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No 28

Ethyl Acrylate
CAS No. 140-88-5

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ECETOC

Joint Assessment of Commodity Chemicals No. 28

Ethyl Acrylate

CAS No. 140-88-5

September 1994

European Centre for Ecotoxicology
and Toxicology of Chemicals

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Joint Assessment of Commodity Chemicals No. 28

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ECETOC JACC Report No. 28

THE ECETOC SCHEME FOR THE JOINT ASSESSMENT OF COMMODITY CHEMICALS

This report has been produced as part of the ECETOC programme for preparing critical reviews of the toxicology and ecotoxicology of selected existing industrial chemicals.

In the programme, commodity chemicals, that is those produced in large tonnage by several companies and having widespread and multiple uses, are jointly reviewed by experts from a number of companies with knowledge of the chemical. It should be noted that in a JACC review only the chemical itself is considered; products in which it appears as an impurity are not normally taken into account.

ECETOC is not alone in producing such reviews. There are a number of organisations that have produced and are continuing to write reviews with the aim of ensuring that toxicological knowledge and other information are evaluated. Thus a Producer, Government Official or Consumer can be informed on the up-to-date position with regard to safety, information and standards. Within ECETOC we do not aim to duplicate the activities of others. When it is considered that a review is needed every effort is made to discover whether an adequate review exists already; if this is the case the review is checked, its conclusions summarised and the literature published subsequent to the review assessed. To assist ourselves and others working in this field we publish annually a summary of international activities incorporating work planned, in hand, or completed on the review of safety data for commodity chemicals. Interested readers should refer to our Technical Report No. 30 entitled "Existing Chemicals: Literature Reviews and Evaluations".

This document presents a critical assessment of the toxicology and ecotoxicology of ethylacrylate (CAS No.140-88-5). The report forms part of a series of on acrylates and methacrylates.

Ethyl Acrylate
CAS No. 140-88-5

CONTENTS

SECTION 1. SUMMARY AND CONCLUSIONS

Ethyl acrylate (EA) is an industrial chemical used in the manufacture of polymers and copolymers, which are used in a variety of products including latex paints, binders, polishes and adhesives. At room temperature it is a clear liquid with a pungent odour. Production in the USA, Western Europe and Japan was 220 kt in 1984.

Data on emissions to the environment are not available. The majority (90%) of EA released to the environment is expected to enter into the atmosphere, where its half-life is estimated to be 6.5 hours. In water, any EA which is not volatilised is expected to biodegrade readily under aerobic conditions, hydrolysis playing only a minor role. No data are available on the fate of EA in soils.

The acute toxicity of EA to aquatic organisms is > 1 mg/l, it is readily biodegradable and does not bioaccumulate. Thus EA need not be classified as dangerous to the environment according to the EC 7th amendment of Council Directive 67/548/EEC. Because of its distribution into the environment and biodegradability in aquatic systems, toxic concentrations of EA are unlikely to occur in water during normal use.

EA is irritant to the skin, eyes and mucous membranes, and may cause skin sensitisation in experimental animals and man. Cross-sensitisation may also occur to other acrylic acid esters.

Studies in experimental animals have shown that EA is of low oral and dermal toxicity, and moderately toxic via the inhalation route. The observed effects of EA are associated with local tissue damage and irritation at the site of contact. The severity of such damage is related to the concentration, duration and frequency of exposure. The absence of any observed systemic effects is consistent with absorption and metabolism studies which show that EA is rapidly absorbed and metabolised following oral or inhalation exposure. There are 2 basic metabolic pathways for EA; both are detoxifying. The first and most significant pathway is carboxylesterase hydrolysis of the ester bond, resulting in the formation of ethanol and acrylic acid, both of which are further metabolised to CO_2 (acrylic acid via the propionic acid pathway). The second and minor pathway is conjugation of EA with glutathione followed by urinary excretion as mercapturic acids.

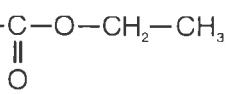
EA is not teratogenic in rats at inhalation exposure concentrations up to 150 ppm, the maximum level examined, which is toxic to the dams. There is no evidence for specific embryotoxicity or foetotoxicity at non-maternally toxic concentrations.

EA is not mutagenic to bacteria or mammalian cells *in vivo*, but has *in vitro* clastogenic activity. EA is considered not to be clastogenic *in vivo* and is expected not to be genotoxic in man.

EA does not induce tumours in dermal, inhalation and drinking water studies of experimental animals. In an oral gavage study, where EA was administered in corn oil to rats and mice for their life-time, the animals developed forestomach tumours at high doses which caused chronic inflammatory changes in the forestomach. No tumours were seen in any other organs or tissue. In a drinking water study which delivered equivalent doses at lower concentrations, neither irritation nor forestomach tumours were produced. Thus, the induction of forestomach tumours by EA in experimental animals is considered not to be relevant to human beings. Epidemiological studies showed no evidence for carcinogenic effects causally related to EA exposure. It is concluded that EA does not present a carcinogenic hazard to man.

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

2.1 IDENTITY

Name:	Ethyl acrylate
IUPAC name:	2-Propenoic acid, ethyl ester
Synonyms:	Acrylic acid, ethyl ester
D:	Ethylacrylat
	2-Propensäure, Ethyl-ester
DK:	Ethylacrylat
F:	Acrylate d'éthyle
EL:	Ακρυλικός αίθυλεστέρας
I:	Acrilato di etile
	Etile acrilato
NL:	Ethylacrylaat
ES:	Acrilato de etilo
CAS name:	2-Propenoic acid, ethyl ester
CAS registry No:	140-88-5
EEC No:	607-032-00-X
EINECS No:	205-438-8
Formula:	$C_5H_8O_2$
Molecular mass:	100.12
Structural formula:	

2.2 PHYSICAL AND CHEMICAL PROPERTIES

Ethyl acrylate (EA) is a clear, flammable liquid with a pungent, fruity odour. It is soluble in water and completely miscible with most organic solvents. Data on the physical and chemical properties of EA are given in Table 1.

A typical commercial sample of EA has a specified purity of ≥ 99.7% (w/w) and may contain the following specified impurities: water (≤ 0.05% w/w) and acid (≤ 0.01% w/w, calculated as acrylic acid) (BASF, 1988a).

EA polymerises readily under the influence of heat or light and by catalysis (e.g. metals). This is a strongly exothermic reaction. To prevent uncontrolled polymerisation, the monomer is stabilised by the addition of an inhibitor such as the monomethyl ether of hydroquinone (MeHQ) at levels of 15±5 ppm (w/w) (BASF, 1988a) (Section 3.2).

2.3 CONVERSION FACTORS

Conversion factors for concentrations of EA in air at 20°C and 1,013 hPa are:

- 1 ppm = 4.16 mg/m^3
- 1 mg/m^3 = 0.240 ppm

2.4 ANALYTICAL METHODS

2.4.1 Environmental Media

The presence of EA in air can be determined by trapping EA from gaseous samples on active carbon then desorbing with CS_2 followed by gas chromatography analysis (GC) equipped with a flame ionisation detector (FID) (White *et al*, 1970); the limit of detection is 2 mg/sample (NIOSH, 1984). Alternative GC column packings have been recommended to improve the separation of EA from other low-molecular-weight esters (Langvardt and Ramstad, 1981). Parsons and Mitzner (1975) and Pellizari *et al* (1984) replaced the active carbon trap by a tube of Tenax followed by thermal desorption before GC. Detection limits for these methods were not specified.

Table 1 Physical and Chemical Properties

Parameter, units	Value	Reference
Melting temperature, °C, approximately	-72	BASF, 1988a
Boiling temperature, °C at 1,013 hPa, approximately	100	BASF, 1988a
Heat of polymerisation, kJ/kg	655	BASF, 1988a
Relative density D_4^{20} (density of water at 4°C is 1,000 kg/m^3)	0.922 0.9224	BASF, 1988a Elf Atochem, 1990
Viscosity, mPa -s at 25°C	0.55	BASF, 1988a
Refractive index, n_D at 20°C	1.404	Elf Atochem, 1990
Vapour pressure, hPa at 20°C	38 39.2	BASF, 1988a Elf Atochem, 1990
Vapour density at 20°C (air=1)	3.5	Elf Atochem, 1990
Threshold odour concentration, ppm	0.0012 0.00047	Amoore and Hautala, 1983 Leonardos *et al*, 1969[a]
Surface tension, mN/m at 20°C	25.2	Gallant, 1958; Dauber and Danner, 1989
Solubility in water, g/kg at 25°C	15-20	Lyman *et al*, 1990; BASF, 1988a
Solubility of water in EA, g/kg at 25°C	15	Lyman *et al*, 1990; BASF, 1988a
Miscible with most organic solvents	Yes	BASF, 1988a
Fat solubility, mg/100 g at 37°C	No data	
Partition coefficient, log P_{ow} (octanol/water) at 20°C	1.33 1.18 1.28	Tanii and Hashimoto, 1982 (measured) BASF, 1988b (measured) Blum *et al*, 1991 (calculated)
Partition coefficient, log K_{oc} (organic carbon/water) at 20°C	1.32	Hansch and Leo, 1985
Henry's Law constant, Pa -m^3/mol at 20°C	25.3	Calculated
Flash point, °C, closed cup	8	BASF, 1988a
Explosion limits, % at 7-43°C	1.8-12	BASF, 1988a
Auto-flammability, ignition temperature, °C	355	BASF, 1988a

a Also cited by Stahl (1973) and Sandmeier and Kirwin (1978)

Tepikina *et al* (1988) reported a detection limit of 4 ng when trapping EA on Polysorb, then thermal desorbing and analysis by a GC/FID. Bosserman and Ketcham (1980) trapped EA on activated silica gel and desorbed it with acetone for GC with a limit of sensitivity of 0.05 ppm.

No methods are available for the determination of EA in water, soil and sediments.

2.4.2 Biological Media

A high-pressure liquid chromatography (HPLC) method for the determination of EA and its metabolites in animal tissues and urine has been described by De Bethizy *et al* (1987). No detection limit was given for this method.

SECTION 3. PRODUCTION, STORAGE, TRANSPORT AND USE

3.1 PRODUCTION

The largest volume of EA is produced commercially by catalysed esterification of acrylic acid with ethanol. Other, less widely used manufacturing processes include the reaction of acetylene with carbon monoxide and ethanol in the presence of nickel carbonyl and hydrogen chloride as catalysts.

Production in the USA, Western Europe and Japan was 220 kt in 1984 (SRI, 1987).

3.2 STORAGE

To prevent polymer formation during storage and shipping, a stabiliser such as MeHQ is added (Section 2.2). The effectiveness of phenolic inhibitors requires the presence of oxygen, and the monomer must therefore be stored in the dark, under air (not under inert gases) and at a temperature below 25°C if peroxide and polymer formation is to be minimised.

EA is normally stored or shipped in containers made of mild or stainless steel, or aluminium.

3.3 USE

EA is used to prepare homopolymers and copolymers with other monomers such as acrylic acid and its salts, amides and esters; methacrylates, acrylonitrile, maleic acid esters, vinyl acetate, vinyl chloride, vinylidene chloride, styrene, butadiene, unsaturated polyesters and drying oils. These polymers and copolymers are used in a variety of products including latex paints, binders, polishes and adhesives. As EA readily enters into addition reactions with numerous organic and inorganic compounds, it is a valuable starting product for chemical synthesis (BASF, 1988a).

The quantities of EA consumed in 1988 were 150 kt in the USA and 20 kt in Japan. The consumption in Western Europe was not reported, but was estimated to be 80 kt in 1987 (SRI, 1990).

The consumption pattern of acrylates in Western Europe in 1984 for different applications is shown in Table 2.

Table 2 Consumption Pattern of Acrylates in 1984 in Western Europe (SRI, 1990)

Application	%
Surface coatings	35 - 40
Textiles, non-wovens, leather	10 - 15
Adhesives	15
Paper coatings	15 - 20
Fibres and plastics comonomer	10
Other	10

SECTION 4. ENVIRONMENTAL DISTRIBUTION AND TRANSFORMATION

4.1 EMISSIONS

4.1.1 Emissions During Production

EA is normally manufactured in a closed plant. EA vapours from vented equipment and tanks are destroyed by flaring, as are vapours resulting from processing. Quantitive information is not available.

Waste-water produced during manufacture and processing of EA is handled in waste-water treatment plants (Section 4.3.4).

4.1.2 Emissions During Use

No data are available.

4.1.3 Natural Sources

EA occurs naturally in pineapples (Haagen-Smit *et al*, 1945), passion fruit (Toulemonde and Beauverdi, 1985) and raspberries (Randolph, 1982).

4.2 ENVIRONMENTAL DISTRIBUTION

EA can be considered to have a significant volatility from aqueous solutions (Thomas, 1982). On the basis of its solubility in water of 20 g/l, Lyman *et al* (1990) estimated a soil sorption coefficient of 19. A moderate to high mobility potential may be expected from this value.

Using the fugacity model of Mackay and Patterson (1981) a theoretical distribution can be calculated indicating that the majority (89.9%) of EA released into the environment will enter the atmosphere. Most of the remainder will be found in the water-phase, with a negligible amount in the soil (Table 3).

Table 3 Estimated Distribution Between Environmental Compartments at 20°C

Compartment	%
Air	89.9
Water	10.0
Soil	0.1
Sediment	0.0

4.3 ENVIRONMENTAL FATE AND BIOTRANSFORMATION

4.3.1 Atmospheric Fate

In the atmosphere, EA will be decomposed by photooxydation with hydroxyl radicals and tropospheric ozone.

Two rate constants for the reaction of EA with ozone have been determined experimentally, 1.96×10^{-18} cm^3/molecule/s at 25°C (Kirchner *et al*, 1976) and 5.7×10^{-18} cm^3/molecule/s (temperature not specified) (Munshi *et al*, 1989). In both cases, the ozone consumption was determined by UV absorption.

The atmospheric half-life of EA is estimated to be 6.5 h (US-EPA, 1987). Based on this very short half-life, it is concluded that EA will not reach the stratosphere and will not present any risk of ozone depletion.

4.3.2 Aquatic Fate

EA is not likely to persist in surface waters because of its ready biodegradability (J-CITI, 1992). Though soluble at ambient temperature, the Henry's Law constant indicates that EA will evaporate into the atmosphere (Table 1). The volatilisation half-life was estimated to be 5.5 hours from a model river (Lyman *et al*, 1990) and 2.4 days from a model pond with inclusion of adsorption effects (US-EPA, 1987). Some hydrolysis may occur, principally under alkaline conditions. The hydrolysis half-life was estimated to be 10.3 days at pH 9, 2.8 and 244 years at pHs 7 and 5 respectively (Mabey and Mill, 1978). The data were confirmed by Archer (1990) who found a hydrolysis half-life of 182 min at pH 11, 1.5×10^3 days at pH 7 and 6.7×10^3 days at pH 3.

4.3.3 Terrestrial Fate

Data on the fate of EA accidentally spilt on soils are not available.

In a spill-type situation EA is likely to polymerise to an innocuous resin (US-EPA, 1987). Diluted EA is unlikely to polymerise, but will evaporate into the atmosphere.

4.3.4 Biodegradation

Aerobic

In Japan, EA is classified as readily biodegradable (J-CITI, 1992). A biodegradation of more than 30% was achieved within 2 weeks in the modified MITI test (Sasaki, 1978). The BOD_5 was equivalent to 74-77% of the COD (BASF, 1986; Flaherty, 1989). This would classify EA as readily biodegradable according to the 7th amendment of Council Directive 67/548/EEC (EEC, 1992).

The biodegradability of EA (3.7 and 10 mg/l) was tested in fresh water, with adapted and non-adapted micro-organisms, and in artificial sea-water with non-adapted micro-organisms. In freshwater, the biodegradation ranged from 11% with unadapted microorganisms to 79% with adapted microrgansisms after 20 days. In sea water, a biodegradation of 53% is achieved within the same period (Price *et al*, 1974).

Anaerobic

A mixture of acetic acid and small amounts of various acrylates, including EA, was tested in 2 continuously operated, anaerobic, experimental reactors for a period of 7 days. The biodegradability of the acrylates was 100%. Methane production was not inhibited (Dohányos *et al*, 1988).

Microorganisms cultured on acetate-rich media caused 95% decomposition of EA after 110 days acclimation (Lin Chou *et al*, 1979).

Waste-water from factories producing acrylic acid-based resins, adhesives, synthetic fibres and other products, contained acrylic acid and small amounts of acetic, valeric and propionic acid as well as acrylic esters. These compounds were biodegraded to 100% over a period of 7 days (Dohanyos *et al*, 1988).

4.3.5 Bioaccumulation

The *n*-octanol/water partition coefficient (log P_{ow}) lies between 1.18 and 1.33 (Table 1), and was concluded that EA has no potential for bioaccumulation (Blum and Speece, 1991). Using the equation: log BCF = 0.76 x log P_{ow} - 0.23 (Lyman *et al*, 1990), a theoretical bioaccumulation factor of 5-6 has been estimated.

4.3.6 Evaluation

The majority (90%) of EA released to the environment is expected to enter into the atmosphere, where its half-life is estimated to be 6.5 hours. In water, any EA which is not volatilised is expected to biodegrade readily under aerobic conditions, hydrolysis playing only a minor role. No data are available on the fate of EA in soils. EA is not expected to bioaccumulate.

SECTION 5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 ENVIRONMENTAL LEVELS

5.1.1 Air

The main environmental compartment for EA is air, where its half-life is short. Ambient air monitoring data are not available.

Inside an administration building in the USA, the indoor air concentration was 0.01-0.50 ppm (Yocom *et al*, 1984).

5.1.2 Water

In one study in the USA, Kaufman (1982) found 200 mg EA/l in only 1 contaminated ground water sample. Because the site and source of the contamination were not specified, it is assumed that this figure is not typical for groundwater contamination.

5.1.3 Soil

No data available.

5.1.4 Biological Media

Foodstuffs

EA is a natural constituent of certain fruits (Section 4.1.1). It has also been detected in preserved pineapple juice (Ohta *et al*, 1987).

EA was detected in spoiled mussels at a concentration of 0.07 mg/kg (fresh weight), whereas it was not found in fresh mussels (detection limit not stated) (Yasuhara, 1987) .

EA is classified in the GRAS list (US-FDA, 1982, 1986a,b,c,d).

Other Biological Media

No data are available.

5.2 OCCUPATIONAL EXPOSURE LEVELS AND HYGIENE STANDARDS

5.2.1 Occupational Exposure

The available data on EA concentrations in workplace air are presented in Table 4.

Table 4 Concentrations in Air at the Workplace

Job category	Country	Number of samples	Concentration (ppm)	Reference
Acrylate production	Not stated	33	1-14[a]	Kuželová *et al*, 1981
Plastic manufacture	New Zealand	Unknown	2.75-155.5[b]	Jones *et al*, 1981
Paint factory - personal exposure - workplace	USA	Unknown	 <0.10-5.8 <0.11-0.54	 Belanger and Coye, 1981
Polystyrene factory[c] - personal exposure - workplace	North America	Unknown	 <0.001-0.844 <0.001-57[d]	 Samimi and Falbo, 1982

a Calculated from 4-58 mg/m^3
b Calculated from 12-670 mg/m^3
c At the monomer discharging ramp
d EA was dripping due to a leaky hose

For additional information concerning North America, see McLaughlin *et al* (1993).

5.2.2 Hygiene Standards

Most industrialised countries have adopted occupational exposure limit values (Table 5).

Table 5 Occupational Exposure Limit Values

Country	8-h TWA		STEL		Reference
	(ppm)	(mg/m^3)[a]	(ppm)	(mg/m^3)[a]	
Australia	5	20	-	-	ILO, 1991
Austria	5	20	-	-	DFG, 1992
Belgium	5	20	25	100	ACGIH, 1992
Denmark	5	20	-	-	ILO, 1991
Finland	5	20	10	40	ILO, 1991
France	5	20	-	-	INRS, 1988
Germany	5	20	-	-	DFG, 1992
Italy	5	20	-	-	ACGIH, 1992
Hungary	-	-	-	10[b]	ILO, 1991
Netherlands	-	100	-	-	Arbeidsinspectie, 1991
Norway	5	20	-	-	Arbeidstilsynet, 1990
Sweden	5	20	10	40	AFS, 1990
Switzerland	5	20	10	40	ILO, 1991
UK	5	20	15[c]	60[c]	UK-HSE, 1992
USA	5	20	15	61	ACGIH, 1992
	-	20	-	100	OSHA/NIOSH, 1986 as quoted in ILO, 1991
USSR	-	-	-	5	ILO, 1991

TWA Time-weighted average concentration (8-h working period)
STEL Short-term exposure limit (15 min, unless specified otherwise)
a Official values; some countries use different conversion factors and/or other ambient temperature
b Ceiling value
c 10 min

SECTION 6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

6.1 MICRO-ORGANISMS

In a bacteriostatic test with *Pseudomonas putida* the effect concentrations determined after 17 hours incubation at 20°C were: EC_{10} 710 mg/l, EC_{50} 1,500 mg/l and EC_{90} 2,400 mg/l (BASF, 1990).

Lin Chou *et al* (1978) investigated the effect of EA on non-adapted micro-organisms from domestic sewage sludge and showed that the addition of 500 mg EA/l caused a 50% reduction of gas production.

Blum *et al* (1991) reported a 24h-IC_{50} of 46.8 mg/l and 132 mg/l respectively for *Nitrosomas* and methanogenic bacteria.

6.2 AQUATIC ORGANISMS

In a test of the inhibition of cell division of *Scenedesmus subspicatus* the effect concentrations determined after 72 hours incubation at 20°C were: EC_{20} 30 mg/l, EC_{50} 48 mg/l and EC_{90} 120 mg/l (BASF, 1991). A 96 hour static EC_{50} of 11 mg/l was found for the algae *Seleastrenum capricornutum* Printz (Forbis, 1990).

Acute toxicity tests with EA have been performed on invertebrates and fish (Table 6).

A 14-day LC_{50} value for the guppy (*Poecilia reticulata*) is 0.74 mg/l (Hermens and Leeuwangh, 1982).

6.3 TERRESTRIAL ORGANISMS

In a 2 week test at 22-26°C, EA vapours (20 mg/2.6 l desiccator, i.e. 1,846 ppm) inhibited fungal growth on bread following inoculation with various fungal spores (Huhtanen and Guy, 1984).

Table 6 Aquatic Toxicity

Test species		Concentration (mg/l)	Reference
Crustacea	Immobilisation		
Daphnia magna	48h EC_{50}	4.4	BASF, 1988c
Daphnia magna	48h EC_{50}	7.9	Burgess, 1990
Artemia salina	24h EC_{50}	12	Price *et al*, 1974
Fish	Lethality		
Leuciscus idus	96h LC_{50}	>10-<22	BASF, 1989
Carassius auratus	72h LC_{50}	5	Paulet and Vidal, 1975
Oncorhynchus mykiss (Salmo gairdneri)	96h LC_{50}	4.6	Bowman, 1990

6.4 EVALUATION

The acute toxicity of EA to aquatic organisms is > 1 mg/l, it is readily biodegradable and does not bioaccumulate. Thus EA need not be classified as dangerous to the environment according to the EC 7th amendment of Council Directive 67/548/EEC (EEC, 1992).

Because of its distribution into the environment and biodegradability in aquatic systems, toxic concentrations of EA are unlikely to occur in water during normal use.

SECTION 7. KINETICS AND METABOLISM

7.1 ABSORPTION AND DISTRIBUTION

Absorption of EA from the gastrointestinal tract and respiratory tract is both extensive and rapid. Ghanayem *et al* (1987), for example, reported that more than 90% of ^{14}C-labelled EA in corn oil, dosed by oral gavage to F344 rats (dose 100, 200 or 400 mg/kgbw), was absorbed within 4 hours with negligible amounts of radioactivity being detected in the stomach contents 24 hours after dosing. Tissue-distribution analysis showed that at 4 hours after dosing the highest concentrations of radioactivity were in the forestomach, glandular stomach, intestine, liver and kidneys. Fractionation of the forestomach and liver showed that in the liver the highest amount of radioactivity was associated with the lipid fraction, while in the forestomach the highest percentage of EA-derived radioactivity was 'bound' to the protein. By 24 hours after dosing, the majority of the radioactivity had been cleared, although in the stomach, significant quantities were still associated with the protein fraction. No binding to nucleic acids could be detected (limit of detection 1 alkylation per 10^4 nucleotides).

Stott and McKenna (1984) demonstrated that in rats exposed 'nose-only' to an atmosphere containing 225 ppm EA, absorption reached an apparent plateau within 10 to 20 min and then remained relatively constant. Approximately 60% of the dose was absorbed through the upper respiratory tract for the duration of the study (2 h).

Absorption of EA through the skin is significantly lower than from the gastrointestinal tract or respiratory tract. Delbressine *et al* (1980), and Seuller and Rijinits (1981) have suggested that EA may be metabolised within the skin and is therefore not widely distributed. An alternative view was presented by Tomlinson *et al* (1989) who considered that the low rate of absorption was due to the rapid evaporation of EA from the skin surface (95% evaporation from a skin sample in a Franz cell held at 37°C).

The effects of absorbed EA on tissue non-protein sulphydryl groups (NPSH), an indicator of cellular glutathione (GSH), has been investigated by De Bethizy *et al* (1987). Severe dose-related depletion of NPSH was observed in the forestomachs and glandular stomachs of rats 1 hour after oral dosing with EA (20, 100 or 200 mg/kgbw in 0.5% aqueous methylcellulose). No adverse effects were noted on hepatic NPSH content. When rats were pre-treated with tri-*o*-cresyl phosphate (TOCP), a carboxylesterase inhibitor, EA produced a dramatic reduction in liver NPSH levels. These findings

serve to indicate the importance of the hydrolytic pathway for EA detoxification (De Bethizy *et al*, 1987).

7.2 METABOLISM AND EXCRETION

Metabolism of EA occurs via 2 basic pathways, hydrolysis and conjugation (Figure 1). Both pathways are detoxifying.

7.2.1 Hydrolysis

Hydrolysis of EA, catalysed by carboxylesterases, is the primary route of metabolism. The ester bond is rapidly hydrolysed, generating ethanol and acrylic acid. The acrylic acid is further metabolised to acetyl coenzyme A (acetyl-SCoA) via the propionic acid pathway (Figure 1) (De Bethizy *et al*, 1987; see also ECETOC, 1994a).

Frederick *et al* (1991) showed that EA is rapidly hydrolysed in the upper respiratory tract (Table 7).

Table 7 Hydrolysis of EA in the Upper Respiratory Tract of the Rat (Frederick *et al*, 1994)

Region	V_{max} (µmol/ml/h)	K_m (mM)	Estimated half-life (s)
Respiratory epithelium	437 ± 70	0.39 ± 0.11	0.23 ± 0.10
Olfactory epithelium (septum)	1,330 ± 180	0.38 ± 0.02	0.07 ± 0.01
Olfactory epithelium (dorsal meatus)	1,362 ± 354	0.33 ± 0.06	0.06 ± 0.01

The importance of the hydrolytic route in detoxification was demonstrated by the potentiation of both lethality and irritancy of inhaled EA following pretreatment of rats with TOCP, which inhibits esterases (Silver and Murphy, 1981). Stott and McKenna (1984) estimated that approximately 50% of the EA that passes through the upper respiratory tract will be hydrolysed by carboxylesterases before reaching the general circulation. The enzymatic hydrolysis of EA was evaluated in tissue homogenates obtained from 14 different F344 rat tissues. Carboxylesterase activity (as evidenced from V_{max}, K_m and estimated half-life) was widely distributed throughout the tissues examined with the liver showing the greatest V_{max} (Table 8).

As shown in Table 7 the hydrolytic half-life of EA in the upper respiratory tract tissues is also short; ranging from 0.06 seconds for olfactory epithelium to 0.23 seconds for respiratory epithelium (Frederick *et al*, 1991).

Figure 2 **Metabolic Pathways in Rats** (after De Bethizy *et al*, 1987)

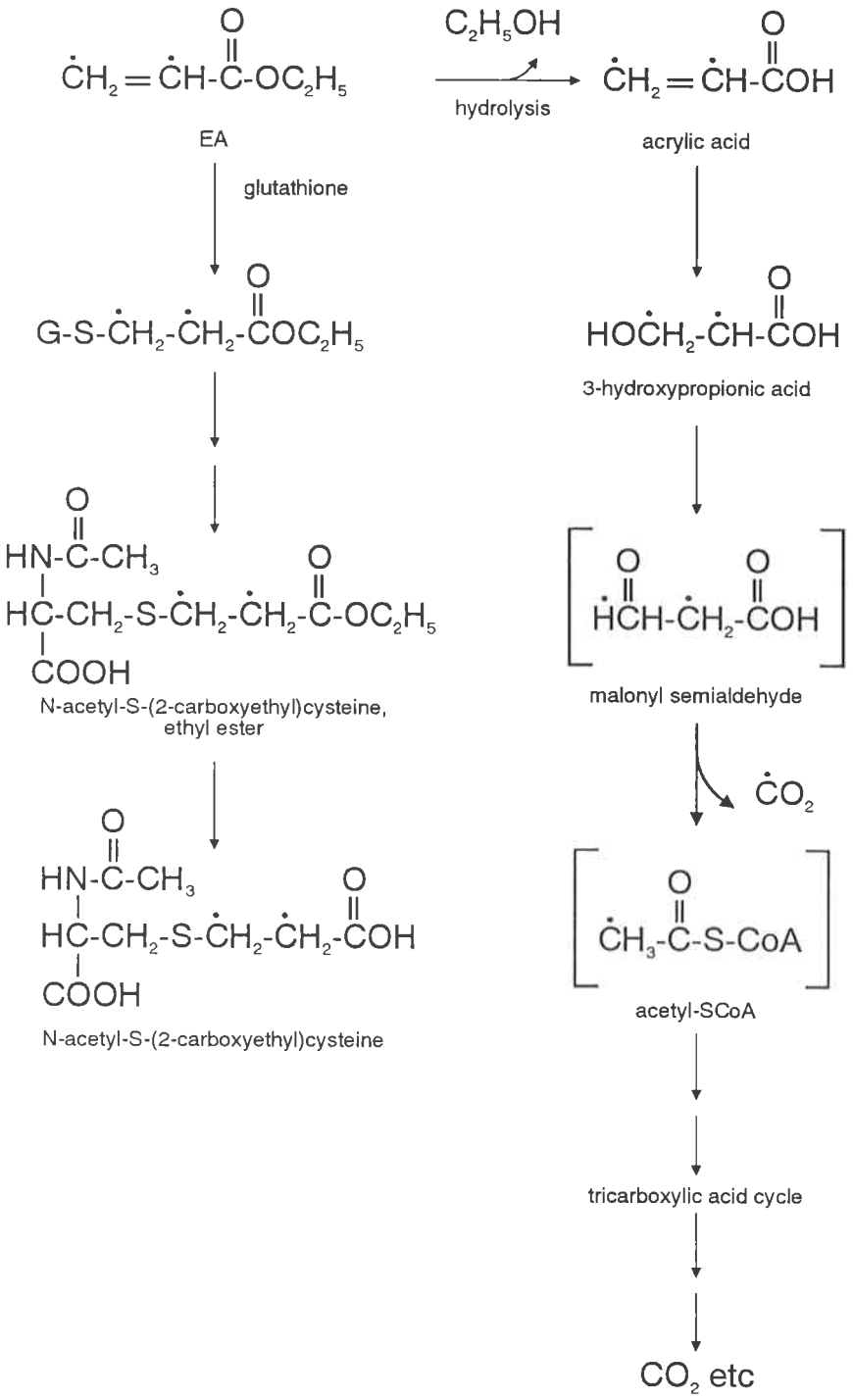


Table 8 Ester Hydrolysis of EA by Tissue Homogenates from Male F344 Rats (Frederick and Chang-Mateu, 1990)

Tissue	V_{max} (μmol[1]/ml tissue/min) mean (range)	K_m mean (range)	Estimated half-life (min)
Liver	32.2 (20.2-47.3)	1.85 (1.32-2.28)	0.04
Lung	5.8 (5.6-6.0)	2.03 (1.47-2.58)	0.24
Kidney	3.5 (2.5-5.4)	15.18 (5.0-21.1)	3.01
Skin	0.86 (0.77-0.95)	15.18 (5.44-5.46)	4.33
Muscle	0.17	4.47	17.33
Fat	1.6	5.02	2.24
Blood	0.18 (0.08-0.27)	4.60 (1.32-7.71)	17.33
Forestomach	0.26 (0.23-0.28)	3.15 (2.38-3.91)	8.66
Glandular stomach	0.32 (0.31-0.33)	4.40 (4.01-4.79)	9.90
Duodenum	0.55	8.23	9.90
Small intestine	0.67	5.21	5.33
Caecum	0.79	3.93	3.46
Large intestine	0.54	4.75	6.30
Colon	0.28 (0.27-0.28)	4.16 (2.25-7.57)	9.90

1 Acrylic acid formed

7.2.2 Conjugation

The second of the 2 pathways of EA metabolism is conjugation of the ethenyl group (CH_2=CH—) with the sulphydryl group of GSH and subsequent excretion of mercapturic acid derivatives in the urine. The reaction with GSH can occur either directly through a Michael addition reaction or enzymatically via GSH transferases.

Conjugation has been demonstrated by identification of mercapturic acid derivatives in the urine of rats (Delbressine, 1981; Delbressine *et al*, 1982), by the *in vivo* reduction of NPSH levels in tissues of experimental animals exposed to EA (De Bethizy *et al*, 1987; Frederick *et al*, 1990) and by *in vitro* binding of EA to GSH (Miller *et al*, 1981; Silver and Murphy, 1981; Tanii and Hashimoto, 1982).

Both N-acetyl-S-(2-carboxyethyl)cysteine and its cysteine, ethyl ester have been detected in the urine of rats dosed with EA. The presence of N-acetyl-S-(2-carboxyethyl)cysteine is thought to

occur via de-esterification of its cysteine, ethyl ester, rather than by reaction of acrylic acid with GSH (De Bethizy *et al*, 1987; Frederick and Reynolds, 1989).

The relationship between glutathione conjugation and the detoxification of EA has been the subject of a number of studies. Silver and Murphy (1981) demonstrated that the lethality of EA increased in animals pretreated with TOCP. This increased lethality corresponded to a decrease in NPSH levels in the lungs, liver, blood, and kidneys and was correlated with the histopathological changes (Pozzani *et al*, 1949; US-NTP, 1983; De Bethizy *et al*, 1987; Frederick and Chang-Mateu, 1990). De Bethizy *et al* (1987) found a linear depletion of the NPSH content of the forestomach following oral doses of 0-20 mg EA/kgbw. Doses of EA that essentially depleted the forestomach NPSH content, produced little effect on hepatic NPSH level. The dose-effect curves of NPSH content of the stomach paralleled the excretion of the sulphydryl derivatives of EA in the urine, suggesting that at low concentrations, the primary site of metabolism is the tissue at the dosing site. Inhibition of carboxylesterases had no significant effect on the EA induced depletion of forestomach NPSH, but produced significant EA induced reductions in hepatic NPSH. The authors conclude that the rodent stomach is a unique tissue as carboxylesterase hydrolysis of EA does not compete effectively with sulphydryl depletion.

7.2.3 Other Possible Metabolic Pathways

EA contains an ethenyl group and it is theoretically possible that epoxidation of this group could occur during metabolic transformation. No evidence has been found for the presence of epoxidation products, namely 2,3-epoxypropionic acid, N-acetyl-S-(2-carboxy-2-hydroxyethyl)cysteine and its ethyl ester, in the urine of rats dosed with EA (Delbressine *et al*, 1982; De Bethizy *et al*, 1987). Furthermore, these metabolites were not found when EA was incubated with 'fortified' rat liver microsomes *in vitro* (De Bethizy *et al*, 1987). Therefore, it is concluded that it is unlikely that the ethenyl group of EA will be epoxidised *in vivo*. Further studies (Frederick *et al*, 1989; Udinsky and Frederick, 1989; Frederick and Chang-Mateu, 1990) indicate that EA induced changes in the rat forestomach only after marked (>75%) depletion of NPSH. In contrast, the same dose of EA did not cause NPSH depletion or changes in the glandular stomach or liver.

7.2.4 Binding to Protein

The direct Michael addition of EA with GSH suggests that it may be able to react with sulphydryl groups in proteins. Ghanayem *et al* (1987) found radioactivity tightly associated with the protein fraction of the forestomachs and livers of rats dosed with ^{14}C-labelled EA (Section 7.1). EA is rapidly metabolised to C_1 and C_2 fragments that freely enter the normal synthetic pathways of the

cell (Figure 1). Thus, while the presence of radioactivity could indicate direct alkylation, it may also indicate metabolic incorporation.

7.3 SUMMARY AND EVALUATION

EA is rapidly absorbed and metabolised following oral or inhalational exposure. There are insufficient data to draw any conclusion on absorption and metabolism following dermal exposure.

In common with the other simple acrylate esters, there are 2 basic metabolic pathways for EA, both are detoxifying. The first and most significant pathway is carboxylesterase hydrolysis of the ester bond, resulting in the formation of ethanol and acrylic acid, both of which are further metabolised to CO_2 (acrylic acid via the propionic acid pathway). In the nasal mucosa, EA is rapidly hydrolysed ($t_{1/2}$ = 0.23 s) to acrylic acid and ethanol, effectively limiting transport of EA from the mucosa into the circulatory system. This, coupled with its relatively rapid half-life in the lung ($t_{1/2}$ = 0.24 min, 14.4 s) may explain why, following inhalation of non-saturating doses, EA would not reach levels where systemic toxicity would be expected.

The second and minor pathway is conjugation of EA with GSH which occurs either spontaneously (Michael addition) or catalysed by GSH transferases. The mercapturic acid derivatives, with or without hydrolysis of the ester link, are rapidly excreted in the urine. There is no evidence for the formation of an epoxide or any other toxic metabolites. The ubiquitous distribution of carboxylesterases, glutathione and its transferases together with non-protein sulphydryl groups (NPSH) groups is likely to prevent or limit the entry of EA into the systemic circulation and internal organs.

SECTION 8. EFFECTS ON EXPERIMENTAL ANIMALS AND *IN VITRO* TEST SYSTEMS

8.1 ACUTE TOXICITY

8.1.1 Oral

Acute oral LD_{50} values are detailed in Table 9.

Table 9 Acute Oral Toxicity

Species	LD_{50} (g/kgbw)	Reference
Rat	1	Pozzani *et al*, 1949 ; Paulet and Vidal, 1975
Rat	0.55 (approximately)[1]	Oettel and Hofmann, 1958
Rat	0.5-5.0	Rohm and Haas, 1984
Mouse	1.8	Tanii and Hashimoto, 1982
Mouse	1.3	Rohm and Haas, 1950
Rabbit	1.8	Tanii and Hashimoto, 1982
Rabbit	0.37 (approximately)[1]	Oettel and Hofmann, 1960
Rabbit	0.28[2]	Treon *et al*, 1949

1 Calculated from ml/kgbw
2 Minimum lethal dose

Based on the available data on acute oral toxicity (Table 9), EA is classified as harmful (LD_{50} 0.2-2 mg/kgbw) in accordance with the 7th amendment of Council Directive 67/548/EEC (EEC, 1992).

Rats dosed orally with EA exhibited 'sluggishness, prostration and narcosis prior to death' (Pozzani *et al*, 1949) or slight tumbling and prone position after 24 hours (Oettel and Hofmann, 1958a). Rats that received a single oral dose of EA in corn oil exhibited signs of general depression and severe gastric irritation (Rohm and Haas, 1984).

Female rabbits dosed with EA exhibited 'lethargy and distention of the veins in the ears soon after dosing followed by running movements of the legs, tremors, spasms of the diaphragm, laboured respiration, cyanosis and reduced body temperature'. All animals treated with EA died within 12

hours after dosing (Treon *et al*, 1949). In rabbits treated at lethal concentrations, atonia, prone and side position shortly before death were seen (Oettel and Hofmann, 1960).

Cats exhibited salivation and vomiting within 10 minutes after gavage (Oettel and Hofmann, 1960).

Clinical observations were not reported in the other studies shown in Table 9.

8.1.2 Dermal

Acute dermal LD_{50} values are detailed in Table 10.

Table 10 Acute Dermal Toxicity

Species	Application	LD_{50} (g/kgbw)	Reference
Rat	Occlusive	2-5	Rohm and Haas, 1986a
Rat	Unocclusive	>5	Rohm and Haas, 1986b
Mouse	Occlusive	2-5	Rohm and Haas, 1986c
Mouse	Unocclusive	>5	Rohm and Haas, 1986d
Rabbit	Unocclusive	1.8[1]	Pozzani *et al*, 1949

1 Calculated from ml/kgbw

No lethality was observed in rabbits following 3 or 24 occlusive dermal applications within 1-2 days (at intervals of 10 or 20 minutes, total exposure time 1 or 4 hours) using undiluted EA (total dose 5.4 or 40.7 g/kgbw). Conversely, all rabbits which received 30 or 38 applications within 1 day (at intervals of 5 or 10 min, total exposure time 5 or 6 h) using undiluted EA (total dose 49.8 or 69.1 g/kgbw) died within 16 hours of treatment. At necropsy, local reddening, oedema, necrosis and inflammation of the skin were observed; the heart, liver and kidneys showed hyperaemia and tissue degeneration, and the lungs hyperaemia and oedema (Treon *et al*, 1949).

EA was applied for 24 hours under occluded or unoccluded conditions to groups of mice and rats. No significant clinical signs were observed during the 14 day observation period and no gross changes were observed at necropsy in either mice or rats treated under unoccluded conditions at 5g EA/kgbw. Under occluded conditions both the mice and rats exhibited signs or general depressed activity, erythema, oedema, blanching and eschar (Rohm and Haas, 1986a,b,c,d).

8.1.3 Inhalation

Acute inhalation LC_{50} values are detailed in Table 11, while lethality data from acute inhalation studies from which LC_{50} values cannot be calculated are presented in Table 12.

Table 11 Acute Inhalation Toxicity

Species	Time (h)	LC_{50} (ppm)	Reference
Rat	4	>1,500	Silver and Murphy, 1981
Rat	4	2,180	Oberly and Tansy, 1985
Rat	Not specified	1,800[1]	Lomonova and Klimova, 1979
Mouse	Not specified	3,890[1]	Lomonova and Klimova, 1979

1 Calculated from 7,500 mg/m^3 and 16,200 mg/m^3

Oberly and Tansy (1985) reported that rats exposed to EA via inhalation exhibited signs of respiratory irritation progressing to dyspnoea, convulsions, sedation and death secondary to anoxia.

Table 12 Acute Inhalation Lethality Data

Species	Time	Concentration (ppm)	Deaths/ animals used	Reference
Rat	5 min	50,000	0/6	Pozzani *et al*, 1949
	15 min	50,000	6/6	
	4 h	1,000	0/6	
	4 h	2,000	5/6	
	4 h	4,000	6/6	
Rat	4 min	Saturated 20°C	0/6	Oettel and Hofmann, 1958
	8 min	Saturated 20°C	2/6	
	15 min	Saturated 20°C	6/6	
Guinea pig	7 h	1,204	2/2	Treon *et al*, 1949
Rabbit	7 h	1,204	4/4	Treon *et al*, 1949

Signs of EA toxicity and findings at necropsy were reported as agitation, dyspnoea, irritation to eyes and nose, hyperaemia and haemorrhages in the lungs. These findings were attributed to the irritant effect of EA (Pozzani *et al*, 1949; Treon *et al*, 1949; Oettel and Hofmann, 1982). In the studies of Treon *et al* (1949), all animals died and exhibited the following clinical signs prior to death: coughing, hiccoughing, salivation, rale, conjunctival and nasal irritation, prostration, ataxia, convulsive movements, spasmodic respiration and diarrhoea.

Concentration-related decreases in respiratory frequency, tidal volume, and rectal temperature were seen in rats exposed to EA at concentrations of 100, 200, 300, and 500 ppm. Pretreatment with the carboxylesterase inhibitor TOCP (which decreases the enzymatic hydrolysis of the ester, thereby increasing the effective concentration of ester in the tissues) enhanced the toxic effects (Silver *et al*, 1981).

8.1.4 Summary

Acute toxicity studies in experimental animals show that EA is of low oral and dermal toxicity, and moderately toxic via the inhalation route. The main signs of toxicity and gross-pathological findings are consistent with the local irritant and corrosive effects.

8.2 IRRITATION AND SENSITISATION

8.2.1 Skin irritation

Single exposures (4 h) of rabbit skin to EA under occluded conditions produced severe erythema and oedema. Pocketing oedema and/or erythema with eschar, sloughing and scar formation persisted for 2 weeks after exposure (Bernacki and Hamilton, 1991). Unoccluded application of EA to the skin of rabbits produced only 'minor injection of capillaries' in 2 out of 5 treated animals and no reaction in the other 3 animals (Pozzani *et al*, 1949).

Undiluted EA (0.2 ml/kgbw) was tested for its irritating effect on the skin of 2 rabbits under occluded conditions following the method of Hill. Exposures for 1, 5 and 15 min induced acute inflammation of the skin in the form of a cushion-like oedema and formation of crust and superficial scar. Similar symptoms occurred after 20 hour exposure. After a 3 week recovering period, no skin damage was seen (Oettel and Zeller, 1958).

Occlusive treatment of the skin of rats with EA for 24 hours resulted in severe erythema, pocketing oedema, eschar and desiccation (Rohm and Haas, 1986a). Unoccluded treatment produced only slight transient erythema (Rohm and Haas, 1986b).

Occlusive application of EA to the skin of mice produced severe erythema, moderate oedema, eschar and blanching of the skin (Rohm and Haas, 1986c), whereas unocclusive application produced no irritation (Rohm and Haas, 1986d).

Occlusive applications (multiple times/d) of EA to rabbit skin for 1-2 days resulted in inflammation of varying severity, intense oedema and in some instances haemorrhagic areas (Treon *et al*, 1949). Repeated applications of EA also resulted in marked hyperaemia, haemorrhage and ulceration (Lomonova and Klimova, 1979). The paper also reports toxicological studies in mice, rats and rabbits, but it is not clear to which species these effects relate.

8.2.2 Respiratory Irritation

Rats and mice were exposed to EA at 25 or 75 ppm for 27 months, or 225 ppm for 6 months, and then held for an additional 21 months. The animals developed concentration-related histopathological changes in the olfactory epithelium of the nasal turbinates, including nasal cell hyperplasia, increased intraepithelial glands, respiratory metaplasia, diffuse atrophy and multifocal mineralisation. Exposure to 225 ppm resulted in clinical signs indicative of irritation and aggression at the start of each 6 hours exposure period and signs of lethargy at the end of the exposure period (Miller *et al*, 1985).

Rabbits, guinea pigs, rats and monkeys were exposed (7 h/d) to EA at increasing concentrations. Exposure to concentrations of 24 to 75 ppm for 50 to 130 days showed no signs of irritation. Exposure to 272 ppm for 28 days produced varying degrees of irritation, including slight salivation, slight conjunctivital and nasal irritation, lethargy and diarrhoea in rats, moderate gasping in guinea pigs, moderate conjunctivital and nasal irritation, lethargy, gasping and convulsive movements in rabbits, and slight irritation of mucous membranes and slight lethargy in a monkey. When the exposure concentrations were increased to 501 or 1,204 ppm, the severity of the respiratory and sensory irritation also increased. The respiratory effects at the highest concentrations were altered by the effects of hypoxia resulting from compromised respiratory function (Treon *et al*, 1949).

Single exposure (4 h) of rats to EA at 1,538 to 3,001 ppm produced signs of irritation of the eyes, nose and respiratory tract including laboured breathing, blanching of the ears and paws, and death (Oberly and Tansy, 1985).

Single exposure (approximately 5 min) of mice to EA at 315 ppm produced a 50% reduction in the breathing rate (RD_{50}) (De Ceaurriz *et al*, 1981).

8.2.3 Gastrointestinal Tract Irritation

Oral administration of EA (dissolved in propylene glycol; dose 180-940 mg/kgbw) to rabbits produced severe local irritation of the gastrointestinal tract (Treon *et al*, 1949).

EA (0.1-4% in corn oil) was administered orally (estimated dose 7-270 mg/kgbw) to starved male Charles-River-strain F344/DU Crj rats for 18 hours. The animals were killed 3 hours later. Forestomach oedema and relative weight had increased in proportion to the EA dose. This effect was not found in the glandular stomach (Morimoto *et al*, 1990). An increase in the weight of the forestomach following administration of EA (4% in 0.5% aqueous methyl cellulose) to male Sprague-Dawley rats was also reported by De Bethizy *et al* (1987).

Single administration by gavage of EA (2, 4 or 8% dissolved in corn oil at a constant volume of 5 ml/kgbw, equivalent to doses of 100, 200 or 400 mg EA/kgbw) to male F344 rats resulted in dose- and concentration-dependent oedema of the mucosa and the submucosa, vacuolation of the muscular coat in the forestomach and oedema of the submucosa in the glandular stomach. There was also an increase in the forestomach-weight/body-weight ratios. The changes were detectable after 2 hours and were pronounced after 8 and 24 hours (Ghanayem *et al*, 1985a).

Single doses of EA (200 mg/kgbw), ethyl propionate (saturated analogue; 204 mg/kgbw) and ethyl methacrylate (corresponding methacrylic ester; 228 mg/kgbw) were administered by gavage to groups of male F344 rats. The rats produced gastric effects only with EA. In an aqueous suspension EA was more irritating than in corn oil. The authors discussed the role of a C_2-C_3 double bond, an ester group and an unsubstituted C_2 for gastric irritation. They concluded that the hydrolysis products of EA, acrylic acid and ethanol are not responsible for the gastric effects (Ghanayem *et al*, 1985b).

The incidence of oedema in the forestomach increased when male F344 rats pretreated with cysteine or cysteamide (sulphydryl containing chemicals) were given orally doses of EA (dissolved in corn oil; 100, 200 and 400 mg EA/kgbw). In contrast, pretreatment with diethyl-maleate or by fasting gave significant protection against EA-induced forestomach oedema. The authors were unable to provide an explanation (Ghanayem *et al*, 1991a,b).

The correlation between glutathione depletion in the forestomach and gastric toxicity was also demonstrated by Frederick *et al* (1990). The quantitative correlation of glutathione induction to labelling index in the rat forestomach was further explored by Gillette and Frederick (1993). This study demonstrated that the severe glutathione depletion in the forestomach resulting from a high dose of EA was followed by a prolonged S-phase induction of epithelial cells in the tissue. By contrast, the glandular stomach, which does not exhibit histopathological indications of toxicity, did not have severe glutathione depletion and only a transient S-phase response. A combined time-course dose-response labelling index study following two weeks of gavage dosing of EA indicated

that a clear threshold in the induction of S-phase activity was observed at 10 mg/kg (0.2 % dosing solution).

8.2.4 Eye irritation

Severe necrosis was observed within 24 hours after application of 0.5 ml of EA to the cornea of rabbit eyes; 0.1 ml produced moderate necrosis under the same conditions (Pozzani *et al*, 1949). No detectable ocular effects occurred following inhalation exposure of rats to EA at 75 ppm for 27 months (Miller *et al*, 1985).

One drop of undiluted EA placed into the conjunctival sac of one eye of each of 2 rabbits produced pronounced reddening and slight cloudiness of the cornea. After 1 day, one rabbit exhibited no adverse reaction to treatment whereas a slight reddening was observed in the eye of the other. After 3 days, no effects could be observed in either animal (Oettel and Zeller, 1958).

8.2.5 Skin Sensitisation

Parsons and Baldwin (1981), using a Buehler protocol modified for 9 induction doses, showed that EA sensitised guinea pigs. In a comparative study, guinea pigs were only sensitised to EA with Freund's Complete Adjuvant (Van der Walle *et al*, 1982b).

Guinea pigs sensitised to EA exhibited cross-sensitisation to challenges with *n*-butyl, *t*-butyl, pentyl, neopentyl, and *n*-hexyl acrylates, but not to the corresponding methacrylates (Van der Walle and Bensink, 1982). Polymerisation inhibitors were not responsible for these cross-reactivities (Van der Walle *et al*, 1982a).

Applications of up to 5% EA were negative in the murine local lymph node assay (Kimber, 1992).

8.2.6 Summary

EA is irritant to the skin, eyes, gastrointestinal tract and respiratory tract of experimental animals at low exposure concentrations. These irritant effects are seen only at the site of first contact, even at high exposure concentrations. EA can produce allergic dermatitis in guinea pigs and may cross-react with other acrylic esters. Although the data are equivocal and variable, it may be concluded that EA does not have a strong sensitising potential.

8.3 SUBCHRONIC TOXICITY

8.3.1 Oral

Groups of F344 rats received EA (dissolved in corn oil) by gavage at a constant volume of 5 ml/kgbw (equivalent to doses of 0, 2, 10, 20, 50, 100, or 200 mg EA/kgbw/d) for 5 or 10 days. Dose-related gastric irritation developed after 5 or 10 days of treatment at doses of 20 mg/kgbw/d and above. No signs of systemic toxicity were detected at any dose (Rohm and Haas, 1986).

The toxicity of EA has been examined in two 14-day gavage studies using F344 rats and $B6C3F_1$ mice (5/sex/group). In the first study, EA was administered as a solution in aqueous ethanol to rats (dose levels 0, 55, 110, 225, 450 or 900 mg EA/kgbw/d) and mice (0, 25, 55, 110, 225, or 450 mg EA/kgbw/d). In the second study, EA was administered as a solution in corn oil to rats and mice (dose levels 0, 100, 200, 400, 600 or 800 mg EA/kgbw/d). In either study, the principal toxic effect of EA was confined to the forestomach of both sexes and species, and there was no evidence of systemic toxicity. In the first study, all rats of the 450 mg/kgbw/d group died within 24 hours. All rats receiving 225 or 450 mg/kgbw/d, 1 female rat of the 110 mg EA/kgbw/d group and 8 or 9 mice receiving 450 mg/kgbw/d (1 mouse of this group died) had thickened necrotic mucosa in the forestomach. No histopathological examinations were performed in the first study. In the second study, using corn oil as the vehicle, the histological lesions of the forestomach included ulceration, inflammation, hyperplasia and hyperkeratosis. The LOEL for histological changes in the forestomach was 400 mg EA/kgbw in the rat and 200 mg EA/kgbw in the mouse (US-NTP, 1986).

A third 14-day study, using drinking water as the exposure vehicle, was poorly conducted and because of severe technical problems, including instability of EA in the drinking water, it is not considered further (US-NTP, 1986).

EA (dissolved in corn oil) was administered by gavage to mice (dose levels 0, 1.5, 3, 6, 12 or 25 mg EA/kgbw/d and 0, 12, 25, 50 or 100 mg EA/kgbw/d) and rats (0, 7, 14, 28, 55 or 110 mg EA/kgbw/d) for 103 weeks. In the 2 mouse studies were there no treatment-related effects on gross or microscopic examination. In the rat study, macroscopic effects were restricted to the top dose group, including reddening of the duodenum (1 male) and dilation of the blood vessels in the cardiac region of the stomach (2 males). There were no compound-related signs of toxicity and no histopathological changes could be attributed to the treatment.

The histopathological and biochemical response of the stomach of male F344 rats (10/group) was examined following oral dosing with EA (dissolved in corn oil) for 2 weeks. The rats were treated

with EA by either gavage (0, 2, 10, 20, 50, 100 or 200 mg EA/kgbw/d) or via their drinking water (0, 23, 99, 197 or 369 mg EA/kgbw/d). Rats dosed by gavage showed histopathological changes of the forestomach characterised by focal epithelial cell hyperplasia, hyperkeratosis, subacute to chronic submucosal inflammation, submucosal oedema and ulceration/erosion. The lesions had increased in incidence and severity over the 20-200 mg EA/kgbw/d dose range. The NOEL for histopathological effects was between 10 and 20 mg EA/kgbw/d. In contrast, rats dosed with EA via their drinking water showed much lower incidences of forestomach effects at corresponding doses, the NOEL being between 23 and 99 mg/kgbw. Non-protein sulphydryl group (NPSH) content of the forestomach, glandular stomach and liver were measured between 2 to 24 hours after the last gavage dose. The data showed, that 6 hour after the final treatment the NPSH levels in the forestomach of rats dosed at 200 mg EA/kgbw/d were 90% lower than the untreated controls. Rats receiving a corresponding dose in their drinking water showed no reduction in forestomach NPSH levels. The authors concluded that bolus dosing of EA produced severe depletion of NPSH in the forestomach with resulting histopathological lesions (Frederick *et al*, 1990). The 2 week dose-response studies with EA in rats were followed by 90-day gavage and drinking water dosing studies (Frederick and Chang-Mateu, 1990) that indicated that there was no progression of the lesions in the forestomach. These studies confirmed hyperkeratosis and hyperplasia at gavage doses of > 100 mg/kg and a NOEL at 10 mg/kg.

When EA (dissolved corn-oil) was administered by gavage to rats (10/sex/group) at doses of 0-110 mg EA/kgbw/d and mice (2 x 10/sex/group)at 0-100 mg EA/kgbw/d; no compound-related gross or microscopic pathological effects were seen in any of the tissues examined including the forestomach (US-NTP, 1986).

8.3.2 Inhalation

Sherman albino rats (10/sex/group) and albino rabbits (4 males/group) were exposed to atmospheres containing EA at concentrations of 0 and 540 ppm (7 h/d, 5 d/wk) for a maximum of 19 days. At 540 ppm, 13 out of 19 rats died by day 19 and the study was terminated. Histopathological examination of the lungs of the rats that had died revealed 'pneumonic involvement'. These changes were usually accompanied by cloudy swelling of the renal tubules and occasionally by congestion and cloudy swelling of the liver. The cause of death of the 13th rat could not be ascertained due to severe autolysis of the tissues before autopsy. The lungs of 5 of the 6 surviving rats showed 'incipient pneumonic involvement' but no renal or hepatic effects. The other surviving rat had normal lungs and light cloudy swelling of the liver. The authors concluded that the renal and hepatic effects might be an effect secondary to the effect observed in the lungs.

All 4 rabbits exposed to EA at 540 ppm died within 2 days, while 2 of the 4 rabbits in the control group died within 30 days (Pozzani *et al*, 1949).

Sherman albino rats (15/sex/group) and albino rabbits (9 males/treatment group; 8 controls) were exposed (7 h/d, 5 d/wk) to EA at 0, 70 or 300 ppm for a maximum of 30 days. Eighteen of the 30 rats exposed to EA at 300 ppm died during the 30-day exposure period. Ten of these rats exhibited the same pneumonic, kidney and liver effects as observed in the rats exposed to 540 ppm (above). Five of the rats exhibited congestion of the lungs, cloudy swelling and congestion of the liver and excessive pigmentation of the spleen. The tissues of the other 3 rats that had died prior to the end of the study could not be used due to autolysis. Most (9 of 12) surviving rats showed no tissue changes, the remaining 3 rats exhibiting only minor histological alterations of the lung or the liver. Rats exposed to EA at 70 ppm showed no differences from control group animals except for an increase in the kidney weight of male rats. Histopathological examination revealed no abnormalities. All 9 rabbits exposed to EA at 300 ppm died within 7 days; 8 rabbits had 'catarrhal pneumonic involvement' usually accompanied by moderate damage of the liver. Three of the 8 control animals died of pulmonary infection. At 70 ppm, 2 of 8 rabbits died within 30 days, compared with 3 of 8 control rabbits. The authors concluded that the mortality caused by pulmonary infection among the rabbits in the control group lead them to view the results with extreme caution (Pozzani *et al*, 1949).

F344 rats and B6C3F$_1$ mice (10/sex/group) were exposed (6 h/d, 5 d/wk) to atmospheres containing 0, 75, 150, and 300 ppm EA for 30 days. Animals exposed to 300 ppm appeared lethargic during the first 2 weeks of exposure. Decreased body-weight gain was seen in male and female rats and male mice exposed to 150 or 300 ppm EA. Alterations in relative kidney and liver weights were also detected but there were no corresponding histological findings. Examination of the nasal turbinates from male mice and rats in the 0 and 300 ppm groups revealed inflammation, degeneration, focal necrosis and squamous metaplasia in rats and less pronounced squamoid alterations of the nasal mucosa in mice exposed to EA. The primary effect was on the olfactory epithelium lining the dorsomedial aspects; some areas of the olfactory epithelium and the respiratory epithelium appeared to be unaffected. Based on the decreased body-weight gain and difference in relative liver and kidney weight, the NOEL was 75 ppm in both species and the LOEL 150 ppm in both species. As only the 0 and 300 ppm groups were subjected to histopathological examination an overall NOEL could not be determined (Miller *et al*, 1979).

In another study, in which rats and mice were exposed (6 h/d, 5 d/wk) to 0.02 mg EA/l (5 ppm) for 24 months, no treatment-related effects in the nasal mucosa were observed. The NOEL on the nasal mucosa was therefore 5 ppm (Miller *et al*, 1985).

The effects of repeated inhalation exposures to EA in the mouse, rat and rabbit were investigated by Lomonova and Klimova (1979). Because of the lack of detail in the report it is not possible to provide an evaluation of the toxicological significance of the results.

Groups of rats were exposed (2 h/d; number of exposure days not specified) to concentrations of 0, 0.01 and 0.02 mg EA/l (0, 2.5 and 5 ppm) for 8 months. A variety of blood enzyme activities and clinical chemistry parameters were measured, the only differences noted being minor decreases in blood cholinesterase and catalase activities, and alterations in carbohydrate metabolism (Gabor *et al*, 1965).

8.3.3 Summary and Evaluation

When dosed subchronically by oral gavage, EA produces severe local effects on the gastric mucosa (marked hyperplasia, ulceration and erosion), the primary lesion in rats and mice being in the forestomach, i.e. the site of application. The toxic effects occur only at doses that significantly reduce NPSH levels in the forestomach.

Only local irritation effects were observed in inhalation studies. No systemic effects were observed.

8.4 GENETIC TOXICITY

In vitro genetic toxicity assays are used routinely as a first screen for assessing the genotoxic activity of chemicals. These assays provide information only on the intrinsic potential of a chemical to cause damage to DNA. To determine whether or not this intrinsic potential is expressed in whole animals it is necessary to conduct *in vivo* genetic toxicity assays which take into account absorption, distribution, metabolism and excretion of the test material. The results of *in vivo* assays are more relevant to human hazard.

8.4.1 *In Vitro* Bacterial Gene Mutation Assays (Tables 13 and 14)

EA has been tested extensively in the presence and absence of auxiliary metabolic activation (S9 mix) in the Ames bacterial gene mutation assay, and gave clear non-mutagenic results in the standard plate incorporation assay (Brusick, 1977; Rohm and Haas, 1979, 1981; Waegemaekers

Table 13 Bacterial Gene Mutation - Plate-incorporation Assays

Strain	+S9 mix	-S9 mix	Concentration (μg/plate)	Result	Reference
TA 98 TA 100 TA 1535 TA 1537 TA 1538	Rat (Aroclor 1254 and Phenobarbital)	Yes	30-2,000	-ve -ve -ve -ve -ve	Waegemakers and Bensink, 1984
TA 100	Hamster	Yes	Not specified	-ve	Warner *et al*, 1988
TA98 TA100 TA1535 TA1537 TA1538	Not specified	Yes	0.001-5μl/plate	-ve -ve -ve -ve -ve	Brusick, 1977
TA98 TA100 TA1535 TA1537	Not specified	Yes	0.001-5μl/plate	-ve -ve -ve -ve	O'Neill and Scribner, 1979
TA98 TA100 TA1535 TA1537	Not specified	Yes	0.001-5μl/plate	-ve -ve -ve -ve	Lohse, 1981

Table 14 Bacterial Gene Mutation - Pre-incubation Assays

Strain	+S9 mix	-S9 mix	Concentration (μg/plate)	Result	Reference
TA 98 TA 100 TA 1535 TA 1537	Rat and Syrian hamster (Aroclor 1254)	Yes	100-10,000	-ve -ve -ve -ve	Haworth *et al*, 1983
TA 98 TA 100 TA 1537	Rat (PCB induced)	Yes	Not specified	-ve -ve -ve	Ishidate *et al*, 1981
TA100	Rat (Arochlor 1254)	Yes	0.001-7,500	±	Byers and O'Neill, 1983
Not specified	Not specified	Not specified	Not specified	-ve	McCarthy, 1984

± Equivocal

and Bensink, 1984; Warner *et al*, 1988) and the liquid preincubation assay (Ishidate *et al*, 1981; Haworth *et al*, 1983). One equivocal result has been reported in a preincubation assay using TA100 in the presence and absence of S9 mix (Byers and O'Neill, 1983), but this has not been reproduced. McCarthy (1984) also cites negative Ames test data for EA from Rohm and Haas.

8.4.2 *In Vitro* Mammalian Cell Gene Mutation Assays

EA has been extensively tested in the Chinese Hamster ovary (CHO) HGPRT mutation assay and the L5178Y $TK^{+/-}$ mutation assay.

EA did not induce significant numbers of mutants in a range of (CHO) HGPRT mutation assays in the absence of S9 mix (Brock *et al*, 1987; Parker *et al*, 1988; Moore *et al*, 1989, 1991). No assays were conducted in the presence of S9 mix.

In contrast, EA has been shown to be active in the mouse lymphoma $TK^{+/-}$ mutation assay using L5178Y cells in the absence of S9 mix (Myhr, 1980; Amtower *et al*, 1986; Brock *et al*, 1987; Doerr *et al*, 1988; McGregor *et al*, 1988; Millis *et al*, 1988; Moore *et al*, 1988,1989; Krehl and Clive, 1989; Dearfield *et al*, 1991) and in the presence of S9 mix (Dearfield *et al*, 1991). McCarthy (1984) also cites Rohm and Haas data showing a mutagenic effect of EA in L5178Y cells. The data are in accordance with the large number of other studies indicating the mutagenic activity of EA in L5178Y cells.

The majority of the mutant colonies induced by EA are reported to be small colonies (Myhr, 1980; Amtower *et al*, 1986; Brock *et al*, 1987; Doerr *et al*, 1988; Millis *et al*, 1988; Moore *et al*, 1989) indicating that the mutants induced by EA are the result of its clastogenic activity.

8.4.3 *In Vitro* Chromosomal Damage Assays

EA is a well documented *in vitro* clastogen inducing chromosomal aberrations in the absence of S9 mix in CHL cells (Ishidate *et al*, 1980, 1981, 1983), CHO cells (Amtower *et al*, 1986; Doerr *et al*, 1988; Loveday *et al*, 1990) and isolated mouse splenocytes (Kligerman *et al*, 1991). EA also induced chromosomal aberrations in the presence of S9 mix in CHL cells (Ishidate *et al*, 1980, 1981, 1983) and CHO cells (Loveday *et al*, 1990).

Zimmerman and Mohr (1992) reported that EA caused chromosomal loss and mitotic recombination in yeast cells *in vitro*. The authors speculated that the chromosomal loss was due to interference with microtubule function during mitosis and that the recombination effect was due to a direct interaction with DNA. As with the mouse lymphoma assay these effects occurred only at cytotoxic doses. This, coupled with the fact that this test system is unvalidated, questions the relevance of the current findings for human risk assessment.

8.4.4 *In Vitro* Sister-Chromatid Exchange

Loveday *et al* (1990) reported EA as an inducer of Sister-Chromatid Exchange (SCE) in CHO cells *in vitro* whereas Kligerman *et al* (1991) reported EA as negative in a SCE assay in isolated mouse splenocytes.

8.4.5 *In Vitro* Cell Transformation Assay

Steele *et al* (1989) reported EA as positive in an *in vitro* cell transformation assay in rat tracheal epithelial cells in the absence of S9 mix. This type of assay is not well validated or routinely used and any results should be treated with caution as their biological significance is questionable.

8.4.6 *In Vivo* Chromosomal Damage Assays

Przybojewska *et al* (1984) reported statistically significant increases in the incidence of micronucleated polychromatic erythrocytes in the bone marrow of Balb/c mice (4 males/ group) following 2 i.p. doses (24 hours apart) of 225, 450, 900 and 1,800 mg EA/kgbw (approximately LD_{50}). The maximum dose level resulted in the death of 2 of 4 of the mice. The animals were killed 6 hours after receiving the second dose. Significant reductions in the ratio of polychromatic to normochromatic erythrocytes were observed at all dose levels, indicating a cytotoxic effect of EA and/or of its metabolites on the bone marrow.

These data could not be reproduced with EA (purity 98.5%) in 4 micronucleus tests in C57BL6 mice (5 or 10 males/group and 10 females/group) and Balb/c mice (10 males/group) utilising single and double i.p. dosing regimes at levels of up to 80% of the LD_{50} (738 mg EA/kgbw for single dose or 812 mg EA/kgbw for double dose) (Ashby *et al*, 1989). The results of these 4 micronucleus tests show EA to be inactive in the mouse bone marrow, even when using test conditions identical to those employed by Przybojewska *et al* (1984). Although there is no obvious explanation for this conflict of data it is clear that any increases in micronucleated polychromatic erythrocytes reported in the literature have not been reproduced in a comprehensive series of experiments. Statistically and biologically significant reductions in the ratio of polychromatic to normochromatic erythrocytes were observed by Ashby *et al* (1989) as seen by Przbojewska *et al* (1984).

Further negative clastogenic results have been reported for EA. No significant increases in the incidence of chromosomal aberrations or sister chromatid exchanges (SCE) were seen in splenocytes isolated from C57BL/6 mice (5/group) 24 hours after i.p. injection with EA (purity 99%) at dose levels of 125, 250, 500 and 1,000 mg/kgbw. A small increase in the incidence of

micronucleated binucleate cells was observed in splenocytes from animals treated at the top dose level. However, this increase was primarily due to a relatively high response in 1 of the 5 animals and the overall increase of less than 2-fold is generally accepted not to be biologically significant. The lack of clastogenic activity of EA *in vivo* is therefore further emphasised by these results from Kligerman *et al* (1990, 1991).

All 6 studies have been conducted using the i.p. route, which is considered useful for detecting intrinsic mutagenicity, but irrelevant for human hazard assessment.

Although the *in vivo* chromosome damage assays on EA have produced conflicting results, the weight of evidence indicates that EA is not clastogenic *in vivo*.

8.4.7 *Drosophila* Sex-Linked Recessive Lethal Test

Valencia *et al* (1985) tested EA in a sex-linked recessive lethal (SLRL) test on *Drosophilia melanogaster* using feeding and i.p. routes of administration. No significant increases in the incidence of SLRL's were observed. A positive control was not used in this study.

8.4.8 DNA Adducts/Damage *In Vivo*

Ghanayem *et al* (1987) investigated the binding of EA to nucleic acids in the forestomach and reported that no DNA adducts were observed (limit of detection 1 alkylation/10^4 nucleotides) in the forestomach of rats treated by oral gavage with carcinogenic doses of 2,3-[^{14}]C-EA up to 400 mg/kgbw. Morimoto *et al* (1990, 1991) also reported no induced DNA damage as detected by alkaline elution in F344 rats treated by gavage with EA (0.1-4%) in corn oil.

8.4.9 Summary and Evaluation

EA is neither mutagenic to bacteria *in vitro* as shown by the large number of negative results in the Ames test nor did it produce any significant mutagenic effect in mammalian cells *in vivo* (CHO HGPRT assay). EA reproducibly induced small colony mutants in the mouse lymphoma gene mutation assay, indicating clastogenic activity. This *in vitro* clastogenic activity has been confirmed by the induction of chromosomal aberrations in CHO and CHL cells and isolated splenocytes.

EA did not induce sex-linked recessive lethal damage in *Drosophilia melanogaster* or DNA damage or adducts in the forestomachs of rats.

Although one publication reported an increase in the incidence of micronuclei *in vivo*, this has not been confirmed in a comprehensive series of 5 subsequent studies. Thus, EA is considered not to be clastogenic *in vivo*.

8.5 CHRONIC TOXICITY AND CARCINOGENICITY

8.5.1 Oral

In a 2-year study, EA (in gelatin capsules containing 5% EA dissolved in corn oil) was administered to Beagle dogs (2/sex/group) at dietary-equivalent concentrations of 0, 10, 100, and 1,000 mg/kg (0, 0.25, 2.5 and 25 mg/kgbw/d). Dogs at the highest dose level exhibited emesis initially; the dose was reduced to 300 mg/kg (7.5 mg/kgbw/d) and then gradually increased to 1,000 mg/kg (25 mg/kgbw/d) over a 16 week period. No systemic toxic effects were detected (Borzelleca *et al*, 1964).

Wistar rats (25/sex/group) received EA in their drinking water over a 2 year period at concentrations of 0, 6, 60 and 2,000 mg/l (the 6 and 60 mg/l doses were increased to 7 and 70 mg/l after 4 months), equivalent to respective doses of 0, 0.46, 4.7 and 115 mg/kgbw/d (males) and 0, 0.69, 6.3 and 163 mg/kg/d (females). Treatment-related decreases in body weight were seen in the high dose animals, i.e. a 15% reduction in females and 5.5% in males. Depressed food and water consumption paralleled the periods of decreased body-weight gain. There were no other adverse effects at any dose and no indication of an oncogenic response (Borzelleca *et al*, 1964).

F344 rats and $B6C3F_1$ mice (50/sex/group) were treated (5 d/wk) for 103 weeks by oral gavage with solutions of EA in corn oil (rats 2% and 4%, mice 1% and 2%) equivalent to doses of 0, 100, or 200 mg/kgbw/d. The results of the study showed that gavage administration of EA was clearly associated with the occurrence of benign and malignant forestomach tumours in both rats and mice (Table 15). When data on forestomach tumours and non-neoplastic lesions were compared on the basis of the concentration of EA in the dosing solution rather than the total dose, the response was similar in the 2 species. The forestomach changes were therefore considered to be related to the concentration of EA delivered as a bolus dose in corn oil, rather to than to the total body dose. There was no evidence of toxicity in any tissues other than the forestomach. The absence of systemic effects was attributed to the fact that EA is rapidly hydrolysed in the blood and liver (US-NTP, 1986).

The NTP (1986) chronic study was followed by 3, 6 and 12 month stop-dose studies with rats which indicated that 12 months of gavage dosing of a 4% solution of EA was required to induce

Table 15 Forestomach Tumours in F344 Rats and B6C3F$_1$ Mice Treated by Oral Gavage with EA (after US-NTP, 1986)

Species, sex (number of animals)	Dose (mg/kgbw/d)								
	0	100	200	0	100	200	0	100	200
	Squamous cell papillomas			***Squamous cell carcinomas***			***Squamous cell papillomas or carcinomas***		
Rat, ♂ (50)	1	15[1]	29[1]	0	5	12[1]	1	18[1]	36[1]
Rat, ♀ (50)	1	6	9	0	0	2	1	6	11
Mouse, ♂ (n[2])	0[a]	4[c]	9[a]	0[a]	2[c]	5[b]	0[a]	5[c]	12[b1]
Mouse, ♀ (n[2])	1[b]	4[d]	5[a]	0[b]	1[d]	2[a]	1[b]	5[d]	7[a]

1 P<0.001 Cochran-Armitage trend, Fisher exact test

2 a, n=48; b, n=50; c, n=47; d,n=49

forestomach tumours when the animals were examined for 2 years following the start of dosing (Ghanayem *et al*, 1991a, 1993). Dosing for 3 or 6 months resulted in marked forestomach hyperkeratosis and hyperplasia that has reversed and returned to a normal epithelium when the tissue was examined at 24 months of age.

8.5.2 Dermal

The dorsal skin of male C3H/HEJ mice was treated with undiluted EA (3x25 µl/wk) for their lifetime (3x/wk). No skin tumours were found. There were no statistically significant alterations in survival. Treatment did, however, produce non-neoplastic skin changes such as dermatitis, dermal fibrosis, epidermal necrosis and hyperkeratosis in several of the mice (De Pass *et al*, 1984).

8.5.3 Inhalation

F344 rats and B6C3F$_1$ mice (60/sex/species in each of 2 control groups and 75/sex/species in treated groups) were exposed (6 h/d, 5 d/wk) to atmospheres containing EA vapour at concentrations of 0, 0.1 or 0.31 mg EA/l (0, 25, or 75 ppm) for 27 months. Additional rats and mice were exposed to 0.92 mg EA/l (225 ppm) for 6 months and held without additional exposure for 21 months. There were concentration-related decreases in body-weight gain in rats and mice of both sexes at all concentrations tested. No effects on organ weight, clinical chemistry, haematology, urinalysis or survival time were observed. Animals exposed to 225 ppm appeared to be 'irritated and aggressive' at the start and lethargic at the end of each exposure period. The only significant histopathological findings were degenerative changes of the olfactory epithelium of the nasal turbinate. The changes seen in all 3 exposure groups were concentration-dependent. In general, areas of the nasal mucosa lined by olfactory epithelium were the most affected, while regions lined

by the respiratory epithelium were relatively unaffected. The underlying reason for this selective effect could not be determined. There was no indication of an oncogenic response in any organ or tissue in either the rat or mouse (Miller *et al*, 1985). In another study, in which rats and mice were exposed (6 h/d, 5 d/wk) to 0.02 mg EA/l (5 ppm) for 24 months, no treatment- related effects in the nasal mucosa were observed. The NOEL on the nasal mucosa for non-neoplastic effects was therefore 5 ppm (Miller *et al*, 1985).

8.5.4 Summary

To date there have been 6 oncogenicity studies with EA; an oral gavage study in rats and mice, a drinking-water study in rats, an inhalation study in rats and mice and a dermal exposure study in mice. Of these, only the gavage studies showed a positive effect, with a concentration-and dose-dependent increase in the incidence of papillomas and carcinomas in the forestomachs of rats and mice. No other tissues were affected and no toxic effects were seen in any tissue or organ remote from the dosing site. The histopathological changes in the forestomach following gavage dosing were consistent with the severe irritant properties of EA. They are considered to have occurred following a saturation of the detoxification pathway and the rapid and sustained reduction in NPSH caused by the high concentration of EA delivered to the target tissue by bolus dosing.

The lack of tumours in the forestomach of animals in the drinking water study can be explained by the fact that the dose of EA delivered to the forestomach never reached the high local level achieved by bolus dosing. Thus the detoxification pathways were not compromised and tissue irritation, fundamental to tumour development, was modulated. The results of the oncogenicity studies are consistent with a mechanism whereby sustained hyperplasia produced by local tissue injury, rather than direct genotoxic action of EA, results in tumour formation.

8.6 REPRODUCTIVE AND TERATOGENIC EFFECTS

8.6.1 Reproductive Effects

No data are available.

8.6.2 Teratogenicity

Pregnant Sprague-Dawley rats (33 females/group) were exposed (6 h/d) to atmospheres containing 0, 50 or 150 ppm EA from days 6-15 of gestation. Maternal toxicity was observed at the highest exposure concentration as shown by reduced body-weight and food consumption. In 3 of the 308

pups examined at this dose level, there were foetal malformations (hypoplastic tail, small anal orifice) or skeletal variations (delayed ossification, missing ribs or vertebrae, or fused ribs). At 50 ppm, there was neither maternal toxicity nor an adverse effect on the developing embryo or foetus. The authors concluded that the findings at maternally toxic doses did not show a teratogenic effect because their incidence was not statistically significant and had been observed in historical control data at the test laboratory (Murray *et al*, 1981).

The teratogenic effect of EA was also examined in Wistar rats following oral gavage. Pregnant Wistar rats were dosed with 0, 25, 50, 100, 200 or 400 mg EA/kgbw/d (vehicle and concentration not specified) from days 7-16 of gestation. Maternal toxicity was manifest as decreased body-weight gain and decreased placental weight. A number of effects were observed on the developing foetus, namely delayed ossification, shortened ribs and skull anomalies, however they did not occur in a dose-related manner. A comprehensive evaluation of the investigation is restricted by deficiencies in the study design. No clinical signs were reported, soft tissues were not examined and maternal toxicity was not adequately assessed (Pietrowicz *et al*, 1980).

8.6.3 Summary

EA was not teratogenic in rats at inhalation exposure concentrations up to 150 ppm, the maximum level examined, which was toxic to the dams. There is no evidence for specific embryotoxicity or foetotoxicity at non-maternally toxic concentrations.

SECTION 9. EFFECTS ON MAN

9.1 IRRITATION

EA is irritating to the skin, eyes and mucous membranes of the digestive and respiratory tracts (Nemec and Bauer, 1978; Sandmeiter and Kirwin, 1978). Solutions of 1 and 5% EA in olive oil were not irritating to human skin (Cavelier *et al*, 1981).

9.2 SENSITISATION

Dermal sensitisation was seen in 10 of 24 human volunteers exposed to 4% EA in Vaseline (Opdyke, 1975). A case of contact dermatitis of the hands has been described by Fregert (1978). When individuals who had been sensitised to 2-ethylhexyl acrylate and N-*t*-butylmaleamic acid were exposed to EA, they showed evidence of allergic cross-reaction (Jordan, 1975).

On the basis of the human maximisation tests performed by Epstein and reported by Opdyke (1975) it would appear that EA has some potential to sensitise man.

9.3 CHRONIC TOXICITY

During 5 years of developmental research, 33 workers (20 women and 13 men) were exposed (regime not specified) to an atmosphere containing concentrations of 4-58 mg/m^3 (1-14 ppm) of EA, up to 50 mg/m^3 (9.4 ppm) of *n*-butyl acrylate and 0.11-2 mg/m^3 (0.05-0.9 ppm) of acrylonitrile. The clinical and laboratory investigations diagnosed neuroautonomic or neurotic disturbances in 14 individuals which were functional in nature as indicated by corresponding EEG recordings (Kuželová *et al*, 1981). Because of mixed exposures and in the absence of further data it is impossible to evaluate this study.

An investigation of olfactory function in 731 workers at a chemical facility manufacturing acrylates and methacrylates showed no associations between chemical exposure and the olfactory test scores. A nested case-control study, designed to evaluate the cumulative effects of exposure, indicated a reversible effect on olfactory function (Schwartz *et al*, 1989).

9.4 EPIDEMIOLOGY

Walker *et al* (1991) published a study of 13,863 workers from 2 Rohm and Haas sites in North America, producing acrylic sheet. The Bristol plant was represented by 2 cohorts, the so-called Early Bristol cohort of 3,934 white males employed between 1 January 1933 and 31 December 1945 (of which 2,904 were hired between 1941 and 1945) and the Later Bristol cohort of 6,548 white males (3,916 hourly paid and 2,632 salaried workers) hired between 1 January 1946 and 31 December 1986. The Knoxville plant was represented by 1 cohort of 3,381 white males employed between 1 January 1943 and 31 December 1982. All groups were followed from the first day of employment or 1 January 1933, whichever came later. Assessment of exposure to EA and/or methyl methacrylate was based on job history and on a job specific exposure scale. The total dose for each job held by every worker was estimated by multiplying exposure intensity by the interval in days from the start to the end of employment in the job, divided by 365.25. In the Early Bristol cohort there was an excess of colon cancer in workers exposed to EA and/or methyl methacrylate when compared to the local rates (Table 16).

Table 16 Mortality from Cancer of the Colon in the Early Bristol Cohort (adapted from Walker *et al*, 1991)

Achieved dose[a]	Observed deaths	Expected deaths	Fitted rate ratio[b]
None (not exposed)	12	9.66	1.24
0-4 units	13	9.39	1.39
5-9 units	6	5.17	1.16
10-14 units	1	2.24	0.45
≥ 15 units	11	4.58	2.4

a Mutually exclusive doses of EA and/or methyl methacrylate at least 20 years since first achieving dose among those employed >10 months

b Fitted mortality ratio of cohort mortality rate and for combined Bucks county and Burlington counties white male mortality rate for the same age and calendar period

The excess mortality appeared at least 20 years after the equivalent of 3 years employment in jobs producing the highest exposure to EA and/or methyl methacrylate vapour and to volatile by-products of polymerisation. Cancer of the rectum was also elevated in the Early Bristol cohort (10 deaths observed versus 5.23 expected; O/E ratio 1.9) although, due to the paucity of data this observation is less robust than the colon cancer. No excesses of either colon or rectal cancer were observed in either the Late Bristol or Knoxville cohorts. The authors conclude that "a causal role for protracted, extremely high exposure to EA, methyl methacrylate or the volatile by-products of the EA/methyl methacrylate polymerisation process in the genesis of colon and rectum cancer is a tenable

explanation of the available epidemiologic data". Despite the "statistical association" between exposure to EA/Methyl methacrylate and deaths from colorectal cancer in the Early Bristol cohort, the data are neither consistent with the animal carcinogenicity data on EA and methyl methacrylate (ECETOC, 1994b) nor with the mechanistic data indicating activity of EA only at or close to the point of contact. In addition, the absence of supporting data from the other 2 cohorts leads to the conclusion that the correlation between exposure to EA and/or methyl methacrylate and death from colorectal cancer is unconvincing.

9.5 SUMMARY

Inhalation and skin contact are the primary routes of exposure to EA in the workplace. Direct contact with the liquid is irritating to the skin and eye, and breathing the vapour can irritate the eyes, nose, mouth, throat and upper respiratory system. Because of these irritant effects and the objectionable smell of EA it is unlikely that human beings would be exposed to high concentrations of EA. However, care should be taken as repeated or chronic exposures to EA vapour may result in damage to the lining of the nose, compromising the sense of smell or taste. EA may cause allergic skin reactions in certain individuals. These sensitised individuals may also be sensitised to other acrylic acid esters.

In a retrospective mortality study of workers employed in an EA and methylmethacrylate production plant prior to 1946, an increase in mortality from colorectal cancer was observed. An examination in a similar population at a different site did not show an increase in colorectal cancer. Increases in colorectal cancer have not been seen in a population of workers employed after 1946.

A causal relationship between exposure to EA by inhalation and the increased risk of colorectal cancer in the single cohort is not supported by the observation of exclusively local toxic and carcinogenic effects of EA, and by the mechanistic data which indicate rapid hydrolysis of EA giving low tissue concentrations at non-exposed organs.

SECTION 10. ASSESSMENT OF HUMAN CARCINOGENIC HAZARD

A major health issue that has been associated with exposure to EA is its possible carcinogenic effect, which has led the International Agency for Research on Cancer (IARC) to classify EA as possibly carcinogenic to man, group 2B' (IARC, 1986, 1987).

In the NTP bioassay (1986), rats and mice treated by oral gavage for their life-time with high doses of EA in corn oil developed forestomach tumours only (no other tissues were affected). Conversely, chronic dosing of EA in drinking water did not produce any excess tumours in treated animals (Borzelleca *et al*, 1964), despite the fact that the daily dose of EA in the high dose animals (110 mg/kgbw/d) was equivalent to a dose which caused forestomach tumours in the oral gavage study. This apparent discrepancy may be explained by reference to both the histopathological findings and the metabolism of EA, and attributed to the difference in dosing regime. Bolus administration produced local concentrations of EA in the forestomach sufficient to produce hyperkeratosis, submucosal inflammation and oedema and ulceration/ erosion of the forestomach (NTP, 1986; Frederick *et al*, 1990). In contrast to the liver, where hydrolysis of the ester bond is rapid (half-life of acrylic acid approximately 2 s), this metabolic route is less effective in both the forestomach and the glandular stomach of the rat, the half-lives being 8.66 and 9.9 min respectively. In these circumstances the second metabolic route, conjugation with NPSH becomes potentially more significant. Under non-saturating concentrations (e.g. drinking water study), NPSH reduction is rapidly replenished, however, following repeat high dose bolus exposure (e.g. gavage study) rapid and prolonged depletion of NPSH would be anticipated. These effects have been observed in the rat model and correlate with the histopathological findings. Thus in the gavage studies significant reduction in NPSH meant that the detoxification pathway was compromised (Frederick *et al*, 1990) (Section 8.3.1). In contrast, administration of EA in the drinking water to achieve the same daily dose, produced no effects on NPSH levels and significantly lower incidences in both the nature and severity of non-neoplastic forestomach lesions and no cancer (Frederick *et al*, 1990). Thus effective detoxification continued throughout the drinking water treatment regime.

The results of the NTP (1986) oral gavage study must be placed in perspective when evaluating the carcinogenic hazard to human beings involved in the manufacture, transportation or processing of EA. Firstly there is no practical situation where EA would be ingested regularly in concentrations high enough to compromise the detoxification system. Secondly, the lesions occurred only in the forestomach, an organ which is not present in man. The forestomach in the rodent is designed to

accommodate the storage of food, i.e. relatively long retention/contact times. The storage function of the rodent forestomach and the bolus application are believed to be fundamental in the development of the tumours by allowing prolonged irritation of the forestomach by EA which caused chronic inflammatory changes. Thirdly, the weight of genetic toxicology data indicates that EA is not a genotoxin *in vivo*. Fourthly, studies on the ability of EA to induce DNA strand damage in the rat forestomach were negative. The absence of *in vivo* DNA binding in the rat forestomach further supports the view that EA is not a site-contact genotoxin. Finally, epidemiological studies in worker populations show no evidence for carcinogenic effects causally related to EA exposure.

In addition to the 2 positive gavage studies (NTP, 1986), there are 4 negative carcinogenicity studies in rats and mice, i.e. the drinking water study (Borzelleca *et al*, 1982) and dermal study (De Pass *et al*, 1984). Inhalation and skin contact are the most relevant routes of exposure in the workplace whereas bolus ingestion is not. A 27 month inhalation study (Miller *et al*, 1985), using concentrations of EA which produced severe nasal irritation, produced no evidence of a carcinogenic response. No carcinogenic response was produced when EA was administered to the skin in a lifetime study in mice (De Pass *et al*, 1984).

Consideration of the available data supports the view that EA does not represent a human carcinogenic hazard. This is in agreement with the conclusion of the EC Specialised Experts who concluded that EA should have 'no classification for carcinogenicity' (CEC, 1991).

SECTION 11. FIRST AID AND SAFE HANDLING ADVICE

11.1 FIRST AID AND MEDICAL TREATMENT

There is no specific treatment or antidote for over-exposure to EA. Supportive medical treatment as indicated by the patient's condition is recommended.

11.1.1 Skin and Eye Injuries

Clothing contaminated with EA should be removed. Affected areas of skin must be washed with copious quantities of water. The skin must be rinsed for at least 10 min. If the eyes are splashed, they should be irrigated immediately with eye-wash solution or clean water, holding the eyelids apart for at least 10 min. A physician should then be consulted.

11.1.2 Inhalation

The patient must be taken into fresh air, kept warm and at rest if he experiences difficulty in breathing after inhaling EA fumes. If the patient stops breathing, artificial respiration should be administered until qualified medical personnel is able to take over. Medical aid should be summoned immediately.

11.1.3 Ingestion

If EA has been swallowed, do not induce vomiting. Never give anything by mouth to an unconscious person. A physician should be consulted immediately.

11.2 SAFE HANDLING

11.2.1 Safety at Work

The main risk of injury stems from EA's irritating action on the skin and mucous membranes. Contact with the skin and eyes should therefore be avoided as should inhalation of high concentrations of EA vapour. EA should be used only in well ventilated areas. EA vapour is denser than air; pits and confined spaces should be avoided.

Suitable respiratory equipment must be worn on occasions when exposure to EA vapour above the recommended exposure limit is likely.

The following protective clothing must be worn when handling EA: eye-face protection and rubber gloves (preferably nitrile) which should be changed regularly to avoid permeation. Rubber boots should also be worn when handling large quantities.

11.2.2 Storage Safety

EA is stable in the presence of a polymerisation inhibitor. It is susceptible to polymerisation initiated by prolonged heating or a catalyst. Therefore, the following precautions must always be observed when storing EA.

- EA must be stored under air as the stabiliser (hydroquinone monomethylether) is only effective in the presence of oxygen
- Heat and direct sunlight must be excluded, as these promote polymerisation
- EA must be stored at temperatures preferably not exceeding 25°C
- Care should be taken to prevent contamination, as contaminants can render the stabiliser ineffective or can react with EA and promote polymerisation.

11.2.3 Fire Safety and Extinguishants

EA is classified as a highly flammable liquid. It can form an explosive mixture in air; adequate ventilation should be provided and smoking prohibited. Precautions should be maintained to eliminate all sources of ignition of EA when in contact with air. EA may polymerise on heating. Sealed containers may rupture if hot. Heat, UV-light, peroxide, azo-compounds, alkalis and oxidising agents may cause rapid polymerisation resulting in explosion. Fires can be extinguished with water, alcohol-resistant foam, dry powder or CO_2.

If fire does break out, neighbouring tanks and pipelines must be kept cool with plenty of water, otherwise the heat generated by the fire will cause their contents to polymerise.

11.2.4 Protection against Fire and Explosion

To avoid ignition, the following precautions are recommended.

- All plant and equipment should be explosion-proof as laid down in national standards
- All containers must be earthed
- All sources of ignition must be excluded
- No smoking is allowed
- No welding should be done until all tanks and pipelines have been drained and thoroughly flushed with water or hot caustic soda.

11.3 MANAGEMENT OF SPILLAGE AND WASTE

In all cases of spillage naked flames should be extinguished. Smoking and sparks must be avoided. Small spills of a few litres can be soaked up with suitable absorbent materials such as sand or earth. EA should not be absorbed onto sawdust or other combustible materials. Larger spills must be prevented from spreading by the use of earth or sand and the material should be pumped into containers.

Surfaces contaminated with EA should be washed well, first with alcohol and then with soap and water. All wastes should be sealed in vapour-tight plastic bags for eventual disposal.

EA should not be allowed to drain into domestic sewers as serious explosion hazards could result. Local authorities should be informed immediately if spilt liquid EA has entered surface water drains.

Waste quantities of EA can be incinerated in accordance with local, state or national regulations. Empty storage drums must be decontaminated before recycling.

When aqueous waste containing EA is discharged to adapted biological waste-water treatment plants it is expected to be mineralised. No disturbance of the bacterial activity of sewage treatment plants is expected if EA is properly diluted.

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