ETHYL CYANOACRYLATE

CAS Number: 7085-85-0

NTP Nomination History and Review

NCI Summary of Data for Chemical Selection

Ethyl cyanoacrylate
7085-85-0

NTP NOMINATION HISTORY AND REVIEW

A. Nomination History

1. Source: National Cancer Institute

2. Recommendation: -Carcinogenicity (Inhalation)
-Neurotoxicity
-Reproductive and developmental effects

3. Rationale/Remarks: -Widespread use as a consumer instant adhesive
-Lack of toxicity data
-Potential biological activity

4. Priority: High

5. Date of Nomination: 5/91

B. Chemical Evaluation Committee Review

1. Date of Review:
2. Recommendations:
3. Priority:
4. NTP Chemical Selection Principles:
5. Rationale/Remarks:

C. Board of Scientific Counselors Review

1. Date of Review:
2. Recommendations:
3. Priority:
4. Rationale/Remarks:

D. Executive Committee Review

1. Date of Review:
2. Decision:

SUMMARY OF DATA FOR CHEMICAL SELECTION

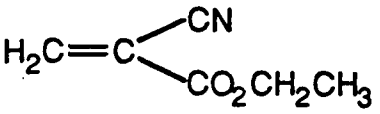
CHEMICAL IDENTIFICATION

CAS Registry Number: 7085-85-0

Chem. Abstr. Name: 2-Cyano-2-propenoic acid, ethyl ester

Synonyms & Trade Names: 910EM; ACE-EE; ACE-E 50; acrylic acid, 2-cyano-, ethyl ester; adhesive 502; Aron Alpha D; Black Max; CA 3; CA 3 (adhesive); CA 8-3A; CN 2; CN 4; Cemedine 3000RP; Cemedine 3000RP Type-II; Cemedine 3000RS; Cemedine 3000RS Type-II; Cyanobond W 100; Cyanobond W 300; Cyanolite 201; Cyanon 5MSP; DA 737S; ethyl α-cyanoacrylate; ethyl 2-cyanoacrylate; Krazy Glue; N 135; Permabond 105; Permabond 200; Permabond 268; Pro Grip 4000; PTR-E 3; PTR-E 40; Super 3-1000; Superbonder 420; Super Glue; TK 200; TK 201

Structure, Molecular Formula and Molecular Weight:



$C_6H_7NO_2$ Mol. wt.: 125.13

Chemical and Physical Properties [From Coover *et al.* (1990) unless otherwise specified]

Description: Clear, colorless liquid with a very sharp odor

Boiling Point: 54-56°C at 1.6 to 3.0 mm Hg

Solubility: Soluble in methyl ethyl ketone, toluene, acetone, nitromethane (Chou *et al.*, 1974)

Reactivity: Rapid polymerization in the presence of moisture

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Density:	1.05 g/ml
Viscosity:	13.9 cps
Flash Point:	181°F
Vapor pressure:	Calculated to be 186 at 125°C and 381 at 150°C (Coover and McIntire, 1972); <1 mbar (Loctite Corporation, 1990)
Solubility:	Soluble in methyl ethyl ketone, methylene chloride, nitromethane, and acetone (Loctite Corporation, 1987, 1989)

Move to P.1.

Technical Products and Impurities: The composition of a typical cyanoacrylate glue is 90.6% ethyl cyanoacrylate, 9.0% polymethylmethacrylate, 0.4% hydroquinone, and trace amounts of organic sulfonic acid (Fisher, 1985).

The commercial product Krazy Glue was introduced in 1973 (Anon., 1979c) and is reported to contain 99.95% ethyl cyanoacrylate and 0.05% undefined acrylic contaminants (Belsito, 1987).

The product Super Glue marketed by Loctite Corporation since December 1973 is essentially ethyl cyanoacrylate. Other companies have marketed similar cyanoacrylate adhesives under the name Super Glue, causing confusion in identifying Super Glue as the ethyl ester (Anon., 1981b; Anon., 1978).

BASIS OF NOMINATION TO THE CSWG

Ethyl cyanoacrylate was considered for nomination because of its widespread use as a consumer instant adhesive combined with a lack of toxicity data.

SELECTION STATUS

ACTION BY CSWG: 12/14/90

Studies Requested: Recommended testing for developmental and reproductive toxicity and neurotoxicity. Carcinogenicity testing by inhalation was also recommended.

Comments: Ethyl cyanoacrylate was nominated with high priority because of its widespread use as a consumer instant adhesive, the lack of toxicity data, and the potential biological activity of the compound. The market for the compound has expanded rapidly in the past few years and the uses

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are so common that virtually everyone comes in contact with a product which has been assembled with it. No information on the environmental occurrence of ethyl cyanoacrylate was found in the published literature and no standards or guidelines have been set for occupational exposures. It was felt that the most meaningful way of testing ethyl cyanoacrylate is by inhalation although it also seems to be absorbed by the dermal route. An analog, methyl cyanoacrylate, was mutagenic in a *Salmonella* strain.

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EXPOSURE INFORMATION

Commercial Availability: The ethyl cyanoacrylate adhesive products available from Permabond International are single component adhesives supplied in 3 gram, 1/3 oz., 1 oz., and 1 lb. sizes (Permabond International, 1987). A 1 pound container provides approximately 30,000 single-drop applications (Anon., 1979b).

The ethyl cyanoacrylate products available from Loctite are available in the following package sizes: 3, 20 or 200 gram metal tubes; 20 gram, 1 pound (454 grams), or 2 kilogram plastic bottle; and a 300 gram cartridge (Loctite Corporation, 1989).

The product Pro Grip 4000 is available as a 1 oz. bottle for maintenance and production applications, a 16-oz. bottle for use with automatic dispensing equipment, and a 1/3 oz. bottle which can be stored in a tool or repair kit (Anon., 1979a).

Production and Producers: Most companies market cyanoacrylate imported from Japan or sell a domestic product made by others (Anon., 1979c). There are presently two major U.S. producers: The Loctite Corporation and Permabond International, a division of National Starch and Chemical Co. (Coover *et al.*, 1990).

Cyanoacrylate adhesives have experienced rapid growth over the last 15 years. Production in North America was 0.7 million pounds in 1978 and 1.1 million pounds in 1983 (Anon., 1983b). The ethyl ester accounts for over 90% of the commercial volume (Coover *et al.*, 1990).

In 1977, 2 plants reported ethyl cyanoacrylate production of under 1,000 pounds; 2 plants reported 1,000 to 10,000 pounds; and 1 plant reported 10,000 to 100,000 pounds (TSCAPP, 1990).

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The most common manufacturing method to produce alkyl cyanoacrylates involves a condensation reaction of an alkyl cyanoacetate with formaldehyde in the presence of a base to yield a polymerized cyanoacrylate which is then depolymerized by heating to a temperature of 140-260°C and then distilling off the liquid monomer (Coover *et al.*, 1990).

Use Pattern: Cyanoacrylates are "instant" setting adhesives that bond a wide variety of substrates including metals, plastics, and elastomers. They are applied as liquids and cure within seconds to minutes at room temperature by a chemical reaction with moisture or other weakly alkaline materials to form clear, hard solids. Methyl cyanoacrylate and ethyl cyanoacrylate are the two major cyanoacrylate adhesives. In general, methyl cyanoacrylate is used to bond to metal while the ethyl cyanoacrylate is used for bonding other substrates, especially plastic (Blomquist, 1985, 1986; Helmstetter, undated, 1984).

The uses of cyanoacrylate adhesives fall into three general categories. (1) They are used as a liquid clamp for sheet metal bonding and wire tacking. (2) They are used as process aids. In manufactured items requiring gaskets, a few drops of adhesive are used to fixture the gasket so that it does not shift out of place during shipping or assembly. In the manufacture of items pressed from preimpregnated fibers, cyanoacrylates have also been used as stiffening agents for areas that were not fully compacted. (3) Cyanoacrylates are used for low stress bonding. This use covers the widest range of applications. Perhaps the single largest use is in the bonding of weatherstripping. Table 1 presents typical cyanoacrylate applications (Blomquist, 1984, 1985; Helmstetter, undated, 1986).

Some miscellaneous uses of ethyl cyanoacrylate follow.

- To affix small blocks of tissue to a slide glass during fixation, dehydration, and embedding (Kushida, 1973).

- As a fuming agent for developing latent fingerprints. The ester reacts with amino acids to form a white outline of ridge detail which is then dusted with fingerprint

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powder (Helmstetter, 1984; Warrener *et al.*, 1984; Anon., 1983a). This technique has been adapted for bloodstain analysis (Duncan *et al.*, 1986).

- For bonding neoprene rubber seals to the forward skirt of solid rocket boosters (Novak & Comer, 1990).

- For dentistry applications including implantation of teeth, cavity linings, protection of injured tissue after gingival ectomy, flap operation, and protection of exposed injured pulp tissue (Kuroda *et al.*, 1976).

Table 1. Typical Cyanoacrylate Applications

Application	Function/End Use
Consumer	Fast bonding applications
Electronics	Speaker magnet bonding, printed circuit boards, bonding small components such as phonograph needle cartridges
Automotive	Engine rubber mounting; shock absorbers; rubber bonding; attaching weatherstripping to bodies; repair of flexible PVC side trim strips; positioning rubber gaskets before assembly; bonding polycarbonate positioning clips to side windows, alternator horn assembly components, and rubber gaskets to automotive thermostats
Toys and Hobbies	Bonding parts of dolls and rubber toys, manufacture of sporting goods and toys (athletic shoes, swim masks, trophies, rubber foam recoil pads for shotguns, etc.)
Cosmetic Containers	Assembly of lipstick tubes, mirrors in compacts, eyeshadow containers, brush tips, and applicator swabs
Appliances	Attaching trim, bonding internal devices
Artificial Fingernails	Attaching
Medical (not approved in the U.S.)	Surgery as chemical sutures and hemostatic agents (used in Viet Nam)
Maintenance, repair	Metal-to-metal, rubber bonding, locking parts

From: Brief (1990); Coover *et al.* (1990)

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Between 1975 and 1989, U.S. industrial consumption of cyanoacrylate adhesives increased 500%, and consumer applications increased from 20% of total volume to over 40%. U.S. consumption of cyanoacrylates was:

Year	Consumption (million pounds)
1977	0.2
1979	0.3
1980	0.3
1982	1.0
1986	2.0
1988	1.5

Cyanoacrylates are now reaching maturity and future growth will be more moderate. Consumption is predicted to be 3.0 million pounds in 1991 (Brief, 1990; Schlechter, 1984; Anon., 1983c; Anon., 1980a; Anon., 1979c).

The cyanoacrylate glues account for 55% of the consumer adhesive market. The main applications are in arts and crafts and home repairs (Anon., 1987).

Human Exposure: The National Institute for Occupational Safety and Health surveyed two plants in which exposure to ethyl cyanoacrylate was a concern. In a plant that manufactured a wide range of industrial, home, and automotive products, the airborne concentration of ethyl cyanoacrylate ranged up to 1.6 mg/m^3. Following improvements to the work stations and ventilation system, the concentration ranged from 0.1 to 0.3 mg/m^3 with a mean of 0.2 mg/m^3 (London *et al.*, 1986). In a plant that manufactured automotive products, the airborne concentration of ethyl cyanoacrylate in the adhesive work area was 4.6 mg/m^3 (Lee & London, 1985).

The uses of ethyl cyanoacrylate are so common that virtually everyone comes in contact with a product assembled using it. In addition, consumers using the instant adhesive in arts and crafts and home repairs have frequent exposure (Coover *et al.*, 1990).

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Environmental Occurrence: No information on the environmental occurrence of ethyl cyanoacrylate was found in the published literature [see Search Resource List].

Regulatory Status: No standards or guidelines have been set for occupational exposures or environmental levels of ethyl cyanoacrylate. A similar compound, methyl cyanoacrylate, has an ACGIH threshold limit value of 8 mg/m^3 (American Conference of Governmental Industrial Hygienists, 1990).

The Ontario Ministry of Labour (1986) has recommended a working exposure guideline of 2 ppm of ethyl cyanoacrylate measured over 15 minutes.

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EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiologic studies or case reports associating ethyl acrylate with a cancer risk in humans was found in the published literature [see Search Resource List]. Allergic responses have been documented in occupational settings and in the consumer population.

Calnan (1979) described an outbreak of irritant dermatitis and eye irritation in electronic assembly workers. These effects were attributed to vapor generated under conditions of low relative humidity from an ethyl cyanoacrylate glue heated during soldering. Similarly, Lozewicz *et al.* (1985) reported that a 53-year-old solderer in an electronics factory developed an asthmatic reaction 2 weeks after starting to use an ethyl cyanoacrylate adhesive to assemble components. Occupational asthma also developed in two women who worked in a factory assembling lampshades after starting to use an ethyl cyanoacrylate adhesive.

NIOSH surveys of plants using ethyl cyanoacrylate indicate that the adhesive can cause adverse reactions. In a plant that manufactured automotive products, NIOSH determined that exposure to ethyl cyanoacrylate caused acute mucosal irritation and possible pulmonary sensitization. The airborne concentrations of ethyl cyanoacrylate in the adhesive work area was 4.6 mg/m^3 (Lee & London, 1985). In a plant that manufactured industrial, home, and automotive products using ethyl cyanoacrylate, asthmatic reactions among workers were reported. Airborne concentrations ranged up to 1.6 mg/m^3. NIOSH decided that it was not possible to determine conclusively whether exposure to ethyl cyanoacrylate resulted in the prevalence of respiratory symptoms; however, NIOSH recommended reduced exposure to ethyl cyanoacrylate (London *et al.*, 1986).

Belsito (1987) reported three cases of contact dermatitis to the ethyl cyanoacrylate-containing product Krazy Glue when used in nail salons during "nail wrapping" to create artificial nails. Patch tests with Krazy Glue were positive. Similarly, Shelley and Shelley (1984) reported chronic contact dermatitis in a woman who used Krazy Glue to strengthen her fingernails. Patch tests to Krazy Glue and to another product containing ethyl

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cyanoacrylate (5 Second Nail Glue) were positive. Kopp *et al.* (1985) reported that a 32-year-old man developed asthma 1 year after he began using an ethyl cyanoacrylate instant glue while making remote control model airplanes. The cause was attributed to vapors generated from the ethyl cyanoacrylate when using the instant glue on balsa wood.

In 1989, EPA received information from an unidentified company of possible reproductive effects due to ethyl cyanoacrylate exposure. Three mothers gave birth to premature babies after exposure to fumes of ethyl cyanoacrylate and another confidential chemical for 6 weeks during gluing operations. The women also packed large plastic auto parts after the gluing process in an adjacent area, where large pedestal fans, but not local exhaust, were provided. Two of the premature babies died and the other continued to live on life support (Anon., 1989).

Animal Data: No animal carcinogenicity tests for ethyl cyanoacrylate were found in PHS-149 or in a manual or computer search of the published literature [see Search Resource List].

An acute inhalation study submitted to the EPA/OTS by Loctite Corporation (1982) concluded that, in rats, the LC50 of ethyl cyanoacrylate is <21.11 mg/liter/hr. A group of five male and five female Wistar-derived rats were exposed for 1 hour to the product Superbonder 420 for a total dose of 1.9 grams of the test material. The estimated concentration was 21.11 mg/liter/hr. Signs of severe respiratory stress, eye irritation, and skin irritation were noted during the exposure period. Mortality was 70% within 4 days after exposure.

Evaluations of ethyl cyanoacrylate as a tissue adhesive have shown inconsistent results, but the worst cases demonstrate severe histotoxicity. Early studies indicated that ethyl cyanoacrylate was associated with little or no tissue reaction. Yodh and Wright (1967) examined the effects after topical application to the optic nerve and orbital cortex of cats and rabbits. Histological examination at 3, 6, and 12 months revealed dural and leptomeningeal fibrosis with minimal inflammation and no damage to blood vessels or

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parenchyma. These results were corroborated by Chou *et al.* (1974) who found minimal histological changes 3 years following topical application of ethyl cyanoacrylate to the cerebral cortex and femoral neurovascular bundle of cats.

Other studies, however, have demonstrated the histotoxicity of ethyl cyanoacrylate. Lehman and Hayes (1967) evaluated the effects of relatively large amounts (approximately 0.2 to 0.3 ml) of ethyl cyanoacrylate applied to the cerebral cortex of dogs and to the optic chiasm of primates. Histological examinations performed on animals sacrificed up to 12 weeks after application showed evidence of severe tissue reaction. Matsui *et al.* (1967) found that ethyl cyanoacrylate implanted subcutaneously (approximately 0.1 gram pellet) in rats elicited a chronic inflammatory reaction, possibly due to continued breakdown or release of toxic products. Diaz *et al.* (1978) studied the effects of ethyl cyanoacrylate applied to the cerebral cortex and femoral neuromuscular bundle of cats. Histological examination performed up to 14 days after application revealed acute meningeal inflammation and necrosis, neuronal and axonal degeneration, vascular wall necrosis, and thrombosis. Zumpano *et al.* (1982) studied the histotoxic effects of ethyl cyanoacrylate applied topically to the cerebral cortex of rabbits. Histological examination carried out in animals sacrificed at 4 and 10 days after application revealed extensive necrosis of the superficial cortex. Smith *et al.* (1985) examined the long-term histotoxic effects of ethyl cyanoacrylate in 25 cats injected transorbitally into the subarachnoid space in the vicinity of the right middle cerebral artery with 0.05 to 0.10 ml of adhesive. Neuropathological examination at intervals ranging from 2 days to 6 months showed marked histotoxic reaction in the meninges, brain parenchyma, and blood vessels. The major abnormalities included acute and chronic granulomatous inflammation of the meninges; severe vascular damage including vessel wall necrosis, inflammation, thrombosis and hemorrhage; and cerebral infarction. They noted that histopathological changes were irreversible for the most part and believed that the vascular damage was most likely related to a direct toxic effect of the adhesive on the blood vessel walls. McFarland *et al.* (1987) found that ethyl cyanoacrylate used to secure a silicone sled in a rabbit eye socket caused a giant-cell response. Toriumi *et al.* (1990) reported that a drop of the product Krazy Glue produced an acute

inflammatory response with a persistent foreign body reaction when used as a surgical glue in rabbit ears. Bone grafts harvested from the anterior wall of the maxillary sinus of 20 white rabbits were placed in a subcutaneous pocket and glued to the auricular cartilage with a small drop of the glue. Examination of the ears revealed a severe acute inflammatory reaction at 1 week; a less intense reaction with an intensifying foreign body giant-cell reaction at 2 weeks; decreased acute inflammation and primarily a foreign body cell reaction with inclusions of adhesive material at 1 month; viable bone grafts, decreased inflammation, a persisting foreign body giant-cell reaction, and increased fibrosis at 3 months; more fibrosis with a mild foreign body cell reaction and almost complete degradation of the glue at 6 months; and complete degradation of the glue and fibrosis at 1 year.

Short-Term Tests: Two studies have assessed the mutagenic action of ethyl cyanoacrylate in the *Salmonella*/microsome assay. Andersen *et al.* (1982) evaluated the mutagenic activity of the commercial ethyl cyanoacrylate adhesive, Cyanolite 201, in a spot test, a modified spot test designed to test volatile substances (microscope glass cover slip placed in the plate, a drop of adhesive placed on the cover slip, petri dish sealed with tape to prevent vapor escape), and in the plate incorporation assay. No significant effect was seen at doses up to 20 mg in the spot test for strains TA100, TA1535, TA98, and TA1538 with and without S9 or in the modified spot test using strain TA100 without S9. In the plate incorporation assay, the adhesive was tested at doses up to 5 mg/plate. Inhibition of background growth was detected at the higher doses; no increase was observed in the number of revertants with increase in dose.

These results were confirmed by Rietveld *et al.* (1987). They reported that 98% pure ethyl cyanoacrylate did not produce a significant increase in the number of revertant colonies when tested in the standard plate test using strains TA1535, TA1537, TA1538, TA98, and TA100 at doses up to 4000 ug/plate with or without Aroclor 1254-induced rat liver S9. Inhibition of background growth was seen at the higher doses. A modified spot test for volatile compounds using stain TA100 with or without S9 was also negative.

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Metabolism: No absorption, metabolism, or biochemical effects information on ethyl cyanoacrylate was found in the published literature [see Search Resource List]. It is possible that ethyl cyanoacrylate may be absorbed through the digestive tract. Animal experiments on polymer powders of methyl- and n-butyl-α-cyanoacrylate concluded that there is absorption of monomer and/or polymer degradation products when applied as a monomer and allowed to polymerize on the oral mucosa of rats. It was also demonstrated that if these materials in polymer form were to be inadvertently swallowed, degradation and assimilation of a significant portion of the polymer would occur (Ousterhout *et al.*, 1969). Another study demonstrated that in rats there is absorption from the intact skin and split-thickness skin graft donor sites of methyl, n-butyl-, and n-heptyl-α-cyanoacrylate (Ousterhout *et al.*, 1968)

Studies on the use of cyanoacrylate adhesives in surgery have included information on the persistence of ethyl cyanoacrylate in the body. Koltai and Eden (1983) noted that a tiny remnant of polymerized ethyl cyanoacrylate remained 60 days after application in the cat middle ear. Lehman and Hayes (1967) observed remnants of ethyl cyanoacrylate 12 weeks after application to the optic chiasm of monkeys and found it enclosed within layers of newly formed dura following application to the cerebral cortex of dogs. Toriumi *et al.* (1990) found complete degradation of ethyl cyanoacrylate (Krazy Glue) in rabbit ears after 12 months.

Several studies have investigated cyanoacrylate degradation. Cyanoacrylate *in vivo* degradation products include formaldehyde, thiocyanate, carbon dioxide, and water. The short chain compounds, such as ethyl cyanoacrylate, are eliminated more rapidly than the longer chained compounds (Coover & McIntire, 1972; Smith, 1968). Cyanoacrylates are degraded *in vitro* to formaldehyde and alkyl cyanoacrylate by hydrolysis of their polymer chains. At neutral Ph, this rate of degradation decreased as the homologous series increased, implying that as the alkyl chain increases, toxicity decreases (Leonard *et al.*, 1966; Woodward, 1965). A recent study (Tseng *et al.*, 1990) assessing the *in vitro* inhibition of Swiss 3T3 cell growth concluded that the cell toxicity of 2-cyanoacrylate polymers,

including poly(ethyl 2-cyanoacrylate), is attributed to formaldehyde released upon polymer degradation.

Data from experiments (Leonard, 1968; Cover and McIntire, 1972) on the mechanism of cyanoacrylate polymer degradation indicated that:

- Cyanoacrylate polymer degrades in the presence of distilled water with the formation of formaldehyde. An equilibrium state is reached slowly at pH 7 at 25°C but faster in neutral boiling water or in cold akaline dispersion.

- Degradation rates are faster for the short chain polymers at pH 7 but show little change between polymers in alkaline solution (pH 8), suggesting the mechanism involves an initial attack by hydroxyl ion leading to a reverse Knoevenagel reaction.

- The degradation of the polymers in solution in acetonitrile in excess water obeys first-order kinetics, indicating a pseudounimolecular reaction.

- *In vitro* hydrolytic degradation is by a chain scission mechanism.

A review by Coover and McIntire (1972) summarized the *in vivo* degradation of cyanoacrylate polymers.

- Methyl cyanoacrylate, when formed in milligram quantities in guinea pig skin, is completely metabolized and excreted in the urine and feces. When quantities up to 8 mg were used, degradation was complete within 107 days. Degradation was 50% complete within 2 days.

- Degradation of methyl cyanoacrylate from implanted Ivalon sponges was linear over 150 days. [Species not reported]

- Methyl cyanoacrylate implanted subcutaneously in rats and dogs increased thiocyanate levels in urine. It was postulated that cyanide ions were formed during degradation and converted to thiocyanate.

- Butyl cyanoacrylate degraded from implanted Ivalon sponges at a slower rate than methyl cyanoacrylate. Over 154 days, less than 10% of the butyl polymer was removed from the sponges and eliminated in urine or feces. [Species not reported]

Structure/Activity Relationships: The carcinogenicity of the butyl and isobutyl cyanoacrylate esters has been investigated. A study designed to evaluate the long-term effect of chronic intraperitoneal implantation of isobutyl cyanoacrylate in the rat indicated a dose-related carcinogenic potential (Samson & Marshall, 1986). A two-year study in rats, however, indicated that isobutyl cyanoacrylate was not carcinogenic following implantation of the liquid monomer directly into the ventral capsule of the liver. Sarcomas in the abdomen found in 16% of the animals were attributed to a solid-state effect. A nonstatistically significant increase in hepatocellular carcinomas was observed in 4 rats, but there was no clear evidence that this could be attributed to the adhesive (Brown *et al.*, 1986). Matsumoto and HeisterKamp (1969) found no evidence of tumor formation when isobutyl or butyl cyanoacrylate (0.5 ml) were sprayed into the abdominal cavity of dogs, rats, or mice. Dogs were studied up to 2 years, rats were treated at age 10 months and were sacrificed at age 22 months, and mice were studied for their lifetime. In addition, no pathological development was found in 80 rats of the second generation born from the polymer-implanted males and females. Soni *et al.* (1975) found no long-term effect of isobutyl cyanoacrylate in rats 62 weeks after an Ivalon sponge containing isobutyl cyanoacrylate was implanted intraperitoneally.

A study by Andersen *et al.* (1982) demonstrated that methyl cyanoacrylate was mutagenic in *Salmonella typhimurium* strain TA100 both with and without S9. The work of Rietveld *et al.* (1987) supported these findings. Methyl cyanoacrylate was positive in the standard plate test when tested at 10-500 ug/plate with and without S9 in strain TA100. A two-fold

increase was seen at 300 ug/plate. In addition, methyl cyanoacrylate tested positive in the NTP Ames test (NTP, 1990). A tissue adhesive, Histoacryl Blue (which chemically is N-butyl cyanoacrylate), is a weak mutagen in TA1537 in the Ames test when incubated with mixed oxidase enzymes (Marck *et al.*, 1982).

Formaldehyde, a cyanoacrylate degradation product, is classified by IARC (1987) as a probable human carcinogen based on limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animals.

IARC (1979, 1987) has evaluated two related compounds, acrylonitrile and methyl methacrylate. It is not clear whether results with these two compounds are relevant for predicting effects of ethyl cyanoacrylate. Acrylonitrile was classified as probably carcinogenic to humans (Group 2A) based on limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals, in addition to the finding that acrylonitrile is mutagenic. Methyl methacrylate was not classifiable as to its carcinogenicity (Group 3) based on a lack of human data and insufficient evidence of carcinogenicity in experimental animals.

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