate

4. Occupational Exposure

Reports on occupational exposure to cyanoacrylates are few. The reports published where cyanoacrylate vapours have been measured are documented in Sections 9.1 and 9.3.

5. Sampling and Analysis of Substance at Workplace

Analysis of methyl 2-cyanoacrylate vapour in workroom air is accomplished by sucking the air to be analysed through a 0.5 M sodium hydroxide/water solution at a rate of approximately 1 litre per minute. The cyanoacrylate is trapped in the solution and degraded to, among other things, formaldehyde. The formaldehyde can be quantified by the Chromotropic Acid Method and the amount and concentration of methyl 2-cyanoacrylate in the air calculated from a standard curve based on known amounts of methyl 2-cyanoacrylate. The method has adequate sensitivity, a 5-litre sample being sufficient in most cases (106). A variant of this method has later been developed with other reagents which has higher sensitivity for the detection of formaldehyde. It also includes the detection and quantification of ethyl and n-butyl cyanoacrylate vapours (166). However, the methods are not specific, i.e. formaldehyde derived from other origins than cyanoacrylate will also be detected (106, 166).

A more specific method for the analysis of airborne monomeric and polymeric ethyl 2-cyanoacrylate or methyl 2-cyanoacrylate has been developed. Air is drawn through a sampling tube containing Tenax GC to which the cyanoacrylate is absorbed. After desorption with acetone, the cyanoacrylate was analysed and quantified by gas chromatography-mass spectrometry. The method is capable of monitoring concentrations of ethyl 2-cyanoacrylate far below 0.01 mg/m^3 (50).

6. Uptake, Distribution, Biotransformation, and Elimination

Studies with humans have not been found. For animals, studies have mainly been conducted with the rat by the dermal route using several different cyanoacrylates. Studies by the inhalation route have not been found.

By the dermal route, it has been shown that the alkyl cyanoacrylates can be absorbed through intact Sprague Dawley rat skin. Ousterhout et al. (117) measured the urinary excretion of radioactivity after topical application of 3-^{14}C-labelled methyl, n-butyl, and n-heptyl 2-cyanoacrylates applied to the shaved backs of rats.

The highest amount of radioactivity recovered in the urine after five days was 12% (total radioactivity) for the methyl homologue and about 0.2% for the other two homologues. The amount recovered was increased by three- to four-hold for each homologue after application to dermatone abraded skin.

Cameron et al. (26) studied the degradation of radioactive methyl 2-cyano-acrylate-3-^{14}C implanted subcutaneously in maleWalter Reed rats. Urine and faeces were collected and analysed for radioactivity for a total of 154 days. At 154 days, 6.6% radioactivity of the administered dose remained at the implantation site and the total radioactivity excreted via the urine and faeces was 46.1 and 5.5%, respectively. Excretion was rapid for the first several weeks and then gradually levelled off. The radioactivity present in the urine was dialysable and not volatile. Radioactivity was not found at any time in the liver, kidney, spleen, brain, muscle, or fat. In a similar study conducted with male Sprague-Dawley rats using n-butyl 2-cyanoacrylate-3-^{14}C, Pani et al. (123) showed comparable results. Radioactivity was also not found in liver, kidney, spleen, brain, abdominal viscera, muscle, or fat at any time. However, at 154 days, 91.7% of the radioactivity remained at the implantation site and the total radioactivity excreted via the urine and faeces was 2.3 and 0.71%, respectively. It was concluded by the authors that the butyl polymer is very slowly degraded as compared with the methyl 2-cyanoacrylate polymer. In addition, Reynolds et al. (135) showed that methyl 2-cyanoacrylate-2-^{14}C was rapidly absorbed from a full-thickness skin incision site of white male Hartley-derived guinea pigs closed with the adhesive. The major portion of the radioactivity was eliminated in the urine and small amounts were found in the faeces, scab, and in the expired air as CO_2. Initially, at day 4 and 18, some radioactivity was detected in liver, kidney, spleen, heart, brain, and blood but at 64 days the radioactivity had returned to background levels, strongly indicating that the absorbed material is completely eliminated and

not retained in the measured tissues. After 107 days, absorption from the incision site was virtually complete. There was a rapid excretion of ether-extractable radioactive metabolites in the urine for the first 2 days, tentatively identified to have the carbon skeletons of the monomer, followed by a slower excretion of non-extractable metabolites, tentatively identified to have the carbon skeletons of dimeric methyl cyanoacrylate.

Using methyl 2-cyanoacrylate-2-^{14}C, -3-^{14}C, and -^{14}CN labelled monomers Wade and Leonard (165) investigated the urinary excretion after implantation of the adhesive subcutaneously in mongrel dogs. About 10% of the applied radioactivity was detected in the urine collected the first 3-4 days after implantation of methyl 2-cyanoacrylate-3-^{14}C. About 40% of the urine metabolites were acidic. Urea recovered from the urine of animals in which the -2^{14}C and -^{14}CN methyl 2-cyanoacrylate were implanted contained less radioactivity compared to when methyl 2-cyanoacrylate-3-^{14}C was implanted. According to the authors these findings are consistent with degradation involving random chain scission with formaldehyde production and ester hydrolysis.

Radioactive (-^{14}C) isoamyl 2-cyanoacryalte was used by Arthaud et al. (9) to investigate its biodegradability, absorption, metabolism, and elimination. No radioactivity appeared to penetrate into the skin after topical application to intact or abraded guinea pig skin followed for 14 days as observed with autoradiography. Similarly, no absorption could be detected in male Sprague Dawley rats after topical application, assessed by measuring the radioactivity in the urine and faeces for 30 days and in isolated internal organs for 14 days. Subcutaneously implanted adhesive in ARS Schmidt white mice showed a very slow biodegradation in vivo and about 98% was recovered at the implantation site after 15 days.

Both ^{14}C labelled methyl and n-butyl cyanoacrylates have been shown to be absorbed from the digestive tract in Sprague Dawley rats (118). By determinating the amount of radioactivity recovered in evaluating the urine, after ligation of the abdominal oesophagus, it was demonstrated that there is absorption of radioactivity when the monomers are applied to intact oral mucosa and allowed to polymerise. Further, when installed as the polymer powders directly into the stomach, a significant percentage of the original radioactivity was recovered in the urine. Both administration procedures gave higher values for the methyl than for the butyl homologue in concordance with their rate of degradation. It could not, however, be concluded if it was the monomer or polymer degradation products that were absorbed.

It has been stated by Kulkarni et al. (81) that about 5% of the cyano groups may be converted to thiocyanate and excreted in the urine when methyl cyanoacrylate is subcutaneously introduced in rats or dogs (species not specified). These results, however, are challenged by a later study that failed to demonstrate formation of urinary thiocyanate after oral or intraperitoneal administration of methyl cyano-acrylate to rats and dogs (79).

7. Mechanisms of Toxicity

The mechanisms responsible for the observed local toxicity of cyanoacrylate adhesives is not fully understood. It has been indicated that the histotoxicity of cyanoacrylates may be due to two factors: the heat evolved during polymerisation and the release of toxic compounds during their degradation (91, 105, 157, 171).

The heat evolved during polymerization is dependent on the amount and alkyl 2-cyanoacrylate used. Woodward et al. (171), measured the temperature rise induced by polymerization at mesenteric sites for the methyl, hexyl, and decyl 2-cyanoacrylate monomers; 0.01 ml of each was used. A mean maximal temperature rise of 4, 2, and 1.8 °C was recorded at 4, 20, and 80 minutes, respectively. Matsumoto et al. (105) recorded temperature increases between 2 to 12 °C with n-butyl cyanoacrylate applied as drops. When applied as an aerosol, temperature changes between minus 1 °C and plus 2 °C were recorded. Hida et al. (64) reported an average temperature rise of 1.5 °C on the retinal surface measured after adjacent application of 0.01 ml n-butyl cyanoacrylate. The amount of heat evolved correlates well with their observed local toxicity, i.e. the methyl homologue is the most histotoxic. Although the temperature rise appears to be small the possibility for thermal effects cannot be dismissed (64, 171). In the case of methyl 2-cyanoacrylate, prepolymerised discs implanted subcutaneously evoked an almost identical inflammatory response to that following injection of the monomer indicating that thermal effects cannot be exclusively responsible for its local toxicity (170). This view is supported by Dutton and Yates (41).

Besides thermal injuries, it has been suggested that cyanoacrylate degradation products are responsible for the toxicity. The most conceivable toxic degradation products are formaldehyde and cyanoacetate (81, 86, 91, 157, 165) but alcohols generated by hydrolysis of the ester bond have also been implicated (87, 165). Tseng et al. (157) compared the inhibition of Swiss 3T3 cell growth by microspheres of different cyanoacrylates and found a linear correlation between the extent of inhibition and the amount of formaldehyde release. Most formaldehyde was released with poly(methyl 2-cyanoacrylate) and poly(ethoxyethyl 2-cyanoacrylate). Poly(ethyl 2-cyanoacrylate) gave intermediate values whereas poly(isobutyl 2-cyanoacrylate) gave the lowest release. They concluded that cell toxicity of 2-cyanoacrylate polymers is attributed to formaldehyde release upon polymer degradation (157). On the other hand, based on the cytotoxic effects of polycyanoacrylate nanoparticles to isolated rat hepatocytes, Kreuter et al. (80) conclude that the toxicity of the nanoparticles cannot be attributed solely to formaldehyde formation during degradation. Kulkarni et al. (81) found methyl cyanoacetate to be exceedingly necrotic to rat tissues and even lethal in 1-ml doses. Lenaerts et al. (87) detected only small amounts of formaldehyde when poly(isobutyl cyanoacrylate) nanoparticles were degraded in buffer solutions at pH 7 or 12, or in the presence of various amounts of liver microsomes. Under the same conditions isobutanol production was pronounced and they concluded that ester hydrolysis with the liberation of free alcohol may be the main route for degradation.

The more intense local histotoxicity seen with short-chain alkyl cyanoacrylates, i.e. methyl and ethyl, has been attributed to their rapid degradation as compared to long-chain alkyl cyanoacrylates. This would generate a higher concentration of histotoxic degradation products locally (87, 91).

Alternatively, a direct toxic action mediated by the cyanoacrylate monomers has been suggested (4, 42, 136). This conclusion is implied from studies on cyanoacrylates mutagenic activity and bacteriotoxic effects (see Section 11).

Further, it has been suggested that the basic mechanism for cyanoacrylate induced histotoxicity is associated with the formation of reactive oxygen intermediates with enhanced formation of thromboxane and prostaglandin biosynthesis resulting in local inflammation and toxicity (124, 125, 126).

7.1 Bacteriological properties

When cyanoacrylates where first used they were believed to be "self-sterilizing" (10, 86). However, it has later been shown that both bacterial spores and bacteria are able to survive in and on cyanoacrylate adhesives (42, 113, 121). Hence, when cyanoacrylates are used as medical adhesive sterilization is necessary (62, 121).

8. Toxicology

8.1 General toxicology

The oral LD_{50} for methyl 2-cyanoacrylate in rats has been estimated to 1.6-3.2 g/kg, and the dermal LD_{50} in guinea pigs to be >10 ml/kg. An LC_{50} of 101 ppm was determined in rats exposed to methyl 2-cyanoacrylate for 6 hours (2).

Heiss (62) failed to estimate a LD_{50} value with pulverized methyl or butyl cyanoacrylate when given orally to rats. Pulverized adhesives suspended in water up to 1.4 g and 2.1 g, respectively, were tolerated; higher amounts caused vomiting. Rats injected with liquid adhesives in quantities from 0.1 to 1 ml did not show any toxic signs (62).

The acute toxicity of Aron Alpha (98% ethyl cyanoacrylate, and 2% methacrylate and hydroquinone together) was tested by intraperitoneal injections in Wistar rats (116). The animals were followed for a week. The LD_{50} was calculated and defined as 6.76 ml/kg.

Repeated inhalation of 31.3 ppm methyl 2-cyanoacrylate, 6 hours/day, 5 days/week (altogether 12 exposures) produced only a slight decrease in the rate of body weight gain in rats. Nasal or tracheal lesions and detectable systemic toxicity were not observed. Neither were changes observed in rats similarly exposed to 3.1 ppm (2).

Oral administration for 90 days of 50, 100, and 200 mg/kg/day of poly(methyl 2-cyanoacrylate) to rats and dogs did not induce any clinical changes to indicate

systemic intoxication (122). In addition, no gross or histopathological changes were observed in several organs examined which could be attributed to systemic effects induced by the oral administration.

Weaning rats were fed n-butyl 2-cyanoacrylate powder, up to 6.4 g/day, for 10 days. The rats were followed for 90 days after ingestion and showed normal weight gain. A lethal dose level was not obtained. After sacrifice, no gross or histopathological changes from ingestion of the compound were found (119).

Poly(n-butyl 2-cyanoacrylate) or poly(isobutyl 2-cyanoacrylate) nanoparticles were injected, 9.2 mg/ml suspension, in the tail vein of mice. The LD_{50} was determined to be 198 or 230 mg/kg, respectively (72). However, the carrier medium alone was also toxic (LD_{50} = 33.4 ml/kg).

In a study by Houston et al. (66) the liver function of dogs was followed for six months after a single subcutaneous dose of 400 mg/kg n-butyl 2-cyanoacrylate. At the end of the study the dogs were necropsied and histologic studies made of the vital organs. No adverse effects were noted on liver function, nor was there any apparent pathology of vital organs. This indicated to the authors that even though the polymerised material will degrade, the degradation products released do not present a toxic threat to the host.

8.2 Local toxicity in different tissues

Because the alkyl 2-cyanoacrylates polymerise in contact with and can adhere to living tissue surfaces, these adhesives have been extensively tested for tissue bonding in medicine and dentistry. However, all cyanoacrylates are more or less histotoxic and the extent of toxic reaction is dependent on the amount and nature of the cyanoacrylate applied as well as the tissue. The local irritation and histotoxicity that these adhesives induce, both in experimental animals and in humans, at the site of application in different organs and adjacent tissues has been comprehensively described for different surgical applications, e.g. vascular surgery (54, 56, 70, 108, 110), neurosurgery (65, 75, 85, 148), ophthalmology (8, 57, 82, 132, 133), otolaryngology (28, 77, 137, 146, 173), cardiovascular surgery (1), oral surgery (15, 16, 63), skin closure after surgery or injuries (51, 62, 71, 74, 155, 164), hemeostasis (29, 31), orthopaedic surgery (43, 167), urology (62, 100, 116), surgery of internal organs (52, 62, 103), female and male sterilisation (79, 92), embolization of aneurysms and atriovenous malformations (73, 107, 143, 162, 163). Poly(alkyl 2-cyanoacrylate) nanoparticles have also been used as drug carriers in drug delivery systems, e.g. for antibiotics and antitumour agents (40, 53, 69, 72). This selection of articles and reviews is by no means complete.

The histopathological findings after adhesive application are initially signs of acute inflammation and later chronic inflammation and may include: zones of necrosis, infiltrates of polymorphonuclear leucocytes, lymphocytes, histiocytes, and plasma cells, giant cells, foreign-body giant-cell reactions, connective-tissue proliferation, fibrosis, sterile abscesses, and capillary proliferation (1, 28, 62, 64, 70, 75, 85, 132, 151, 155, 170, 171). Variable amounts of residual adhesives are

frequently observed depending on tissue, time past since application, and alkyl 2-cyanoacrylate used.

A generalisation from this large number of investigations is that the short-chain alkyl cyanoacrylates elicit a more intense acute inflammatory reaction as compared to the long-chain alkyl cyanoacrylates, whereas the long-chain alkyl cyanoacrylates tend to give a more prolonged chronic inflammation due to their slower degradation. Medical application of methyl and ethyl cyanoacrylates was generally abandoned early in development of their use because of their excessive inflammatory response (19, 105). An exception is the application where sclerosing properties are required, e.g. in sterilisation (79) and endoscopic sclerotherapy of esophageal varices (149).

8.3 Peripheral neuropathy

Cyanoacrylates are histotoxic when applied directly to neural tissues (39, 65, 75, 85) as well as to other tissues (see Section 8.2). However, one case has been reported of a man with signs of peripheral neuropathy after the exposure to cyanoacrylate vapours (58). He had been exposed to multiple contacts to wood and plastic glues at his work site for more than 20 years. The patient developed a peripheral neuropathy first in his hands and then in his feet in a glove and stocking-type distribution. The symptoms experienced were exquisite pain and numbness. Metabolic parameters were normal. Vibration and pain sensation were absent distally in the extremities, bilaterally. Nerve conduction velocity studies indicated a decreased distal latency, bilaterally. The authors considered the patients symptoms to be caused by exposure to cyanoacrylate vapour (58). Information is however not documented concerning which type of cyanoacrylate he had used or the level of exposure.

8.4 Reproductive and developmental toxicity

Only one report concerning reproductive and developmental toxic properties of cyanoacrylate adhesives is available (104). This report describes the lack of effects in the second generation, followed for 6 and 12 months, of rats sprayed with butyl or isobutyl 2-cyanoacrylates on the surface of the liver (see Table 5 in Section 12).

9. Irritating and Sensitizing Properties

9.1 Irritation

In a workbench simulated exposure of 14 subjects using 1 to 60 ppm methyl 2-cyanoacrylate vapour, McGee et al. (106) reported that the odour from the adhesive is perceptible at about 1 ppm for some subjects. Throat and nasal irritation usually occurred at approximately 2 to 3 ppm and ocular irritation and burning at

approximately 4 ppm. At concentrations greater than 20 ppm, the subjects reported lacrimation and rhinorrhoea. These symptoms were pronounced at 50 to 60 ppm with indication of painful eye irritation. Two of the 14 subjects experienced blurred vision which after the exposure lasted for about two hours. The authors conclude that it seems reasonable to limit exposures to 3 ppm or less (106). Ten to 50% of attentive persons can detect the odour of 2 ppm methyl cyanoacrylate (3).

Lenzi et al. (88), however, reported symptoms of irritation at lower concentrations when studying the working conditions, during a 5-year period, in a factory for the application of pearls and stones with methyl 2-cyanoacrylate. Cases of contact dermatitis and inflammatory symptoms of nasal, pharyngal, and conjunctival mucosae were observed. The exposure to cyanoacrylate vapours was not measured but exposure in an experimental working situation was implied to be 2 mg/m^3 (0.4 ppm). The irritative manifestations of the skin and mucosae disappeared following installation of a purification system and a semi-automatic working system when observed for a two-year period. The authors believe that the exposure should not exceed 1 mg/m^3 (0.2 ppm).

Calnan (25) described an outbreak of facial irritant dermatitis from a glue, containing ethyl 2-cyanoacrylate, among a group of electronic assembly workers. It was caused by vaporisation of monomers under conditions of low relative humidity. The vapour concentration in the air was not reported. No further outbreak occurred when the humidity of the working environment was raised above 55%. The author concluded that alkyl cyanoacrylate monomers in the vapour became polymerised by the water content of the air to an inert material. This observation is in agreement with that of Lozewicz et al. (94) who reported that a woman suffering from occupational asthma due to cyanoacrylate, experienced relief of her symptoms on the days that a humidifier was operating.

The risk of occupational skin and respiratory disease from cyanoacrylates can be reduced by appropriate ventilation. In addition, it has been shown that a high relative humidity (>55%) at the workplace can decrease dermal and respiratory symptoms probably by lowering the concentration of cyanoacrylate monomers in the ambient air by initiating polymerisation (25, 94). It is also possible to lower the concentration of cyanoacrylate vapour by the installation of activated carbon filters in a ventilation system (13).

In contact with skin, methyl 2-cyanoacrylate causes mild irritation (2, 159). If large amounts of cyanoacrylates come into contact with the skin, the heat of polymerisation may cause burns (47, 171).

9.2 Skin sensitization (type IV allergy)

Skin sensitization to cyanoacrylates was long thought to be virtually impossible because of its rapid polymerisation and bonding induced by water an other nucleophilic groups present in the horny layer, e.g. amine groups on keratin. The adhesive was therefore believed never to come into contact with immunocompetent cells further down in the epidermis (25, 97). For instance, Parker and Turk (127) were unable to sensitize guinea pigs with methyl or butyl 2-cyanoacrylate using a

sensitizing protocol according to Polak et al. (129). However, in the last decade some case reports have been published which strongly indicate that cyanoacrylates are able to induce type IV allergy.

In 1984, Shelley and Shelley (144) first described a case of chronic contact dermatitis simulating small plaque parapsoriasis which was found to be due to an allergic reaction to cyanoacrylate adhesive (Krazy Glue®). The dermatitis was spread over the trunk and thighs but did not involve the nails or periungual areas. The patient used the adhesive together with teabag paper to strengthen her fingernails. A patch test to the dried adhesive gave a strong positive reaction. The patient was not sensitive to hydroquinone, acrylic monomer, or to formaldehyde, which is a degradation product of the cyanoacrylates (see Section 2.4). Four normal controls had negative patch test reactions to the adhesive. The eruptions cleared within a month after the patient stopped using the cyanoacrylate adhesive. Krazy Glue® nail preparations contain 99.95% ethyl cyanoacrylate and 0.05% undefined acrylic contaminants. It does not contain stabilizers such as hydroquinone (12). However, many cyanoacrylate adhesives contain methyl methacrylates, an established human contact allergen (46). The US FDA has consequently prohibited the use of methyl methacrylate monomer in nail preparations (45). There seems to be a lack of cross-reactions between acrylic monomer and cyanoacrylates (45, 128, 144, 153).

Later Shelley and Shelley (145) reported another case of allergic contact dermatitis in a 25-year-old woman. The patient had suffered for nearly a year with nail dystrophy and fingertip dermatitis. Careful questioning disclosed that she used cyanoacrylate adhesive (Dragon Lady Nail Glue) to attach false nails to her fingernails. Patch testing with the glue polymerised and dried 24 hours before application gave a positive reaction. After six months discontinuous use of the glue, her nails and surrounding skin were normal while still continuing to work as a hairdresser and bartender.

Pigatto et al. (128) reported that a 14-year-old boy had bilateral red, oedematous, scaly lesions on the medial surface of and behind the ears after about 20 days of applying a commonly used cyanoacrylate adhesive (ATTAK®) in an attempt to correct his flapping ears. Patch test were positive with the glue, 10% in petrolatum which was "rapidly applied". Tests with acrylic monomer, hydroquinone, and polymerized glue were negative. Ten control subjects showed negative or slightly irritant reactions. The glue applied undiluted was strongly irritant. Sertoli et al., as quoted by Pigatto et al. (128), described two women in a lamp shade factory giving similar results.

Belsito (12) reported sensitization to ethyl cyanoacrylate glue (Krazy Glue®) in three women. Pruritic eczematous eruption of the hands concentrated principally at the periungual folds and tips of the fingers were observed. In one of the patients the finger dermatitis was associated with chronic eyelid dermatitis. Two of the patients had been undergoing nail wrapping for approximately 6 months and the third patient was a manicurist who specialized in nail wrapping. All three patients were positive to open and closed patches with the glue. None were allergic to

formaldehyde. Twenty-four out of 25 normal controls gave negative reactions to open and closed patches with the glue: one person developed an irritant response to the closed patch. The authors concluded that the results strongly suggest that ethyl cyanoacrylate was the responsible allergen.

Fisher (45) described a 35-year-old woman who after using "Krazy Glue" nail preparation for three months developed painful paronychia, onychia, dystrophy, and discolouration of the nails. The patient also had an eyelid dermatitis that disappeared after she stopped using cyanoacrylate nail preparations. The "Krazy Glue" nail preparation was applied to an adhesive bandage and allowed to dry for 10 minutes and then placed on the arm for 48 hours. A positive eczematous reaction was obtained in the patient, but not in six control subjects tested.

Tomb et al. (153) reported a case of a young hairdresser who developed an occupational allergic contact dermatitis to two instant glues (DSA Bergmann® and Cyanolit®, each containing more than 99% ethyl cyanoacrylate) which she used to attach false hair. The eczematous eruption involved the fingers and face slightly but mainly the eyelids. Patch test reactions were strongly positive to both the ethyl cyanoacrylate adhesives at 1 and 5% in petrolatum. Methyl methacrylate and hydroquinone gave no reactions. Ten months after starting a new job she experienced no recurrence of the symptoms.

A 51-year-old woman was recently described by Fitzgerald et al. (48) with a 15-month history of dermatitis of the fingers, dorsa of the hands, face, including the eyelids, and large areas of the trunk. She had been working for four years as a nail technician and also applied preformed plastic nails to herself. The patient was patch test positive to High Tech Stikr Glue® (according to the manufacturer, it contains ethyl and isopropyl 2-cyanoacrylate) and to a pure sample of ethyl 2-cyanoacrylate. After wearing polypropylene gloves at work and discontinuing her own use of plastic nails the patient´s dermatitis disappeared rapidly and completely.

Finally, Bruze et al. (22) described a 38-year-old man who had worked as an apprentice cobbler for six months when he developed dermatitis on the back of his hands. The dermatitis gradually spread to the whole hands, lower arms, and abdomen. The patient was found to be positive to patch tests with an ethyl cyanoacrylate-containing glue as well as to pure ethyl cyanoacrylate. Twenty tested control subjects were negative. The authors conclude that the patient was suffering from an occupational allergic contact dermatitis and that ethyl cyanoacrylate was the causative factor. In addition, the authors discuss the possibility of false-negative reactions when patch testing with cyanoacrylates using patch test chambers of aluminium.

To summarize the information presented in this section, 12 cases are reported in the literature where cyanoacrylates are suspected or strongly suspected to be the cause of the allergic contact dermatitis. Considering the widespread industrial and domestic use of cyanoacrylates, sensitization seems to be rare, indicating that cyanoacrylates are not strong skin sensitizers. However, Bruze et al. (22) suspect that hypersensitivity to cyanoacrylates may be more common than hitherto

believed because they are neglected to be considered as possible sensitizers, they are not included in test series with other acrylics, and because of difficulties in establishing contact allergy when patch testing.

9.3 Respiratory sensitization (type I allergy) and asthma

Two health hazard evaluation reports on workers occupationally exposed to ethyl cyanoacrylates are available (83, 93).

The first was conducted at a plant with about 90 employees where a wide array of automotive products were manufactured (83). The airborne concentration of ethyl cyanoacrylate determined as two measurements at the adhesive work area was 4.6 mg/m^3 (≈1 ppm). Further details concerning these measurements were not given in the report. Sixteen workers, identified to and have worked with ethyl cyanoacrylate were selected and received a questionnaire. The cyanoacrylate workers had a higher incidence of upper respiratory symptoms as compared with five lead-exposed workers in the same plant. A number of workers described shortness of breath, often occurring in the evening or during the night, after having worked with cyanoacrylate during the day. On the basis of the data collected the authors concluded that exposure to ethyl cyanoacrylate caused acute mucosal irritation and possibly pulmonary sensitization.

The second investigation was performed at an industrial plant where industrial, home, and automotive products were manufactured (93). The facility had approximately 80 employees and ethyl cyanoacrylate was the primary chemical to which exposure was possible, but there was also concern about exposure to methyl-ethyl-ketone. The levels of ethyl cyanoacrylate vapours in the room where the glue was applicated, were measured to be from non-detectable to 1.6 mg/m^3. Further details concerning these measurements were not given in the report. A questionnaire was completed by 73 workers. Twenty-six workers were classified as symptomatic, i.e. they reported either wheezing or whistling breath, chest tightness, or shortness of breath. For 23 of these workers, a medical survey was performed. Eight workers were considered to have occupational asthma. The authors concluded that it was not possible to determine whether exposures to ethyl cyanoacrylate resulted in occupational asthma. However, they recommended that exposure to ethyl cyanoacrylate should be reduced.

Several case reports of asthma due to occupational and one to domestic exposure to cyanoacrylates have been published.

Kopp et al. (78) reported observations for a man who developed asthma due to an ethyl cyanoacrylate based glue that he used when building model aeroplanes. Typical asthma and rhinitis symptoms developed after one year of exposure. He showed a delayed onset of symptoms that were consistently related to the use of the glue. These symptoms lasted for several days after the use of the glue was discontinued. A methacholine test showed hyperreactive of the airways. Bronchial provocation to the glue vapours resulted in a late asthmatic response with rhinorrhoea and lacrimation and increased reactivity to methacholine. Avoidance of the glue resolved the patient´s asthma symptoms and a challenge to methacho-

line was negative six months later. The authors concluded that the ethyl cyanoacrylate in the glue most likely caused the patient´s late occurring asthmatic reactions and suggested that an immunological mechanism was involved.

Lozewicz et al. (94) reported five cases of occupational asthma due to cyanoacrylates, specified to be methyl cyanoacrylate in one case and ethyl cyanoacrylate in three cases. The exposure time before onset of the symptoms ranged from two weeks to one month. The symptoms were primarily coughing, rinitis, wheezing and shortness of breath. In each case, inhalation testing that mimicked exposure to cyanoacrylate exposure at the work place provoked an asthmatic reaction with a fall in FEV_1. Three of the patients showed a non-immediate (late) and two patients a dual asthmatic reaction. In three of the patients, histamine reactivity was measured before challenge with cyanoacrylate and was found to be normal. One of the patients had a humidifier installed at her place of work and an improvement of her symptoms, verified by a lower decrease in FEV_1, occurred on days when the humidifier was operating. The authors suggest that cyanoacrylates were the primary cause of asthma observed in the patients and that cyanoacrylates did not act as a non-specific provocation stimulus in individuals with hyperreactive airways.

In two companies, three cases of possible occupational asthma and rhinitis attributed to the use of ethyl cyanoacrylate containing adhesives have been reported by Roy et al. (138). In the first company, manufacturing radar detecting equipment and satellite receivers, a woman working with a gluing operation developed a chronic rhinitis, nasal itching and burning, dry irritating cough, and some chest tightness after four to five months of this work. The symptoms, except the chronic rhinitis, developed within one hour after beginning the gluing operation. After one month of being away from her job, the symptoms had completely ceased. Air sampling showed that cyanoacrylate vapours at the breathing zone of the gluing table and in the surroundings never exceeded 0.2 ppm. At the second company, manufacturing communication assemblies for full-face respirators, two women where described who developed symptoms of choking, heavy coughing, and sensation of difficulty in breathing after working with the ethyl cyanoacrylate-containing adhesive for three to five months. Symptoms appeared approximately 30 minutes after starting the gluing work and subsided within 30 minutes after they were removed from the exposure area. At this factory, the vapour concentration was not reported. The relative humidity at the two factories was 32-43, and 45%, respectively. The authors conclude that ethyl cyanoacrylate-containing glues may cause respiratory sensitization, especially under conditions of low humidity even when air levels of cyanoacrylate vapours are below occupational exposure limit recommendations.

A case of occupational asthma due to an alkyl cyanoacrylate containing glue (Aron Alpha) was described in a young woman by Nakazawa (112). Four months after starting to work with the glue she experienced sneezing, nasal discharge, coughing, stridor, and dyspnoea several hours after work. Histamine provocation indicated an increased responsiveness in her airways. Provocative exposure

testing with the glue induced immediate and delayed asthmatic responses. The author suggested the possibility of an immunological mechanism (type I allergy), but an irritant action was not excluded.

DeZotti and Larese (38) reported a case of occupational asthma due to a cyanoacrylate based glue (Loctite 406). The patient developed irritation of the skin and mucosae of the face and late bronchial asthma. The patient was patch test negative to methyl acrylate and to the glue.

More recently, 12 cases of cyanoacrylate induced asthma/respiratory disease have been reported by Savonius et al. (142). Between January 1985 and October 1991, 880 patients at the Institute of Occupational Health in Helsinki were diagnosed as having occupational asthma/respiratory disease. Of these patients, 12 (1.4%) had problems caused by cyanoacrylates. The 12 patients, one man and eleven women, worked in different industrial branches, of which the electronic industry was the largest. The exposure time before onset of the symptoms ranged from one week to 14 years. Cyanoacrylate glue, in one case specified to be methyl cyanoacrylate, was the causetive in all cases. Ten of these patients were diagnosed as having asthma and the remaining two having rhinitis and pharyngolaryngitis, respectively. Three of the patients showed immediate, three dual, and six late reactions. Attempts to prick-test three of the patients with a cyanoacrylate-albumin conjugate did not give a positive reaction. The authors concluded that to date there is no evidence for a specific IgE-mediated reaction and that an irritating mechanism cannot be excluded.

10. Long-Term Toxicity

Reports concerning the long-term toxicity of cyanoacrylates describe the local toxicity after one application of adhesive to different tissues. Depending on the amount applied, the nature of cyanoacrylate used and the tissue, variable acute and chronic inflammatory reactions are induced and remaining adhesive can be detected months or years after application (for further details see Section 8.2 and Table 5 in Section 12). No systemic toxicity from a local application has been reported.

11. Mutagenicity

Two commercial methyl 2-cyanoacrylate adhesives have been shown to be mutagenic in one (TA 100) of four tested strains of Salmonella typhimurium in the Ames test (4). The result were dose-dependent and independent of the presence of a S9 mix prepared from rat liver. No mutagenic effect was observed with the ethyl, allyl, and butyl-2 cyanoacrylate adhesives or prepolymerised methyl 2-cyanoacrylate adhesive tested in the same manner with the four Salmonella typhimurium strains (TA98, TA100, TA1535, TA1538). Methyl 2-cyanoacrylate was also mutagenic in strain TA100 in a modified Ames test for volatile com-

pounds (4). The mutagenic action of methyl 2-cyanoacrylate and its vapour on strain TA100 was later confirmed by Rietveld et al. (136) using one pure and two commercial preparations of methyl 2-cyanoacrylates. They also did not find the ethyl, isobutyl, and n-butyl derivatives tested to be mutagenic in five Salmonella typhimurium strains (TA98, TA100, TA1535, TA1537, TA1538). All the alkyl 2-cyanoacrylate adhesives tested were toxic to the bacteria with the methyl derivative being the most toxic (4, 136). In two other studies it has been reported that methyl 2-cyanoacrylate also was mutagenic in Salmonella mutagenicity studies (6, 172), strain not specified, whereas the 2-ethylhexyl-2-cyano-3,3-diphenylacrylate gave negative results.

Histoacryl® blue (n-butyl 2-cyanoacrylate) has been shown to have a weak, dose-dependent, mixed oxidase enzyme dependent mutagenic activity in one (TA 1537) of the six tested strains of Salmonella typhimurium in the Ames test (98). However, it was not established whether the mutagenicity was due to the activity of the cyanoacrylate or the blue dye or other possible additives.

Kante et al. (72) were unable to demonstrate any mutagenic activity with poly(methyl 2-cyanoacrylate) or poly(n-butyl 2-cyanoacrylate) nanoparticles in five strains of Salmonella typhimurium (TA 98, TA 100, TA 1530, TA 1535, TA 1538) in the Ames test. Both intact and degraded nanoparticles were tested, with and without metabolic activation. At higher concentrations both cyanoacrylate nanoparticles were toxic or showed an inhibitory effect on the bacteria (72). Poly(alkyl cyanoacrylate) nanoparticles has been used as drug carrier (see Section 8.2).

12. Carcinogenicity

Table 5 summarises long-term studies for carcinogenic effects of cyanoacrylates in different animal species. Of these, only four studies showed evidence of neoplastic changes.

In one study, Page et al. (120, 122) detected tumours (fibrosarcomas) in rats of both sexes, after subcutaneous injection of 0.4 ml methyl 2-cyanoacrylate; the rats were followed for up to 19.5 months. Only one suspected sarcomatous transformation was observed in another group that received 0.1 ml. In the same report, tumour formation was not observed in dogs for a 2-year observation period during which they received the same two doses of methyl 2-cyanoacrylate. In addition, one unpublished study demonstrated the carcinogenic action of methyl 2-cyanoacrylate (E J Larson, unpublished data, as quoted by Weber et al., Ref. 167) and methyl 2-cyanoacrylate was subsequently banned by the US FDA for human use.

Table 5. Summary of long-term studies with cyanoacrylate tissue adhesives.

Species and strain	Amount and administration route[1]	Duration of study	Observations at the end of study[2] and number of animals treated[3]	(Ref) Year
Methyl 2-cyanoacrylate				
Dogs Mongrel	0.1 ml or 0.4 ml, injected sc	2 years	Tumour formation or other untoward effects were not found as judged on the basis of appearance, growth, gross and microscopic examination of various tissues and organs that could be attributed to the adhesive. Lesions or persistent adhesive were not found at the site of injection in either of the two groups consisting of 8 dogs per group.	(120) (122) 1966
Rats Sprague-Dawley	0.1 ml or 0.4 ml, injected sc	up to 19.5 months	In the 0.4 ml group, fibrosarcomas were found at the site of injection in 8 out of 59 rats. In two of these rats, metastases were found in the lungs. One of the 56 rats injected with 0.1 ml adhesive showed a suspected sarcomatous transformation. Systemic effects were not observed. Except at the injection site, histopathological changes were not found in several organs examined in either of the two groups which could be attributed to the adhesive.	(120) (122) 1966
Rats Unspecified	0.01 to 0.5 ml, sc., im., or ip. in liquid, solid, or pulverized form	6 months	Initially, hard lumps of adhesive formed at the site of implantation in animals treated with 0.5 ml. These lumps gradually decreased in size. Other observations, e.g. histopathological changes, exact number of animals, were not reported.	(62) 1970
Ethyl 2-cyanoacrylate				
Rabbits Unspecified	1 drop, to glue bone graft on auricular cartilage	1 year	Three rabbits were used. Complete degradation of the polymer and fibroses at the site of application. There was no evidence for carcinogenesis. Systemic effects were not reported.	(154) 1990

Table 5. Cont.

Species and strain	Amount and administration route[1]	Duration of study	Observations at the end of study[2] and number of animals treated[3]	(Ref) Year
Butyl 2-cyanoacrylate				
Mice Walter Reed	≈0.5 ml, sprayed on the surface of the liver	12 months	Thirty mice were used. Scattered adhesions with removable polymer fragments were seen. Microscopic findings of examined liver revealed no pathological changes. Systemic effects were not reported.	(104) 1969
Dogs Mongrel	≈0.5 ml, sprayed on wounds induced on the liver, kidney, femoral artery, or small bowel	12 to 18 months	About 30 dogs were used. On the surface of the organs, polymer fragments were seen. On microscopic examination small particles of polymer were observed implanted in the tissue, surrounded by granulomatous reaction with giant cells. Changes suggestive of neoplasm were not observed. No systemic effects were reported.	(104) 1969
Dogs Mongrel	unspecified amount, sprayed onto liver wounds, ≈25 cm^2	15 to 21 months	Some animals showed sepsis at the site of application. No evidence of degradation of the polymer. No local or remote malignant changes were found. No systemic effects were reported. The exact number of animals studied was not given.	(31) 1969
Rats Walter Reed	≈0.5 ml, sprayed on the surface of the liver	12 months	Initially, 30 rats were treated. Scattered adhesions with removable polymer fragments were seen. Microscopic findings of examined liver revealed no pathological changes. No systemic effects were reported. No pathologic development was found in the second generation after 6 and 12 months.	(104) 1969
Rats Unspecified	0.01 to 0.5 ml, sc., im., or ip. in liquid, solid, or pulverized form	1.5-2 years	Local tumour formation could not be found in any of the animals at any doselevel or site of implantation. Other observations, e.g. histopathological changes, number of animals used were not reported.	(62) 1970

Table 5. Cont.

Species and strain	Amount and administration route[1]	Duration of study	Observations at the end of study[2] and number of animals treated[3]	(Ref) Year
Rats Sprague-Dawley	0.25 g used totally, drops ip, wounds made in peritoneum and skin closed with adhesive	10 to 23 months	Rats were examined after spontaneous death. Of 44 rats, 11 cases of sarcomas developed at the implantation site in peritoneum and skin. In the centre of the tumours, persistent adhesive was found. No tumours were found intraperitoneally.	(134) 1987
Rabbits Unspecified	1 drop to glue bone graft on auricular cartilage	1 year	Three rabbits were used. Some persistent adhesives with rare foreign body giant cells and fibrosis at the site of application. There was no evidence of carcinogenesis. Systemic effects were not reported.	(154) 1990
Isobutyl 2-cyanoacrylate				
Monkeys Chimpanzees	0.4 ml used to glue the ulnar nerve on the forearm	5.5 to 15 months (average 11.5 months)	Ten out of 19 deposits of adhesive in 13 animals were examined. In all cases dense connective tissue surrounding remaining fragments of adhesive was found. Microscopic examination revealed a connective tissue response and collections of leucocytes and eosinophiles. No evidence of tumour formation. Systemic effects were not reported.	(85) 1966
Monkeys Rhesus	0.2 to 0.3 ml applied onto the optic chiasm region	30 and 36 weeks	Two animals were examined. No signs of malignancy were reported. Remnants of the adhesive could be detected after 30 weeks but not after 36 weeks. Tissue injuries in the optic chiasm, the frontal lobes, and the circle of Willis could be observed.	(84) 1967
Dogs Mongrel	≈0.2 ml onto the cerebral cortex	30 and 36 weeks	Two animals were examined. No signs of malignancy were reported.	(84) 1967

Table 5. Cont.

Species and strain	Amount and administration route[1]	Duration of study	Observations at the end of study[2] and number of animals treated[3]	(Ref) Year
Dogs Mongrel	≈0.5 ml, sprayed on wounds induced on the liver, kidney, femoral artery, or small bowel	12 to 18 months	About 20 dogs were used. On the surface of the organs, polymer fragments were seen. On microscopic examination small particles of polymer were seen implanted in the tissue, surrounded by granulomatous reaction with giant cells. No changes suggestive of neoplasm were seen. No systemic effects were reported	(104) 1969
Dogs Mongrel	unspecified amount sprayed onto liver wounds, ≈25 cm^2	15 to 21 months	Some animals showed sepsis at the site of application. No evidence of degradation of the polymer. No local or remote malignant changes were found. No systemic effects were reported. The exact number of animals studied was not given.	(31) 1969
Mice Walter Reed	≈0.5 ml sprayed on the surface of the liver	12 months	Thirty mice were used. Scattered adhesions with removable polymer fragments were seen. Microscopic findings of examined liver revealed no pathological changes.	(104) 1969
Rats Walter Reed	≈0.5 ml sprayed on the surface of the liver	12 months	Initially, 30 rats were treated. Scattered adhesions with removable polymer fragments were seen. Microscopic findings of the examined livers revealed no pathological changes. No systemic effects were reported. No pathologic development was found in the second generation after 6 and 12 months.	(104) 1969
Rats Wistar	unspecified amount on Ivalon sponge implanted ip.	62 weeks	Five rats were examined. No microscopic evidence of a pathologic condition or residual adhesive material were found. Remnants of Ivalon sponge present but no foreign-body reaction could be seen. There was no evidence of any abnormalities or pathological condition associated with the use of the adhesive.	(150) 1975

Table 5. Cont.

Species and strain	Amount and administration route[1]	Duration of study	Observations at the end of study[2] and number of animals treated[3]	(Ref) Year
Rats Fischer-344	10 or 100 µl applied onto the ventral capsule of the liver	2 years	In 16% of the animals (number of animals not specified), sarcomas were observed in the abdomen. The sarcomas were attributed to a solid-state effect. A non-statistically significant increase in hepatocellular carcinomas was observed. No effect on survival, weight gain, or the clinical condition of the rats was observed.	(21) 1990
Heptyl 2-cyanoacrylate				
Dogs Mongrel	unspecified amount, sprayed onto liver wounds, ≈25 cm^2	15 to 21 months	Some animals showed sepsis at the site of application. No evidence of degradation of the polymer. No local or remote malignant changes were found. No systemic effects were reported. The exact number of studied animals was not given.	(31) 1969
Unspecified 2-cyanoacrylate				
Rats Fisher [sic]	0.120 g injected sc. at different sites	741 days	Subcutaneous, infiltrative, and unencapsulated tumours were induced in 7 out of 11 female rats at the site of injection. Histopathological examinations revealed that features of the induced tumours were consistent with those of human fibrous malignant histiocytoma. No metastatic lesions were detected.	(60) 1993

[1] sc = subcutaneously, im = intramuscular, ip = intraperitoneal. In all studies, the substances were administered once.

[2] Only observations made at the end of the studies are included, i.e. untoward effects, e.g. acute histotoxicity, inflammation, infections, foreign body giant cell reactions, observed more or less with all cyanoacrylates at shorter time periods, see Section 8.2, are not described in this Table.

[3] In several studies the exact number of animals used was not given. Where possible, the number or approximate number is given.

n-Butyl 2-cyanoacrylate was shown by Reiter (134) to induce sarcomas in Sprague-Dawley rats of both sexes. Of 44 animals, 11 cases of sarcomas developed at the implantation site. The authors conclude that the sarcomas were directly caused by the n-butyl 2-cyanoacrylate and that its use therefore should be strongly restricted in humans.

Brown and coworkers investigated isobutyl 2-cyanoacrylate in a two-year carcinogenicity bioassay in Fischer-344 rats of both sexes (21). The adhesive was administered by surgical implantation of the liquid monomer onto the ventral capsule of the liver. Two doses were used, 10 and 100 µl, respectively. A dose-related increase in the incidence of clinically observed intra-abdominal masses was observed among cyanoacrylate-treated animals of both sexes. The treatment had no effect on survival, weight gain, or clinical condition of the rats. At the end of the study, sarcomas were observed in the abdomen in 16% of the isobutyl 2-cyanoacrylate treated animals. The authors conclude that the sarcomas induced by isobutyl 2-cyanoacrylate were attributed to a solid-state effect which is not present in man. Also, a non-statistically significant increase in hepatocellular carcinomas was observed but according to the authors there was no clear evidence that this could be attributed to the isobutyl 2-cyanoacrylate implants. The report is published as an abstract in Govt Reports Announcements & Index (21).

In the fourth study by Hatanaka et al. (60), tumours were induced subcutaneously with an unspecified alkyl 2-cyanoacrylate ("which has been used as an adhesive agent") in female Fisher [sic] rats. No metastatic lesions were detected. However, metastatic lesions were observed in the lungs of syngeneic rats in which seeds of the 5th generation of tumours cells had been transplanted into subcutaneous tissues. The histopathological features of the cyanoacrylate induced subcutaneous tumours were consistent with those of malignant fibrous histiocytoma in humans. In the same study, the cyanoacrylate-induced subcutaneous tumours showed the same histopathological features as tumours induced by other foreign bodies, i.e. silicone, polyvinyl chloride, and zirconia, although Oppenheimer et al. (114) reported earlier that these foreign-body sarcomas were fibrosarcomas. The authors states that further examination is necessary to establish if tumourigenesis of the cyanoacrylates is based on their chemical character (60).

In the middle of the eighties, the US FDA was made aware of the preliminary results of a long-term study with isobutyl 2-cyanoacrylate in rats. These data strongly suggest a dose-related carcinogenic potential for isobutyl 2-cyanoacrylate in this specific animal model (14, 139, 140, 141). Subsequently, the manufacturer (Ethicon Inc.) discontinued the production of isobutyl 2-cyanoacrylate (20). It is not clear if this, at the time, unpublished study is identical to the report by Brown et al. (21)

Some investigators (14, 21, 32, 62, 154) believe that the carcinogenic properties observed with cyanoacrylates may represent an Oppenheimer effect (114), for a review of solid state carcinogenesis see Ref. 17, i.e. a solid state (foreign body)

carcinogenesis induced by any polymeric material, e.g. vinylchloride, that is not specific for the chemical nature of the polymer.

Several long term-studies have failed to show any carcinogenic properties with different cyanoacrylates in mice, rats, rabbits, dogs, and monkeys (31, 62, 84, 85, 104, 150, 154) (see Table 5).

No reports are available on the carcinogenic potential of cyanoacrylate adhesives in humans. However, considering the small amounts applied and the long time that cyanoacrylates have been tested as a medical adhesive, several researchers believe that cyanoacrylates are probably not carcinogenic in man (14, 19, 62, 107, 130).

13. Accidental Tissue-to-Tissue Bonding

Because of the rapid setting time of cyanoacrylate adhesives and their ability to glue skin and mucous membranes, all handling of cyanoacrylate containing glues involves a hazard of accidental gluing of tissue-to-tissue. Case reports describes skin adhesion (36, 96, 168), eyelid to eyelid or eyeball adhesion (37, 55, 95, 96, 99, 109, 131, 147), or adhesives on the lips and in the mouth (35). This may result in pain, corneal abrasion, punctate epithelial keropathy, conjunctival inflammation and epithelial abrasion, loss of lashes, skin excoriations, and burns. The majority of the cases of accidently installing cyanoacrylate adhesives in the eyes seems to have been caused by mistakenly using the glue instead of eye drops because of the similarities between the glue and eye drop bottles (37, 55, 95, 99, 109, 147). Generally the injuries heal without sequelae.

First aid for accidental skin, eye, and mucosal adhesion caused by cyanoacrylate adhesives has been outlined (44, 47) and include prolonged soaking in tepid/warm water and in the case of skin bonding, acetone or ethanol may be used. Bonded surfaces should never be pulled apart with force in a direct opposing action. Surgical separation is seldom required and the affected tissue surfaces usually separate on their own accord after hours or days (44, 47).

14. Dose-Effect and Dose-Response Relationships

The acute irritating effects of methyl cyanoacrylate vapours on eyes and mucous membranes in humans have been studied under experimental conditions by McGee et al. (106) (see Section 9.1). The relation between air concentration of vapours and symptoms are summarized in Table 6. To establish other dose-effect or dose-response relationships for cyanoacrylates, e.g. for skin sensitization or asthma/respiratory disease, is not possible due to difficulties in defining and quantifying the exposure in these reports (see Sections 9.2 and 9.3).

Table 6. Acute irritating dose-response relationship in 14 human volunteers exposed to methyl cyanoacrylate vapours, ranging from 1 to 60 ppm. Data are taken from Ref. 106.

Exposure[1] (ppm)	Symptom
1-5	Odour threshold
2-3	Throat and nasal irritation
4	Ocular irritation and burning
>20	Lacrimation and rhinorrhoea
50-60	Marked eye and nose irritation, indication of painful eye irritation, delayed transient blurred vision were experienced in two individuals

[1]Considerable variation between individuals exists and the stated exposure values are rough approximations of threshold values for the majority of the test subjects.

15. Previous Evaluations by (Inter)National Bodies

The American Conference of Governmental Industrial Hygienists (ACGIH) and the US Occupational Safety and Health Administration (OSHA) have established occupational exposure limits (OEL) for methyl 2-cyanoacrylate. These limits have been recommended to minimize the potential for undue irritation from methyl 2-cyanoacrylate vapours and protect exposed workers against the significant risk of nasal and eye irritation (2, 160).

US Environmental Protection Agency (EPA): EPA has added methyl, ethyl, n-butyl, and isobutyl 2-cyanoacrylate and seven additional cyanoacrylate derivatives to the Testing Priority List (158) (see Section 2.1, Table 1). This requires manufactures, importers, and processors of these substances to report unpublished health and safety data, production, use, and related data to EPA.

The Swedish National Chemicals Inspectorate has recently concluded that methyl and ethyl cyanoacrylate meet the Swedish criteria to be classified as allergenic substances (115). The conclusion is based on most of the reports accounted for in Section 9.

Handling of curable plastics, including cyanoacrylates, are in Sweden regulated by ordinance (AFS 1993:4) of the Swedish National Board of Occupational Safety and Health (5).

16. Evaluation of Human Health Risks

16.1 Groups at extra risk

Based on the data evaluated, no identification of groups or individuals at extra risk in the human population can be made.

16.2 Assessment of health risks

Besides the acute irritating properties of cyanoacrylate vapours (see Sections 9.1 and 14), there is a significant risk for cyanoacrylate induced asthma/respiratory diseases (see Section 9.3). In a study conducted at the Institute of Occupational Health in Helsinki, Savonius et al. (142) reported that cyanoacrylates were the cause of occupational asthma/respiratory disease in 1.4% of 880 patients during a seven-year period. Without knowledge of the reception area and the amount of cyanoacrylates used in Finland, no conclusions about the incidence among cyanoacrylate exposed workers can be made. The investigation, however, indicates that cyanoacrylate-induced asthma/respiratory disease may constitute a significant occupational health hazard.

Considering the few case reports published to date, skin sensitization from cyanoacrylates does not seem to constitute a major health hazard except perhaps when the purpose is to use the glue on the body (see Section 9.2). However, Bruze et al. (22) speculate that contact allergy to cyanoacrylates may be more common than hitherto believed.

Based on the data evaluated, a risk assessment for mutagenic and carcinogenic effects or peripheral neuropathy from cyanoacrylate exposure is not possible (see Sections 11, 12 and 8.3, respectively).

During the industrial use of cyanoacrylates attempts should be made to maintain the vapour levels low. However, when developing fingerprints, cyanoacrylate vapours are intentionally generated to flush the area to be investigated (see Section 3). This may constitute an occupational health hazard if the appropriate personal protection measures are not taken.

16.3 Scientific basis for an occupational exposure limit

The scientific basis for established occupational exposure limits for cyanoacrylates are the irritating properties of methyl cyanoacrylate vapours on eyes and mucous membranes. These limits are entirely based on one report by McGee et al. (106) who in a simulated workbench exposure, studied the irritating effects of methyl cyanoacrylate vapours. These dose-response relationships are summarized in Table 6. In the reports by Lee and London (83) and London and Lee (93) the measured air concentrations of ethyl cyanoacrylate were 4.6 (0.9) and 1.6 mg/m^3 (0.3 ppm), respectively, i.e. well below the recommended OEL values for methyl and ethyl cyanoacrylate (see Appendix 1). Yet, several workers experienced dermal and respiratory problems with suspected occupationally induced asthma. Roy et al. (138) reported one case of possible occupational asthma and rhinitis where the measured air concentrations of ethyl cyanoacrylate in the working area never exceeded 0.2 ppm (1.0 mg/m^3) (see Section 9.3). This indicates that respiratory hypersensitivity/asthma may be induced to a substantial extent at concentrations of ethyl cyanoacrylate well below the present OEL values for cyanoacrylates. Likewise, in the study by Lenzi et al. (88) they found dermal, eye, and respiratory symptoms of irritation in workers exposed to methyl 2-

cyanoacrylate. In an experimental working situation, they estimated the concentration of methyl cyanoacrylate vapours at work to be 2 mg/m^3 (0.4 ppm). The authors recommend that the concentration of methyl cyanoacrylate should not exceed 1 mg/m^3 (≈0.2 ppm) (see Section 9.1). If the estimation of exposure is correct, this indicates that long-term exposure to low concentrations of vapours may cause irritation.

These observations raise the question to whether the occupational exposure limits for cyanoacrylates is too high to protect exposed workers from adverse effects such as nasal and eye irritation and cyanoacrylate-induced asthma/respiratory diseases.

The most critical effects of cyanoacrylate exposure are the irritating properties of cyanoacrylate vapours on the skin and mucous membranes and their ability to induce asthma/respiratory disease.

17. Research Needs

The most obvious research need is to reexamine the irritating properties of cyanoacrylate vapours as only one such investigation was conducted in 1968.

Because present OELs do not consider adverse effects such as skin sensitization, asthma, or mutagenic and suspected carcinogenic effects, all these established and other possible adverse effects should be better elucidated and subjected to experimental as well as descriptive and analytical epidemiological research.

Future studies should also be aimed at elucidating the mechanism of cyanoacrylate-induced asthma/respiratory disease. It would be disirable if a radioallergosorbent test (RAST) for the detection of specific IgE antibodies to cyanoacrylates or adequate cyanoacrylate preparations for prick-testing were developed to aid in the elucidation of this mechanism. Such methods could also be used as diagnostic tests.

To discuss the research needs of cyanoacrylates as medical adhesive is beyond the scope of this document.

18. Summary

Montelius J. 118. Cyanoacrylates. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. *Arbete och Hälsa* 1995;25:1-48.

Cyanoacrylate-based adhesives have a widespread use in many industrial and domestic applications and have been tested as a medical adhesive. This criteria document reviews the literature on medical and toxic effects of cyanoacrylate exposure. The most apparent critical effect is the acute irritating properties of cyanoacrylate vapours on the eyes and respiratory organs. The established occupational exposure limits are based on that effect. However, cyanoacrylates have also been shown to cause skin sensitization, occupational asthma, and to be mutagenic in the Ames test. Furthermore, cyanoacrylates are suspected to be carcinogenic and to induce peripheral neuropathy. The established occupational exposure limits are discussed.

Key words: adhesive, allergy, carcinogenicity, cyanoacrylates, irritation, mutagenicity, occupational exposure limits, risk assessment, sensitization, toxicity.

19. Summary in Swedish

Montelius J. 118. Cyanoacrylater. Nordiska Expertgruppen för kriteriedokumentation av kemiska hälsorisker. *Arbete och Hälsa* 1995;25:1-48.

Cyanoakrylatbaserade limmer används inom industrin och för hushållsbruk. De har också testats som kirurgiskt klister. Detta kriteriedokument sammanfattar litteraturen om medicinska och toxiska effekter av cyanoakrylatexponering. Den mest påtagliga effekten är irritation av ögon och luftvägar av cyanoakrylatångor. De hygieniska gränsvärden som idag är satta baseras på denna effekt. Emellertid har cyanoakrylater också visats orsaka hudsensibilisering, yrkesinducerad astma samt vara mutagena i Ames test. Dessutom förmodas cyanoakrylater vara carcinogena och orsaka perifer neuropati. Nuvarande hygieniska gränsvärden diskuteras.

Nyckelord: allergi, carcinogenicitet, cyanoakrylater, hygieniskt gränsvärde, irritation, lim, mutagenicitet, riskvärdering, sensibilisering, toxicitet.

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21. Databases Used

The following databases have been used:
On-line (Medlars-at-Mic);
- Arbline
- Cancerline (NLM, via gateway)
- Medline
- Nioshtic

On-line (STN, The Scientific and Technical Information Network);
- Beilstein
- Chemical abstracts
- Registry

CD-ROM (SilverPlatter Information);
- Toxline

CD-ROM (CCINFO, Canadian Centre for Occupational Health and Safety)
- Cheminfo
- RTECS

Current Contents on Diskette
- Life Sciences

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Appendix 1.

Permitted or recommended maximum levels of Cyanoacrylates in air

Country	ppm	mg/m^3	Comments	Year	Ref.
Denmark	2	8	Methyl-2-	1994	1
	2	10	Ethyl-2-	1994	1
Finland	2	9	Methyl-2- *	1993	2
Germany	2	8	Methyl-2- S	1995	3
Iceland	2	9	Methyl-2- *	1989	4
Netherlands	2	8	Methyl-2-	1995	5
Norway	2	8	Methyl-2- S	1989	6
Sweden	2	9	Methyl-2- *	1993	7
	2	10	Ethyl-2- *	1993	7
USA (ACGIH)	2	9.1	Methyl-2- *	1995-96	8
(NIOSH)	2	8	Methyl-2- *	1994	9
(OSHA)	-	-		1994	9

* = Short-term value = 4 ppm
S = Risk for sensitization

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CRITERIA DOCUMENTS FROM THE NORDIC EXPERT GROUP

The Criteria Documents are in a Scandinavian language, with summary in English. Those marked with * are in English. Those marked with D are published in collaboration with the Dutch Expert Committee for Occupational Standards (DECOS). Those marked with N are published in collaboration with NIOSH, USA.

Acetaldehyde	Arbete och Hälsa 1986:25
Acetone	Arbete och Hälsa 1986:39
Acetonitrile	Arbete och Hälsa 1989:22, 1989:37*
Acrolein	Arbete och Hälsa 1991:45
Acrylates	Arbete och Hälsa 1983:21
Acrylonitrile	Arbete och Hälsa 1985:4
Allyl alcohol	Arbete och Hälsa 1986:8
Aluminium	Arbete och Hälsa 1992:45, 1993:1*
Ammonia	Arbete och Hälsa 1986:31
Arsenic, inorganic	Arbete och Hälsa 1981:22, 1991:9, 1991:50*
Arsine	Arbete och Hälsa 1986:41
Asbestos	Arbete och Hälsa 1982:29
Benomyl	Arbete och Hälsa 1984:28
Benzene	Arbete och Hälsa 1981:11
Boric acid, Borax	Arbete och Hälsa 1980:13
1,3-Butadiene	Arbete och Hälsa 1994:36*, 1994:42
1-Butanol	Arbete och Hälsa 1980:20
Cadmium	Arbete och Hälsa 1981:29, 1992:26, 1993:1*
7/8 Carbon chain aliphatic monoketones	Arbete och Hälsa 1990:2*D
Carbon monoxide	Arbete och Hälsa 1980:8
Chlorine, Chlorine dioxide	Arbete och Hälsa 1980:6
Chloromequat chloride	Arbete och Hälsa 1984:36
4-Chloro-2-methylphenoxy acetic acid	Arbete och Hälsa 1981:14
Chlorophenols	Arbete och Hälsa 1984:46
Chromium	Arbete och Hälsa 1979:33
Cobalt	Arbete och Hälsa 1982:16
Cobalt and cobalt compounds	Arbete och Hälsa 1994:39*
Copper	Arbete och Hälsa 1980:21
Creosote	Arbete och Hälsa 1988:13, 1988:33*
Cyanoacrylate	Arbete och Hälsa 1995:25
Cyclohexanone, Cyclopentanone	Arbete och Hälsa 1985:42
n-Decane	Arbete och Hälsa 1987:25, 1987:40*
Deodorized kerosene	Arbete och Hälsa 1985:24
Diacetone alcohol	Arbete och Hälsa 1989:4, 1989:37*
Diesel exhaust	Arbete och Hälsa 1993:34, 1993:35*
2-Diethylaminoethanol	Arbete och Hälsa 1994:25*N, 1994:42
Diethylamine, Diethylenetriamine, Dimethylamine & Ethylenediamine	Arbete och Hälsa 1994:23*, 1994:42
Diisocyanates	Arbete och Hälsa 1979:34, 1985:19
Dimethyldithiocarbamates	Arbete och Hälsa 1990:26, 1991:2*
Dimethylethylamine	Arbete och Hälsa 1991:26, 1991:50*
Dimethylformamide	Arbete och Hälsa 1982:28
Dimethylsulfoxide	Arbete och Hälsa 1991:37, 1991:50*
Dioxane	Arbete och Hälsa 1982:6

Epichlorohydrin	Arbete och Hälsa 1981:10
Ethyl acetate	Arbete och Hälsa 1990:35*D
Ethylbenzene	Arbete och Hälsa 1986:19
Ethylene bisdithiocarbamates	Arbete och Hälsa 1993:24, 1993:35*
Ethylenediamine	Arbete och Hälsa 1994:23*, 1994:42
Ethylene glycol	Arbete och Hälsa 1980:14
Ethylene glycol monoalkylethers	Arbete och Hälsa 1985:34
Ethylene oxide	Arbete och Hälsa 1982:7
Ethylene thiourea	Arbete och Hälsa 1993:24, 1993:35*
2-Ethylhexanoic acid	Arbete och Hälsa 1994:31*, 1994:42
Formaldehyde	Arbete och Hälsa 1978:21, 1982:27
Furfuryl alcohol	Arbete och Hälsa 1984:24
Gasoline	Arbete och Hälsa 1984:7
Glyoxal	Arbete och Hälsa 1995:2*
Halothane	Arbete och Hälsa 1984:17
n-Hexane	Arbete och Hälsa 1980:19, 1986:20
Hydrazine, Hydrazine salts	Arbete och Hälsa 1985:6
Hydrogen fluoride	Arbete och Hälsa 1983:7
Hydrogen sulfide	Arbete och Hälsa 1982:31
Hydroquinone	Arbete och Hälsa 1989:15, 1989:37*
Industrial enzymes	Arbete och Hälsa 1994:28*, 1994:42
Inorganic acid aerosols	Arbete och Hälsa 1992:33
Isophorone	Arbete och Hälsa 1991:14, 1991:50*
Isopropanol	Arbete och Hälsa 1980:18
Lead, inorganic	Arbete och Hälsa 1979:24, 1992:43, 1993:1*
Limonene	Arbete och Hälsa 1993:2, 1993:35*
Manganese	Arbete och Hälsa 1982:10
Mercury, inorganic	Arbete och Hälsa 1985:20
Methacrylates	Arbete och Hälsa 1983:21
Methanol	Arbete och Hälsa 1984:41
Methyl bromide	Arbete och Hälsa 1987:18, 1987:40*
Methyl chloroform	Arbete och Hälsa 1981:12
Methylcyclopentadienyl manganese tricarbonyl	Arbete och Hälsa 1982:10
Methylene chloride	Arbete och Hälsa 1979:15, 1987:29, 1987:40*
Methyl ethyl ketone	Arbete och Hälsa 1983:25
Methyl formate	Arbete och Hälsa 1989:29, 1989:37*
Methyl-t-butylether	Arbete och Hälsa 1994:22*D, 1994:42
Methyl isobutyl ketone	Arbete och Hälsa 1988:20, 1988:33*
Microorganisms	Arbete och Hälsa 1991:44, 1991:50*
Mineral fibers	Arbete och Hälsa 1981:26
Nickel	Arbete och Hälsa 1981:28
Nitrilotriacetic acid	Arbete och Hälsa 1989:16, 1989:37*
Nitroalkanes	Arbete och Hälsa 1988:29, 1988:33*
Nitrogen oxides	Arbete och Hälsa 1983:28
N-Methyl-2-pyrrolidone	Arbete och Hälsa 1994:40*, 1994:42
N-Nitroso compounds	Arbete och Hälsa 1990:33, 1991:2*
Nitrous oxide	Arbete och Hälsa 1982:20
Oil mist	Arbete och Hälsa 1985:13
Organic acid anhydrides	Arbete och Hälsa 1990:48, 1991:2*
Ozone	Arbete och Hälsa 1986:28

Paper dust	Arbete och Hälsa 1989:30, 1989:37*
Permethrin	Arbete och Hälsa 1982:22
Petrol	Arbete och Hälsa 1984:7
Phenol	Arbete och Hälsa 1984:33
Phthalate esters	Arbete och Hälsa 1982:12
Propene	Arbete och Hälsa 1995:7*
Propylene glycol	Arbete och Hälsa 1983:27
Propylene glycol ethers and their acetates	Arbete och Hälsa 1990:32*N
Propylene oxide	Arbete och Hälsa 1985:23
Refined petroleum solvents	Arbete och Hälsa 1982:21
Selen	Arbete och Hälsa 1992:35, 1993:1*
Silica, crystalline	Arbete och Hälsa 1993:2, 1993:35*
Styrene	Arbete och Hälsa 1979:14, 1990:49, 1991:2*
Sulfur dioxide	Arbete och Hälsa 1984:18
Synthetic pyretroids	Arbete och Hälsa 1982:22
Tetrachloroethylene	Arbete och Hälsa 1979:25
Thiurams	Arbete och Hälsa 1990:26, 1991:2*
Toluene	Arbete och Hälsa 1979:5, 1989:3, 1989:37*
1,1,1-Trichlorethane	Arbete och Hälsa 1981:12
Trichloroethylene	Arbete och Hälsa 1979:13, 1991:43, 1991:50*
n-Undecane	Arbete och Hälsa 1987:25, 1987:40*
Vanadium	Arbete och Hälsa 1982:18
Vinyl acetate	Arbete och Hälsa 1988:26, 1988:33*
Vinyl chloride	Arbete och Hälsa 1986:17
Welding fumes	Arbete och Hälsa 1990:28, 1991:2*
White spirit	Arbete och Hälsa 1986:1
Wood dust	Arbete och Hälsa 1987:36
Xylene	Arbete och Hälsa 1979:35
Zinc	Arbete och Hälsa 1981:13