FOREWORD INTRODUCTION

HYDROXYETHYL ACRYLATE

CAS N°: 818-61-1

SIDS Initial Assessment Report

For

SIAM 20

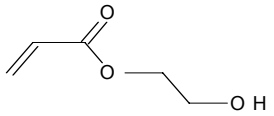
Paris, France, 19-22 April 2005

1. Chemical Name:	Hydroxyethyl acrylate
2. CAS Number:	818-61-1
3. Sponsor Country:	United States Oscar Hernandez Director, Risk Assessment Division (7403M) U.S. Environmental Protection Agency 1200 Pennsylvania Ave, N.W. Washington, DC 20460 Phone: 202-564-7641
4. Shared Partnership with:	HEA/HPA Consortium
5. Roles/Responsibilities of the Partners:	The HEA/HPA Consortium prepared the initial documents, which were then reviewed by U.S. EPA
• Name of industry sponsor /consortium	Elizabeth Hunt, HEA/HPA Consortium 941 Rhonda Place SE Leesburg, VA 20175 703-669-5688
• Process used	Data searches included published scientific literature, databases and handbooks as well as the internal files of the member companies of the consortium.
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme ?	The IUCLID Data Set has been revised and the SIAR prepared by a consortium of chemical industry producers in 2004. Data searches included published scientific literature, databases and handbooks as well as the internal files of the member companies of the consortium.
7. Review Process Prior to the SIAM:	See 5 above
8. Quality check process:	U.S. EPA reviewed the information in the industry sponsor's submission.
9. Date of Submission:	February 15, 2006
10. Date of last Update:	27 July 2005

11. Comments:

Date of First Submission: The IUCLID Data Set for HEA was first submitted in 1995 by The Dow Chemical Company in cooperation with BASF. Production quantities were updated in January 2004.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	818-61-1
Chemical Name	Hydroxyethyl Acrylate (Acrylic Acid, Monoester with Ethylene glycol, HEA)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The metabolism and excretion of HEA has been examined in male Fischer 344 rats using oral, intraperitoneal, and dermal and inhalation routes of exposure. Results indicated rapid metabolism via hydrolysis of the ester functionality, similar to many other acrylic acid esters. Rapid metabolism to CO_2 and urinary metabolites was observed for hydroxyethyl acrylate and was not route-dependent. The half-lives of elimination of radioactivity were approximately 14 hours for urine and 17 hours for CO_2. The half-life of elimination of radioactivity from plasma was approximately 26 hours.

Studies on the acute toxicity of hydroxyethyl acrylate indicate oral LD_{50} values of 540 – 1070 mg/kg bw. Clinical signs (following administration of 10% aqueous solution) included hypoactivity, rough fur, labored breathing, muscle weakness, GI tract hemorrhage in animals that died. Neat material may have burned the tissues of the mouth, throat, and GI tract. Acute dermal toxicity studies showed LD_{50} values of 154 (rabbits, undiluted material) and >1000 mg/kg bw (rats, vehicle olive oil). At high concentrations, the following were noted: decreased eyelid tone, decreased corneal reflex, loss of righting reflex, and muscle coordination. The acute inhalation data indicate that exposures of rats to 333 to 394 ppm for 4 or 8 hours caused irritation and were in the threshold area for lethality. Nearly 100% lethality was observed for rats at exposures of 500 ppm and above.

Hydroxyethyl acrylate is severely irritating to the skin. Upon eye contact, hydroxyethyl acrylate caused severe irritation with irreversible corneal injury. Skin sensitization studies in animals and humans indicate that hydroxyethyl acrylate is a sensitizer and may cross-react with other acrylates in some exposed individuals.

Repeated exposures to vapors of hydroxyethyl acrylate to rats via inhalation (7 hr/day, 5 days/week for four weeks) caused severe nasal irritation, resulting in death due to respiratory failure at higher concentrations. Concentration-related local irritation (focal ulcerative rhinitis) was seen at sub-lethal exposures. The LOAEC for subchronic exposure, based on irritation, was 5 ppm (24 mg/m^3) for hydroxyethyl acrylate. The principal treatment-related effects observed following 18 months exposure of laboratory rats to 5 ppm of hydroxyethyl acrylate were also related to irritation of the respiratory tract, without significant evidence of systemic toxicity.

Hydroxyethyl acrylate was not mutagenic to *Salmonella typhimurium* (bacterial reverse mutation assay) *in vitro* with or without metabolic activation but was positive with metabolic activation when tested with two *E. coli* strains. No evidence of chromosomal damage was seen when as part of the 18-month chronic inhalation study, four rats/sex/group were killed after 12-months exposure and the bone marrow cells examined for chromosomal damage. Hydroxypropyl acrylate (an analog) was not mutagenic in an *in vivo* mouse micronucleus study. Overall, hydroxyethyl acrylate did not show evidence of mutagenic potential *in vivo* by the inhalation route of exposure

Histopathological examination of the reproductive organs of rats from the 18-month inhalation study revealed an increase relative to controls in a normally observed age-related lesion (fibrinoid degeneration in the vascular channels of the testes) and uterine inflammation (without any other associated histopathological effects). Neither effect was considered treatment-related or adverse to reproduction. Dietary administration of hydroxyethyl acrylate to rats or dogs did not result in treatment-related effects on testicular weight or histopathology of the testes or uterus.

In a well-conducted inhalation study exposing pregnant rats to hydroxyethyl acrylate from gestation day 6 to 20 to 0, 1, 5 or 10 ppm (0, 4.8, 24 or 48 mg/m^3) hydroxyethyl acrylate, maternal body weight gain was reduced at 10 ppm over the entire exposure period, and found to be statistically different from controls on days 6-13, but no embryo-fetal or developmental toxicity or teratogenicity was observed. Based on the available studies, hydroxyethyl acrylate does not show evidence for developmental toxicity.

No evidence of a carcinogenic effect was observed in a chronic toxicity/oncogenicity study conducted by the inhalation route of exposure.

Environment

The melting point is –60.2°C and the boiling point is 210°C. The vapor pressure is 0.06974 hPa at 25°C. The measured log Kow has been reported to be – 0.21. Hydroxyethyl acrylate is miscible in water at 25°C. The specific gravity is 1.101 g/cm^3 at 25°C.

Hydroxyethyl acrylate is photodegraded by reaction with hydroxyl radicals in the atmosphere with a half-life of 10 hours (calculated). The hydrolysis rate of hydroxyethyl acrylate at 25°C is pH dependent with no hydrolysis observed at a pH of 3; rapid hydrolysis at pH 11 with a half-life of 0.051 days; and a half-life of >270 days at pH 7. The hydrolysis half-life at 40°C and pH 7 or 9 is 39.6 days and 15 hours, respectively.

Distribution modeling using Mackay Level I indicates hydroxyethyl acrylate released into the environment partitions almost completely (99.9%) to the water phase. Fugacity model Level III with 100% of the hydroxyethyl acrylate release to air distribution is: <1% (air), 37% (water), 62.5% (soil) and <0.1% (sediment). Fugacity model Level III distribution with 100% of the hydroxyethyl acrylate release to water (assuming accidental release) is: <0.1% (air), 100% (water), <0.1% (soil) and <0.1% (sediment).

A low bioaccumulation potential is expected based on the partition coefficient and other physical/chemical parameters (BCF of 0.41, calculated). Hydroxyethyl acrylate is readily biodegradable.

Hydroxyethyl acrylate is acutely toxic to aquatic organisms. The 96-hour LC_{50} for fathead minnow was. 4.8 mg/L (measured), the 48-hour EC_{50} for *Daphnia magna* was 0.78 mg/L (nominal) and the 96-hour EC_{50} values for biomass and growth rate of algae (*Selenastrum capricornutum*) were 4.12 and 8.26 mg/L (nominal), respectively.

Exposure

In 2001, the worldwide production volume of hydroxyethyl acrylate was estimated to be 15,000 tonnes. Of that, the US production volume was approximately 10,000 tonnes. Hydroxyethyl acrylate is produced and used mainly in closed systems. Its principle use is either as a co-monomer in the manufacture of polymers or as a chemical reactant in the manufacture of chemical intermediates. The polymers and chemical intermediates made with hydroxyethyl acrylate find applications in automotive top coatings, architectural coatings, photocure resins, and adhesives.

Results from workplace measurements at a US production site indicated that hydroxyethyl acrylate did not exceed an occupational exposure limit of 1 ppm in 140 samples collected over 20 years. Worker exposure is limited by the use of enclosed processing systems, industrial hygiene controls and personal protective measures such as goggles, gloves, protective clothing and organic respirator, if necessary. Hydroxyethyl acrylate has a characteristic acrylic odor, which can provide a measure of warning of the presence of hydroxyethyl acrylate vapors. End-use consumer products contain only trace levels of acrylic acid and esters (as a result of polymerization). Therefore, consumer exposure to acrylate monomers is not anticipated.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical possesses properties indicating a hazard for human health (severe eye irritation with corneal injury which may result in permanent impairment of vision, even blindness, skin and upper respiratory tract irritation, skin sensitization, and acute toxicity from inhalation exposure). Based on exposure data

presented by the Sponsor Country (relating to production in one country which accounts for 67% of global production and relating to the use pattern in the Sponsor country), this chemical is currently of low priority for further work. Countries may wish to investigate any exposure scenarios that were not presented by the Sponsor country.

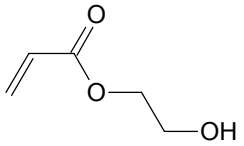
Environment: The chemical possesses properties indicating a hazard for the environment (fish, invertebrate, and algae). However, the chemical is of low priority for further work for the environment because of its ready biodegradability and the limited potential for bioaccumulation.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 818-61-1
IUPAC Name: 2-Propenoic acid, 2-hydroxyethylester
Molecular Formula: $C_5H_8O_3$
Structural Formula:



Molecular Weight: 116.12
Synonyms: Acrylic acid, 2-hydroxyethylester
2-(Acryloyloxy)ethanol
Diethylene glycol monoacrylate
Ethandiol-1,2-monoacrylate
Ethylene glycol acrylate
Ethylene glycol monoacrylate
Ethylene glycol acrylate
Ethylene glycol monoacrylate
Hydroxyethyl acrylate
β-Hydroxyethylacrylate
2-Hydroxyethyl-2-propenoate
Propenoic acid: 2-hydroxyethyl ester

1.2 Purity/Impurities/Additives

A typical commercial sample of HEA has a specified purity of >96.5% (w/w) and may contain diethyleneglycol monoacrylate (2.1% w/w), acrylic acid (< 1% w/w), other esters (< 2% w/w), ethylene glycol (0.25% w/w) and ethylene oxide (0.001% w/w). Methyl ether of hydroquinone may be added at 250 to 650 ppm as an inhibitor of spontaneous polymerization.

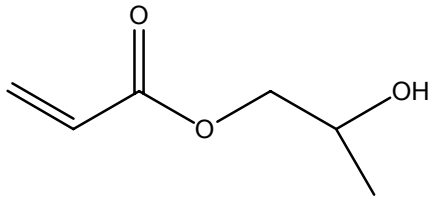
1.3 Physico-Chemical properties

Table 1 Summary of Physico-chemical Properties

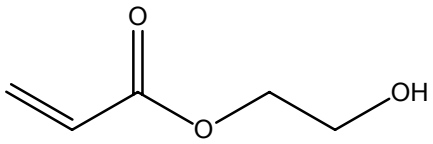
Property	Value	Reference
Physical state	Liquid	
Melting point	-60.2 °C	Rowley et al. in DIPPR, 2004
Boiling point	210 °C at 1013 hPa	Rowley et al. in DIPPR, 2004
Relative density	1.101 g/ml at 25°C	Dow, 2002
Vapour pressure	0.06974 hPa at 25°C	Rowley et al. in DIPPR, 2004
Water solubility	1 x 10^6 mg/L at 25°C	Ullmann, 1992
Partition coefficient n-octanol/water (log value)	–0.21	Reinert, 1987 Hansch and Leo, 1995
Henry's law constant	8.1 x 10^{-4} Pa x m^{-3}/mol at 20°C	Mackey, 2001
Flammability, 100°C	1.8% v/v	Dow, 1995
Flash point, closed cup	101 °C	Dow, 1995

1.4 Read-Across Justification

Justification for Use of Limited Hydroxypropyl Acrylate Data to Support Hydroxyethyl Acrylate: Hydroxyethyl acrylate (CAS RN 818-61-1) is a member of the acrylate ester family with similar structure, physical/chemical properties and fate and effects profile as hydroxypropyl acrylate. The molecules are very similar structurally with the addition of a single carbon on the ester chain of hydroxypropyl acrylate. The structures are shown below:



2-Hydroxypropyl acrylate



2-Hydroxyethyl acrylate

As noted in the study reviews below, the LOAEC values from inhalation studies for the two chemicals are similar (10 ppm for hydroxypropyl acrylate and 5 ppm for hydroxyethyl acrylate) and are based on local irritation. As with other acrylates, at sub-lethal levels, the major effects of both chemicals are related to irritation at the site of contact (stomach from gavage dosing, nasal and respiratory irritation from inhalation exposure, skin irritation from cutaneous exposure). Sufficient data are available for all HPV endpoints with hydroxyethyl acrylate however data for an *in vivo* study of the genotoxicity potential of hydroxypropyl acrylate are included herein to further support the toxicological profile of hydroxyethyl acrylate.

2 GENERAL INFORMATION ON EXPOSURE

HEA may be released into the environment in fugitive and stack emission or in wastewater during production and use of the monomer. HEA is rapidly degraded in the air, is readily biodegradable

and it will not bioaccumulate. Exposure of aquatic species to high concentrations may result in toxicity.

HEA monomer is produced and used mainly in closed systems. The main populations likely to be exposed to HEA are workers involved in production and use of HEA. The primary routes of exposure to HEA are skin contact and inhalation. In an industrial setting, ingestion is not an anticipated route of exposure. Few results are available from workplace measurements at the production or processing sites. Worker exposure is limited by the use of enclosed processing systems, industrial hygiene controls and personal protective equipment.

A review of the results of 140 samples (over 20 year period) of workplace measurements at one HEA production site has shown that no exposures exceeded an 8hr TWA of 1 ppm (Dow, 2003).

Two industrialized countries have adopted occupational exposure limit (OEL) values. Sweden adopted an 8-h TWA (time-weighted average concentration during an 8-h working period) of 1 ppm (~5 mg/m^3) and a STEL (short-term exposure limit during 15 min) of 2 ppm (~10 mg/m^3), with a skin notation and a note "sensitiser" (AFS, 1997). In the Netherlands, the maximum acceptable concentration expressed as 8-h TWA is 0.05 ppm (0.24 mg/m^3) (Arbeidsinspectie, 1996).

2.1 Production Volumes and Use Pattern

In 2001, the total worldwide annual production volume of hydroxyethyl acrylate (HEA) was estimated at 15,000 tonnes. Of that, the HEA production in the United States was estimated to be 10,000 tonnes.

HEA is used mainly either as a co-monomer in the manufacture of polymers or as a chemical reactant in the manufacture of chemical intermediates. In the manufacture of polymers, HEA can be co-polymerized with acrylic acid, acrylates, methacrylates, vinyl acetate, vinyl chloride, vinylidene chloride, styrene, butadiene, and the like. Co-reactants with HEA include aromatic and aliphatic isocyanates, anhydrides, and epoxides. The polymers and chemical intermediates made with HEA find applications in automotive top coatings, architectural coatings, photocure resins, and adhesives. Globally about half of the HEA produced is used in the production of acrylic enamels for the automotive industry, where a clear topcoat is applied to a pigmented base coat to increase corrosion protection and durability (SRI, 2004). Examination of the Substances in Preparation in Nordic Countries database indicated no additional uses.

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

HEA may be released into the environment in fugitive and stack emission or in wastewater during production and use of the monomer. HEA does not occur naturally.

2.2.2 Photodegradation

HEA released into the atmosphere is estimated using EPIWIN to have an atmospheric half-life of 10 hours based on its reaction rate with hydroxyl radicals. Based on its UV absorption spectrum it may also directly photolyze (Brunn, 1976).

2.2.3 Stability in Water

Studies of the hydrolysis of HEA in sterile, buffered water at 25°C reported that the half-life (t1/2)of HEA was 0.051 days at pH 10.87 but was >270 days at pH 7.03; no hydrolysis occurred at pH 2.84 (Gonsior et al., 1997a). Hydrolysis of HEA in sterile, buffered synthetic seawater at a pH of 8.1 and 25°C was found to be more rapid than the estimated t1/2 in buffered water at pH 8.1 with an estimated t1/2 of 17 days (Gonsior et al., 1997b). Based on these data, the hydrolysis of HEA will be significant in alkaline water.

In a study conducted according to OECD guideline 111 ("Hydrolysis as a Function of pH") but without GLP, the half-life ($t_{1/2}$) of HEA at 40°C was 15 hours at pH 9 and 39.6 days at pH 7; no hydrolysis occurred at pH 4 (Luley, 1995); the reliability rating of these data were 4.

2.2.4 Transport between Environmental Compartments

The theoretical distribution of HEA has been estimated using the fugacity model of Mackay, Level I (Mackay 2001). According to this model HEA released into the environment partitions almost completely (99.9%) to the water phase.

Table 2 Estimated Distribution Between Environmental Compartments (Mackay, 2001; Level I)

Compartment	%
Air	0.016
Water	99.9
Soil	0.055
Sediment	0.012

The theoretical distribution of HEA has been estimated using the model of Mackay, Level III (Mackay 2001). Results are shown in the table below.

Table 3 Estimated Distribution among Air, Water, Soil, and Sediments under Various Emission Scenarios (Mackay, 2001; Level III)

Emission Scenario	**Percentage and amount distributed to**				**Residence Time (days) [without advection in brackets]**
	Air	**Water**	**Soil**	**Sediment**	
1,000 kg/hr to Air	0.1 % 4.8 x 10^2 kg	37.4 % 1.6 x 10^5 kg	62.5 % 2.7 x 10^5 kg	1.4 x 10^{-2} % 61.5 kg	17 [29]
1,000 kg/hr to Water	3.9 x 10^{-6} % 1.3 x 10^{-2} kg	100.0 % 3.4 x 10^5 kg	2.1 x 10^{-3} % 7.4 kg	3.9x 10^{-2} % 1.3 x 10^2 kg	14 [22]
1,000 kg/hr to Soil	1.4 x 10^{-3} % 8.3 kg	35.8 % 2.1 x 10^5 kg	64.1 % 3.8 x 10^5 kg	1.4 x 10^{-2} % 82.9 kg	25 [32]
1,000 kg/hr simultaneously to Air, Water, and Soil	3.6 x 10^{-2} % 4.9 x 10^2 kg	52.4 % 7.2 x 10^5 kg	47.5 % 6.5 x 10^5 kg	2.0 x 10^{-2} % 2.8 x 10^2 kg	19 [28]

Conclusion

This material has very high water solubility, very low vapor pressure, and very low log K_{ow}. These properties dictate that the material has low potential to volatilize from water to air, or adsorb to soil and sediments. When released to water (the most likely emission scenario), the material will remain dissolved in water and will be removed through biodegradation and hydrolysis. When released to soil, the material will be primarily dissolved in soil pore water (groundwater), and be removed through rapid biodegradation and hydrolysis. Since this material is susceptible to destructive reactions such as indirect photolysis, biodegradation, and hydrolysis, this material is expected to be short-lived in the environment.

2.2.5 Biodegradation

HEA is readily biodegradable under aerobic conditions as shown by the studies described in the table below. The reliability of the BASF studies could not be determined since full reports were not available to the authors. For the Modified Sturm Test conducted by the OECD 301B guideline (Handley and Horton, 1992), the results confirmed that HEA is readily biodegradable as yields of CO_2 exceeded 60% of theoretical values within a 10-day window following onset of biodegradation. The lag periods required before greater than 10% biodegradation occurred were approximately 6.5 and 8.2 days, at the 10 and 20 mg/l concentrations, respectively. Within ten days following these lag periods, biodegradation averaged about 72 and 75% for the 10 and 20 mg/l reactions, respectively.

Table 4 Aerobic Biodegradation Tests

Test	Method	Inoculum	Concentration of test substance (mg/l)	Degradation (%)	Duration (d)	Result	Reference
Modified Sturm	OECD 301B	Activated sludge	10 and 20	79 & 80, respectively	28	Readily biodegradable	Handley and Horton, 1992
OECD Screening	OECD 301E			85% of DOC	28		BASF, 1981
MITI	OECD 301C	Activated sludge	100	78%	28	Readily biodegradable	CITI, 1992
Modified Zahn-Wellens	OECD 302B			>95% of DOC		Inherently biodegradable	BASF, 1981

2.2.6 Bioaccumulation

Using the regression equation log BCF = 0.76 x log P_{ow} - 0.23 (as quoted in Lyman *et al*, 1990) and the log Pow value of –0.21 (Table 1), a bioconcentration factor (BCF) of 0.41 is calculated. Following EC Technical Guidance, using the formula BCF = a x P_{ow} (where a is the fat content, 0.02-0.2) (CEC, 1994a), the BCF is 0.012. Based on these low values, it is unlikely that HEA will bioaccumulate.

2.3 Human Exposure

2.3.1 Occupational Exposure

HEA is manufactured by the reaction of acrylic acid and ethylene oxide; this process is carried out within closed systems due the reactivity and toxicity of the reactants. The primary potential routes of exposure to HEA are skin contact and inhalation although the low vapor pressure limits the potential for vapor inhalation exposure. The primary use of hydroxyethyl acrylate in the production of polymeric coatings (used predominantly in the automotive industry) results in virtually no unreacted monomer in the finished coatings. The potential exposure to aerosols of hydroxyethyl acrylate is, therefore, highly unlikely. In industrial settings, ingestion is not an anticipated route of exposure. Occupational exposure may potentially occur during manufacture, transportation and industrial use. Worker exposure is limited by the use of enclosed processing systems, industrial hygiene controls and personal protective equipment such as goggles, gloves, organic material respirators and slicker suits during work activities where a there is greater risk of potential exposure.

Few results are available from workplace measurements at the production or processing sites. A review of the results of 140 samples (over 20 year period) of workplace measurements at one HEA production site has shown that no exposures exceeded an 8hr TWA of 1 ppm (Dow, 2003).

2.3.2 Consumer Exposure

It is highly unlikely that any consumer product would contain a significant amount of unreacted HEA due to HEA reactivity as a co-monomer in polymers or a reactant to make chemical intermediates. Hence, consumer exposure to HEA is expected to be negligible.

HEA is included in the positive list of monomers and other starting substances for plastics and coatings intended to come into contact with foodstuffs (CEC, 2002). While there are no recommendations for a specific migration limit or residual level the European Commission has suggested a group maximum total daily intake of 0.1 mg/kg body weight (measured as acrylic acid).

Exposure of the general public through indirect exposure via the environment is not considered likely due to the principal use of HEA in closed systems and its biodegradation and instability in the environment.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

Studies in Animals

In vivo Studies

The metabolism and excretion of HEA has been examined in male Fischer 344 rat using oral, intraperitoneal, dermal and inhalation routes of exposure (Domoradzki et al., 1992). For the oral and intraperitoneal routes of exposure the rats (4 animals/dose level/route of exposure) received a single dose of 2.5 or 50 mg/kg body weight (approximately 15-20 μCi). For the inhalation exposure six rats were exposed to a target concentration of 8 ppm ^{14}C HEA for 6 hours in a head only inhalation chamber. For the dermal exposure 4 rats were treated with ^{14}C HEA at a dose of 12.5 mg/kg body

weight. No qualitative differences in urinary metabolites between routes were observed, indicating no marked route-dependent differences in the metabolic fate of HEA. The results of the study indicate that once the chemical becomes systemically available it is rapidly metabolized and eliminated from the body as either CO_2 in the expired air or urinary metabolites. The available metabolic data on HEA is consistent with information on substances with other acrylates where hydrolysis of the ester functionality is the primary metabolic pathway. By analogy with ethyl acrylate and acrylic acid it is expected that a minor metabolic pathway for HEA will be via conjugation with glutathione with the resulting mercapturic acid derivatives being excreted in the urine.

For the oral and intraperitoneal routes (2.5 mg/kg body weight) 35-36% of the administered dose was expired as $^{14}CO_2$ and 43-47% of the dose excreted via the urine by 48 hours post-dosing. At 50 mg/kg body weight 40-45% of the dose was expired as $^{14}CO_2$ and 33-36% of the dose was excreted in the urine. Following dermal administration 66% of the dose was absorbed within 48 hours of the application with remaining 33% being associated with the application site. Of the absorbed dose 27% was excreted in the urine as metabolites of HEA and 27% was excreted in the expired air as $^{14}CO_2$. For inhalation 39% of the absorbed dose was eliminated in the urine by 48 hr and 41% was expired as $^{14}CO_2$. For all routes, 9-16% was found in the tissues and carcass and less than 3% in the feces. The half-lives of elimination in the urine and for expired $^{14}CO_2$ were 14 h and 17 h, respectively. The half-life of elimination in the plasma was determined to be 26 hr and did not represent parent chemical.

Conclusion

Animal studies indicated rapid metabolism *via* hydrolysis of the ester functionality with the subsequent rapid metabolism of the hydrolysis products to produce exhaled CO_2 or urinary metabolites (mercapturic acid derivatives). There were no marked route-dependent differences in the metabolic fate of HEA when administered by the oral, intraperitoneal, dermal or inhalation routes of exposure.

3.1.2 Acute Toxicity

Studies in Animals

Inhalation

The limited inhalation data available on HEA indicate that a 7 hour exposure of 264 ppm (1250 mg/m^3) had no lethal effect. Inhalation exposures to 333 to 394 ppm for 4 or 8 hours respectively caused irritation and were in the threshold area for lethality. At exposures at 500 ppm and above, close to 100% lethality was observed.

Table 5 Acute Inhalation Toxicity

Species	Concentration[a] ppm	mg/m^3	Duration (h)	Comment	Reference
Rat	(333)	1,580[b]	8	1 out of 6 animals died. Clinical signs included eye, ear and nose irritation, and diarrhea.	West and Carpenter, 1966
Rat	(394)	1,870[b]	4	1 out of 6 animals died. Clinical signs included ocular irritation and diarrhea.	West and Carpenter, 1966
Rat	(264[c], 2231[d])	1,250, 10,580	7	264 ppm was without effect; when HEA was heated to 100°C (2231 ppm) all 5 rats died within 5 hours, possible liver and kidney effects.	Olson, 1962
Rat	500	(2370)	4	5 out of 6 animals died	Smyth *et al*, 1951
Rat	Saturated vapour	-	1	No deaths (12 exposed)	Smyth *et al*, 1951

[a] Converted values are given in parentheses

[b] Reported as 1.58 and 1.87 mg/l at 22°C, respectively

[c] Nominal concentration at room temperature

[d] Test material heated (100°C) to produce vapor

Dermal

The key study evaluating the acute dermal toxicity of HEA used 20 New Zealand White (NZW), albino rabbits (two/sex/dose level) and applied undiluted test material (Carreon et al., 1981). Topical doses of 63, 130, 160, 200 or 250 mg/kg body weight were applied for 24 hours under a plastic occlusive bandage. The acute percutaneous LD_{50} was 154 mg/kg body weight with a 95% confidence interval of 131-174 mg/kg body weight. Marked erythema and edema of the skin was seen in all treated animals and slight to moderate necrosis of the skin was observed in some animals. Clinical signs of toxicity were lethargy, decreased activity, loss of appetite and at 250 mg/kg body weight only, rapid shallow breathing. The results of acute dermal toxicity studies are summarized in the table below.

Table 6 Acute Dermal Toxicity

Species	Sex	LD_{50} (mg/kg body weight)	Comment	Reference
NZW Rabbit	Males & Females	154	Undiluted HEA applied to the intact skin (not abraded) on the shaved trunk of albino rabbits (~ 30% of body surface); 24 hours under impervious plastic sheeting; 95% confidence limits 131 to 174 mg/kg body weight	Carreon et al., 1981 (Key study)
Rabbit	Male	154	During 24-h contact period HEA was held in place with an impervious sheet on the clipped intact skin (not abraded).	West and Carpenter, 1966
Rabbit	Male	250	Undiluted, 24-h contact with closely shaven intact skin (not abraded)	Rohm and Haas, 1975
Rabbit	Male & Female	298	Undiluted HEA applied to the shaved trunk (intact skin, not abraded) of albino rabbits (~ 30% of body surface); 24 hours under impervious plastic sheeting; 95% confidence limits 220 to 402 mg/kg body weight	Hintz and Kretchmar, 1974
Rat	Male & Female	>1000	HEA in olive oil applied to ~50 cm^2 clipped intact skin (not abraded), 24 hours, semiocclusive	Wiemann and Hellwig, 1999

Oral

The key study evaluating the acute oral toxicity of HEA established a LD_{50} of 548 mg/kg body weight with a 95% confidence limits of 460.5 to 652.1 (Hintz and Kretchmar, 1974). In this study, HEA was administered as a 10% solution by gavage to groups of four Sprague-Dawley rats (two of each sex per dose group) at doses of 266.7, 400, 600 and 900 mg/kg body weight. The animals were observed for 14 days post-dosing. The mortality was 0/4, 0/4, ¾, and 4/4 at each dose level, respectively. Clinical signs (following administration of 10% aqueous solution) included hypoactivity, rough fur, labored breathing, muscle weakness, GI tract hemorrhage in the animals that died. Neat material may burn the tissues of the mouth, throat and gastro-intestinal tract. Acute LD_{50} values ranging from 540 to 1070 mg/kg body weight were reported as shown in the following table.

Table 7 Acute Oral Toxicity

Species	LD_{50} (mg/kg body weight)	Remark	Reference
Rat	548	Male and female, Sprague-Dawley rats; 4 animals per dose group, doses of 266.7, 400, 600 and 900 mg/kg body weight; 95% confidence limits of 460.5 to 652.1 mg/kg body weight	Hintz and Kretchmar, 1974 (Key Study)
Rat	540	Male rats, Sherman strain; 5 animals per dose group, doses of 126, 252, 500, 1,000 or 2,000 mg/kg body weight; 95% confidence limits 390 - 750 mg/kg body weight	Olson, 1962
Rat	650	5 animals per group dosed with undiluted HEA (0.5 or 1.0 ml/kg body weight)	West and Carpenter, 1966
Rat	810	Dose range 500 to 1,500 mg/kg body weight. All animals survived 500 mg/kg body weight with no ill effects	Nalco Chemical, 1979
Rat	1,070	Undiluted HEA administered to groups of 5 rats	Smyth *et al*, 1951
Mouse	601	Only 4 animals/group, 4 different doses	Tanii and Hashimoto, 1982

Conclusion

Inhalation exposures to 333 to 394 ppm for 4 or 8 hours respectively caused irritation and were in the threshold area for lethality. At exposures at 500 ppm and above, close to 100% lethality was observed. The acute percutaneous LD_{50} was 154 mg/kg body weight with a 95% confidence interval of 131-174 mg/kg body weight. Studies on the acute oral toxicity of hydroxyethyl acrylate indicate LD_{50} values ranging from 540 to 1070 mg/kg body weight.

3.1.3 Irritation

Skin Irritation

Studies in Animals

Several studies have shown that undiluted HEA is severely irritating to the skin if left in contact with the skin for a sufficient period of time. Carpanini (1981) reported that HEA produced severe skin damage in albino rabbits following exposure under occlusion. West and Carpenter (1966) reported that the application of undiluted HEA to rabbit skin produced necrosis, erythema and edema while application to the ear produced moderate necrosis and severe edema after 24 hours and moderate necrosis after 8 days. In a study carried out by the Industrial Bio-Test Laboratories (Hintz and Kretchmar, 1974) HEA was applied, using gauze patches, to the shaved skin of albino rabbits. The gauze patches were held in place for 24 hours under impervious plastic sheeting. Treatment was reported as being extremely irritating producing skin necrosis.

Dermal studies to test for skin corrosivity classification by the US Department of Transportation (DOT) (Rampy and Keeler, 1973 & Lockwood and Borrego, 1981) indicate however that dermal contact for 4 hours produced reversible irritation with no corrosive effect.

In another study (Olson, 1962), the abdominal skin of two New Zealand White rabbits was shaved and 0.5 ml of undiluted HEA or a 10% solution of HEA was placed under a cotton pad on four skin areas. The undiluted HEA produced slight redness at 15 minutes and 1 hour exposure and moderate

erythema with extensive edema and burn at 4 hours. Treatment with the 10% solution for 15 minutes did not produce skin irritation. Treatment with the 10% solution for 1 or 3.25 hours produced slight erythema, and /or edema. The 6-hour treatment with a 10% solution produced moderate redness, swelling and slight burn which healed with a scab after 5 days.

Conclusion

Undiluted HEA was a severe irritant to rabbit skin and direct contact for 24 hours was corrosive to the skin. Dermal contact with undiluted HEA for times up to and including 4 hours produced reversible irritation with no corrosive effect in rabbits. Direct contact with undiluted HEA for 6 hours produced irritation and tissue damage with evidence for recovery.

Eye Irritation

Studies in Animals

Several studies have shown that undiluted HEA is severely irritating and can damage the eye. In a key study, 0.1 ml of undiluted HEA was instilled into the conjunctival sac of the right eye of six New Zealand White rabbits; the left eye was left untreated and served as the control, rabbits were examined at 1 and 60 minutes post-treatment, as well as at 1, 3, 7 and 14 days after treatment (Hintz and Kretchmar, 1982). Treatment with HEA caused severe eye irritation in all six rabbits, with either maximum or near maximum scores for effects on the conjunctiva, iris and cornea achieved in 5 of 6 rabbits by 3 days post-treatment and persisting through 14 days.

In another study (Olson, 1962) undiluted and a 10% aqueous solution of HEA was instilled directly into the conjunctival sacs of New Zealand Albino rabbits. Within about 30 seconds of treatment one eye of each animal was washed with flowing water the other treated eye was left unwashed. One hour after treatment with undiluted material the washed and unwashed eye showed inflammation of the conjunctival membranes with corneal opacity over 50% of the eye. The response was essentially unchanged 2 and 7 days later. Treatment with the 10% aqueous solution caused some slight irritation which persisted in the unwashed eye for 2 days. The washed eye showed no sign of irritation one hour post-instillation.

Smyth *et al.*, (1951) and West and Carpenter (1966) also reported that a single instillation of 0.005 of undiluted HEA into the conjunctival sac of rabbits produced corneal necrosis and eye irritation.

Conclusion

Undiluted HEA caused severe irritation with corneal injury when instilled directly into the eyes of laboratory rabbits. Direct contact with the eye may result in permanent impairment of vision, even blindness. Treatment with the 10% aqueous solution of HEA without immediate washing caused slight eye irritation which persisted for 2 days.

3.1.4 Sensitisation

Studies in Animals

Skin

Ashby et al., 1995 and Scholes, 1992 have reported positive responses in the local lymph node assay indication that HEA dermal sensitization. Other sensitization studies conducted are summarized in the table below and indicate that HEA can produce dermal sensitization in laboratory animals.

Table 8 Sensitization Tests in Laboratory Animals

Species	Test method	Result	Reference
Mouse	Local Lymph Node Assay	Sensitization	Ashby et al., 1995 (Key Study)
Mouse	Local Lymph Node Assay	Sensitization	Scholes, 1992
Guinea pig	Maximization test 0.5% solution of HEA in a 9:1 mixture of Dowanol DPM:Tween 80.	Sensitization (10 of 10 animals)	Norris, 1970
Guinea pig	Buehler test Day 1, 3, 8, 10, 14 and 16: 50% HEA in 60 % acetone (0.5 ml) by dermal route Day 42: 50% HEA in 60% acetone (0.5 ml) by dermal route	Sensitization (10 of 10 animals)	Kapp, 1977
Guinea pig	Maximization test. Induction 10% solution of HEA in 97% ethanol. Challenge, 5% solution of HEA in 97% ethanol	Sensitization (10 of 10 animals)	Auletta et al, 1982 Report from Bio/dynamics Inc.
Guinea pig	Maximization test Day 0: in presence of Freund's Complete adjuvant (FCA), 0.5% HEA (50 µl) in sterile water i.p. Day 7, 8: HEA , 25%, (400 µl) by cutaneous route, Day 21: 0.3% (25 µl) in petrolatum on the flank, occlusive patch for 24 hours Evaluation: 48 and 72 hours after patch removing.	Sensitization (12 of 12 animals)	Clemmensen, 1984
Mouse	Local lymph node assay	Positive local lymph node response	Basketter and Scholes, 1992

Conclusion

The results of the sensitization studies clearly demonstrate that HEA is a dermal sensitizer in animals.

Studies in Humans

Skin

There are several case reports of skin sensitization resulting from occupational exposure to HEA. For example, Kanerva *et al.,* (1995a,b) reported 14 positive patch tests to HEA in a tested population of 124 individuals exposed to acrylates and methacrylates. Other cases are reported by Tobler *et al*., (1990), Kiec-Swierczynska (1996), and Kanerva *et al*., (1988). Some studies indicate that indicate that hydroxyethyl acrylate is a sensitizer and may cross-react with other acrylates in some exposed individuals.

Conclusion

Clinical reports indicate that HEA is a dermal sensitizer in humans and may cross-react with other acrylates in some exposed individuals.

3.1.5 Repeated Dose Toxicity

Studies in Animals

Inhalation

In a 4-week inhalation study 15 to 20 male rats per group were exposed for 7 hours/day, 5 days/week to HEA vapors at concentrations of 0, 5, 10 or 25 ppm (23.7, 47.4 or 118.5 mg/m^3) (Leong and Trice, 1970). Interim sacrifices were performed on the 5 and 10 ppm groups after 2 weeks of exposure. All animals were subjected to a gross and microscopic examination irrespective of whether they died during the treatment or were killed at the termination of treatment. There were two deaths during the 13-week study. One male in the 60 mg/kg/day dose group died on day 31 and one female in a saline control group died between days 45 and 47. General necropsy did not reveal the cause of death.

Histopathological examination found ulcerative keratitis (superficial loss of cornea with inflammation) in all groups exposed to HEA. The incidence of this effect increased with the exposure concentration with the lesion occurring in 14, 6 and 3 animals in the 25, 10 and 5 ppm treatment groups respectively. Focal ulcerative rhinitis (superficial loss of nasal epithelial tissue with inflammation) was observed in 7 and 4 rats in the 25 and 10 ppm treatment groups, respectively, but was not seen in the control rats. Clinical signs of nasal irritation were observed at 10 ppm and 25 ppm produced dyspnea (shortness of breath) and abdominal bloating which became more severe as the number of exposures increased. There were 17 spontaneous deaths in the 25 ppm treatment group. Unfortunately because of the high incidence of chronic murine pneumonia in all groups (not treatment-related) it was impossible to characterize any lung pathology which might have been caused by exposure to HEA. At termination, mean body weights of rats exposed to 10 ppm for 20 days were significantly lower than controls. Relative weights of livers were higher for rats that were exposed to 10 and 5 ppm, relative kidney weight was increased at 10 ppm only. Testicular atrophy was observed histopathologically in one of 9 rats exposed to 10 ppm HEA for 20 exposures but was judged not to be treatment-related. No testicular atrophy was found in the highest exposure group. The lowest observed adverse effect concentration (LOAEC), based on corneal irritation, was 5 ppm.

Oral

Groups of male and female Sherman strain rats (10/sex/group) were maintained for 100 days on a diet containing 0, 0.03. 0.1 or 0.3% HEA (equivalent to doses of 6, 20 and 60 mg/kg body weight/day). Treatment did not cause any toxic effects as judged by mortality, growth, behavior, food consumption, hematological values, clinical chemistry measurements, organ weights and gross and microscopic examination of tissues (McCollister et al., 1967a).

Groups of male and female Beagle dogs (2/sex/group) were maintained for 97 days on a diet containing 0.06, 0.2, or 0.4% HEA in diet (equivalent to doses of 21, 60 and 125 and 22, 63 and 131 mg/kg body weight/day for males and females respectively). No adverse effects were found in male and female dogs. There were no treatment-related changes in organ weights, histopathology or other parameters (McCollister et al., 1967b).

Intraperitoneal

Moser *et al*., (1992) conducted a subchronic neurotoxicity study where HEA in saline was injected intraperitoneally into Long-Evans rats (10/sex/group) at dosages of 0, 3, 20 and 60 mg/kg body weight/day, 5 days a week for 13 weeks. HEA treatment resulted in a statistically significant decrease in body weight gain for male rats in the 60 mg/kg body weight dose group. The authors observed abdominal bloating as result of the intraperitoneal (i.p.) injection of HEA which was

sometimes extreme. This bloating was likely was responsible for some of the changes in the functional observational battery (FOB) that are described below. Irritation of the peritoneum due to the i.p. injection of HEA at all dosages is consistent with "extreme" bloating, however gross and histological examination of the peritoneum and found no evidence overt peritonitis or other abnormalities. Histologic examination of the liver, kidneys, bladder, diaphragm and brain, spinal cord and peripheral nerve following fixation of tissues by perfusion revealed no treatment-related effects.

Baseline data FOB for each animal were collected prior to treatment. Male (not female) rats had a transiently decreased hindlimb grip at the higher dosage at 90 days. The FOB showed increased reactivity to handling and to external stimuli, likely due to bloating of the abdominal area with tenderness (that could have interfered with behavioral measurements), as well as mild hypothermia; however, no information was given about dose-response relationship or magnitude of these effects. Righting reflex was significantly impaired in males at 90 days, but the effect was slight and there was no dose-response relationship. Gait was affected, but the authors indicated that the HEA-treated rats did not show a clear dose-response relationship in the gait score. In fact, examination of the data presented in Figure 2 shows that the baseline differences can account for most of the differences seen among dose groups. HEA produced no changes in foot splay. Body weights in male rats showed an effect in the high-dosage group, but no effect was seen in females. Neuropathological evaluation (after perfusion of 6 rats/sex/dosage) included evaluation of 6 brain sections, dorsal and ventral roots and ganglia, sciatic (2 locations), tibial and sural peripheral nerves. No neuropathological changes were detected either in the central, or in the peripheral nervous systems. Acrylamide was also used in this study as a positive control agent, and time-course and dose-related changes in gait, splay and neuropathology were demonstrated and were consistent with the literature.

Female gait score data were also presented, but failed to show a convincing effect (abnormal control data points may account for statistical significance). The authors did not comment about how bloating (pear-shaped belly) could have eventually affected gait scores. The suggestion of an indication of minimal neurotoxicity based on increased urination was not persuasive and overall there is no convincing evidence that HEA was neurotoxic.

Conclusion

The primary treatment-related effects of inhalation exposures of rats to HEA at doses up to and including 25 ppm was corneal keratitis occurring at the lowest exposure concentration of 5 ppm. Clinical signs of nasal irritation were observed at 10 ppm and 25 ppm produced dyspnea and abdominal bloating which became more severe as the number of exposures increased. Focal ulcerative rhinitis was observed histopathological in a dose-dependent manner. Results of repeat dose dietary studies in the rat fed concentrations up to 0.3% in the diet indicate that ingestion of HEA did not produce evidence of toxicity. No adverse effects were found in male and female dogs fed HEA in the diet for 97 days at doses up to 125 and 131 mg/kg body weight/day. Urine staining, abdominal bloating and reduced body weight was observed in the high-dose group in male rats repeatedly injected i.p. with HEA for 13 weeks though these effects were probably due to the i.p. dosing itself and not the test substance.

3.1.6 Mutagenicity

Studies in Animals

In vitro Studies

HEA was not mutagenic in *Salmonella typhimurium* with or without metabolic (S9) activation (strain TA100, 0.01-7.5 µl/plate [0.01-7.5 mg/plate]; Lohse and Melly, 1982; strains TA98, TA100, TA1535, TA1537 and TA1538) Dow Chemical Co., 1976; concentration not stated). HEA (0.038 – 5 mg/plate) was not mutagenic *Salmonella typhimurium* strains TA102 or TA2638 with or without metabolic (S9) activation but was but was positive (~2-3 fold increase in revertants as compared to controls) at 1.25 mg/plate and above in *E. coli* strain WP2/pKM101 and at 2.5 mg/plate and above in strain WP2 uvrA/pKM101 (Watanabe *et al.*, 1996).

Dearfield *et al.,* (1989) reported that HEA produced a clear dose-response related increase in mutant frequency in the mouse lymphoma cell assay (L5178Y, $TK^+/-$) without metabolic (S9) activation (0, 10, 15, 20 and 25 ug/ml concentrations tested).

Dearfield *et al*., (1989) also reported a dose related increase (0, 15, 18 and 20 ug/ml concentrations tested) in chromosomal aberrations and micronuclei in L5178Y mouse lymphoma cells treated with HEA in the absence of metabolic (S9) activation.

In vivo Studies

As part of the chronic inhalation study (exposure 0.5 and 5 ppm HEA; 6 h/day, 5 days/week) some of the rats (i.e. 4 rats/sex/dose group) were killed after 12-months exposure and the bone marrow cells examined for chromosomal damage. No evidence of chromosomal damage was seen (Johnston et al., 1977; Rampy et al., 1979).

A mouse micronucleus assay (conforming to OECD Guideline 474) was carried out with the HEA analog hydroxypropyl acrylate (HPA) (*i.e.* similar results would be expected with HEA) using NMRI mice (5 males and 5 females per group) and administering single gavage doses of 0, 100, 300 or 600 mg/kg body weight. *In vivo* toxicity as evidenced by slightly reduced spontaneous reactivity was observed for up to six hours post-dosing at the dose of 600 mg/kg body weight but there was no increase in the frequency of micronuclei at any dose level of HPA as compared to the control animals at either 24 or 48 hours post-dosing (Hamann, 2000).

Conclusion

The limited data on the genotoxicity of HEA are generally consistent with information from other acrylates, i.e. absence of mutagenic effect in *Salmonella typhimurium* but some evidence of a positive effect in an *in vitro* mouse lymphoma (L5178Y, $TK^+/-$) cell mutation assay. While HEA showed evidence of a clastogenic effect *in vitro*, there is no evidence for an effect *in vivo*.

3.1.7 Carcinogenicity

In vivo studies in animals

Inhalation

In a chronic inhalation study male and female Sprague-Dawley rats (99 or 100 animals per sex per dose group) were exposed to HEA 6 hours per day, 5 days/week for 18 months at concentrations of 0.5 ppm (2.4 mg/m^3) or 5 ppm (24 mg/m^3). The control group consisting of 100 animals of each sex was exposed to air. After termination of treatment the male and female animals were left for a recovery period of 5 and 6 months respectively before being killed for examination *post mortem*.

The study included a 12-month interim kill for pathological and cytogenetic examination. Histopathological examination was carried out for the following tissues of the control and 5 ppm groups, at interim and terminal sacrifice: brain, heart, liver kidneys, testes, lungs, thoracic and/or mesenteric lymph nodes, salivary glands, pancreas, adrenals, spleen, thymus, aorta, skeletal muscle, small intestine, large intestine, thyroid gland, trachea, spinal cord, peripheral nerve, pituitary gland, epididymides, urinary bladder, accessory sex glands, adipose tissue, ovaries, uterus, nasal turbinates, and any gross lesion suggestive of a pathologic process or with tumor formation. At 0.5 ppm terminal sacrifice the following tissues were examined by light microscopy: lungs, livers, kidneys, lymph nodes tracheas and grossly visible lesions from all surviving animals; at interim sacrifice grossly visible lesions or tissues where lesions seen at 5 ppm. Rats dying or culled during the course of the study, complete necropsy and microscopic exam as described above (except when autolysis precluded evaluation) and the presence and absence of neoplasms recorded.

Body weights, terminal organ weights and cumulative mortality, urinalysis, clinical chemistries and hematology did not appear to be altered by chronic HEA exposure. Overall treatment was not associated with adverse effects except that the rats in the 5 ppm treatment group developed yellow staining of the fur and a marginal increase in *Mycoplasma*-induced pneumonia which was interpreted as being treatment-related. No treatment-related effects were seen in the 0.5 ppm group. Overall chronic inhalation exposure to HEA at a dose of 5 ppm caused only a minimal toxicological effect while no toxicity was seen at 0.5 ppm. Gross and histopathological examination of tissues showed no indication of significant chronic toxicity or a carcinogenic effect in either the 5 or 0.5 ppm treatment groups (Kociba et al., 1979).

Conclusion

Exposure to HEA vapors was carried out for 18 months and rats were maintained without further HEA exposure for approximately 6 months. Therefore this study does not meet current guideline requirements of a 24 month exposure period for a standard oncogenicity study. Despite these and other limitations (i.e.: *Mycoplasma* bacterial infection) the study provides evidence that HEA was not carcinogenic *via* inhalation, which is potentially a route of occupational exposure.

3.1.8 Toxicity for Reproduction

Studies in Animals

Effects on Fertility

No reproductive toxicity studies are available. As part of the chronic inhalation study described above (Kociba et al., 1979) a detailed pathological examination of the male and female reproductive organs was conducted. In this study, male and females Sprague-Dawley rats were exposed to HEA vapors for 6 hours per day, 5 days/week for 18 months at doses of 0.5 ppm (2.4 mg/m^3) or 5 ppm (24 mg/m^3). The control group consisting of 100 animals of both sexes was exposed to air. After termination of treatment the male and female animals were left for a recovery period of 5 and 6 months respectively before being killed for examination *post mortem*. The pathological examination indicated that the female rats in the 5 ppm group showed an increased incidence of uterine inflammation as compared to the negative control animals. The incidence of uterine inflammation was 2/21 in controls and 1/3 and 11/27 for the 0.5 and 5 ppm groups, respectively. No other statistically significant differences for histopathologic observations of the female reproductive organs were found, including the ovaries and the effects in the uterus are not considered indicative of reproductive toxicity potential for HEA.

An evaluation of the histopathological data from the male animals exposed to 5 ppm indicated a statistically significant increase from the controls in the incidence of fibrinoid degeneration in the

vascular channels of the testes which was a local vascular manifestation of mesenteric periarteritis syndrome [inflammation of the outer coat of an artery] observed as age-related lesion in this rat strain (8/14 in controls *vs.* 17/19 for the 5 ppm group). The authors of the study indicate that the fibrinoid degeneration in the testes was not a substance-specific toxic effect as the laboratory conducting this study commonly observed this lesion in aging rats of this strain at similar incidence as was observed in this study (the historical control incidence of this lesion in the testes from seven chronic toxicity/oncogenicity studies ranged from 37 to 85%). Polyarteritis (polyarteritis or periarteritis nodosa, that is: simultaneous inflammation of a number of arteries) is the most conspicuous inflammatory lesion of the blood vessels of rats. The etiology is unknown and the incidence varies among strains and colonies (Mitsumori, K. (1990) Chapter 29 in Pathology of the Fischer Rat. Eds: Boorman et al., Academic Press, Inc. p 477). Common sites in male rats are the arteries of the testicle and to a lesser extent the arteries of the spermatic cord (Burek, J.D. (1978) Pathology of the Aging Rat, CRC Press p. 87). Carlton and Engelhardt (Polyarteritis, In: Cardiovascular and Musculoskeletal Systems Eds: Jones, T.C., Mohr, U. and Hunt, R.D., Springer-Verlag, 1991, p 71) also indicate that this lesion can be present in spermatic arteries.

In summary, histopathological examination of both male and female reproductive organs showed no indication of any treatment-related reproductive toxic effects.

Dietary studies with HEA in dogs (97 days) and rats (100 days) produced changes in body weights and organ weights changes related to the altered body weight (McCollister, 1967a and 1967b). HEA did not alter the histopathology of the testes or uterus in either species (dogs up to 0.4% in the diet (~131 mg/kg body weight/day); rats up to 150 mg/kg body weight/day).

Developmental Toxicity

In a study where the developmental toxicity of seven acrylates was investigated (Saillenfait 1999), groups of 25 pregnant rats were exposed to 0, 1, 5 or 10 ppm (0, 4.8, 24 or 48 mg/m^3). HEA was administered by inhalation

6 hrs/day from days 6 through 20 of gestation. Maternal toxicity was demonstrated at 10 ppm as a statistically significant decrease in maternal body weight gain over the entire exposure period, which was also statistically different from controls on days 6-13. A statistically significant decrease in food consumption as compared to controls was also observed for the 10 ppm group on days 6-21. Uteri were removed and weighed, and the number of implantation sites, resorptions, and dead and live fetuses were recorded. Uteri which had no visible implantation sites were stained with ammonium sulfide to detect very early resorptions. Live fetuses were weighed, sexed, and examined for external anomalies including those of the oral cavity. Half of the live fetuses from each litter were preserved in Bouin's solution and examined for internal soft tissue changes. The other half were fixed in ethanol, eviscerated, and then processed for skeletal staining with alizarin red S for subsequent skeletal examination.

There were no treatment-related increases in the number of implants, embryo/fetal mortality or fetal malformations observed. There was no treatment effect on fetal body weight. The NOEL for maternal toxicity was 5 ppm, the NOEL for developmental effects and fetotoxicity was 10 ppm.

Conclusion

Inhalation exposure of pregnant rats to HEA produced no evidence of developmental or fetal toxicity or teratogenicity. Histopathological examination of the reproductive organs from repeated dose toxicity studies and a chronic toxicity/oncogenicity study of HEA produced no evidence of a treatment-related effect.

3.2 Initial Assessment for Human Health

The metabolism and excretion of HEA in the rat appears to be independent of the route of administration and once systemically available, HEA was rapidly metabolized and eliminated from the body regardless of whether it was administered orally, intraperitoneally, dermally, or by inhalation. The major routes of excretion were *via* the expired air as CO_2 and in the urine as metabolites of HEA. The rate of absorption of HEA was route-dependent and was complete within 4 hours or less when given by the oral or intraperitoneal routes. Following dermal administration, an average of 66% of the applied dose was slowly absorbed within 48 hours with 33% of the dose remaining at application site. Nevertheless, it appears that dermal absorption can occur in amounts sufficient to result in lethality and the dermal LD_{50} was lower than the oral LD_{50} in nearly all studies conducted.

The oral LD_{50} for HEA was in the range of 540 to 1070 mg/kg body weight. Inhalation exposure to HEA at 333 - 394 ppm for 4 or 8 hours caused irritation and was in the threshold area for lethality. In studies where acute exposures of laboratory animals to HEA vapors were conducted at 500 ppm and above, overt lethality occurred.

HEA has been determined in acute and chronic animal studies as producing local irritation at the site of contact by either the inhalation route and by skin contact. Regarding the development of primary irritation following inhalation of HEA, repeated dose inhalation studies suggest that the upper respiratory tract is likely to be the target organ. In addition, contact dermatitis resulting from skin contact with HEA is clearly and strongly evident in both animal studies and clinical reports describing occupational exposures. A critical effect of undiluted HEA was its severe irritancy to the eye, direct contact with liquid undiluted material caused serious irreversible damage to the eyes of rabbits, although diluted material was less irritating. In addition, evidence of corneal damage by HEA vapor was observed in rats at sufficient high concentrations in a subchronic inhalation study. A subchronic neurotoxicity study by the intraperitoneal route of administration produced abdominal bloating in all treatment groups but did not yield convincing evidence of neurotoxicity or other systemic effects.

HEA produced a clear dose-response related increase in mutant frequency in the mouse lymphoma cell assay (L5178Y, TK^{+}/-) without metabolic (S9) activation. Data from the 18-month inhalation study indicate that HEA is not an animal carcinogen. The absence of effects on the reproductive organs that would adversely alter reproduction in the chronic inhalation study and a lack of developmental toxicity in a well conducted inhalation study provide evidence that HEA is not a developmental or reproductive toxicant.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute toxicity to fish (Geiger *et al.*, 1986; Russom *et al.*, 1988) yielded a 96-hour LC_{50} for fathead minnows of 4.8 mg/L (NOEC = 4.2 mg/L). This study followed ASTM (1980) guidelines using a flow-through design. Nominal exposure concentrations ranged from 2.7 to 16 mg/L and analyses at 96 hours ranged from 3.18 to 16.1 mg/L. Mortality occurred in the three highest concentrations (5.92, 9.14 and 16.1 mg/L, measured). The LC_{50} was determined based on analytical values.

An acute toxicity study with *Daphnia magna* (Handley and Grant-Salmon, 1992) indicated the 48-hour EC_{50} was 0.78 mg/L (NOEC = 0.32 mg/L). This study followed OECD Guideline 202 and Directive 84/449/EEC, C.2 using a static design. Nominal exposure concentrations ranged from .01

to 10 mg/L; no analytical confirmation was performed. Immobilization occurred in the two highest concentrations (5.6 and 10 mg/L, nominal).

A toxicity study with *Pseudokirchneriella subcapitata* (formerly known as *Selenastrum capricornutum)* (Scheerbaum, 2004) indicated the 96-hour EC_{50} values for biomass and growth rate were 4.12 mg/L and 8.26 mg/L, respectively and the 96-hour NOECs were 0.625 mg/L and 2.5 mg/L, respectively. This study followed OECD Guideline 201 using a static design. Nominal exposure concentrations ranged from 0.625 to 10 mg/L. Growth inhibition of algae was observed at concentrations of 2.5 mg/L and greater. The EC_{50} values were determined based on nominal values.

Table 9 Acute Aquatic Toxicity Test Results

Fish Toxicity					
Species	**Test Method**	**Time (h)**	**Effect/ parameter**	**Concentration (mg/l)**	**Reference**
			Lethality		
Pimephales promelas	Flow-through	96	LC_{50}	4.8	Geiger, 1986 Russom et al., 1988 (Key Study)
Cyprinodon variegatus	Flow-through	96	LC_{50}	17.5	Emmitte, 1978
Leuciscus idus	Static	96	LC_{100}	10	BASF, 1982
Invertebrate Toxicity					
Species	**Test Method**	**Time (h)**	**Effect/ parameter**	**Concentration (mg/l)**	**Reference**
			Mobility		
Daphnia magna	Static[a]	48	EC_{50}	0.78	Handley and Grant-Salmon, 1992
[a] OECD guideline 292 [b] Confidence limits (6.9 - 9.2)					

Algae Toxicity		
	Inhibition based on Biomass [mg/L]	
	72 h	96 h
E_bC_{50}	3.96	4.12
95 % confidence interval	3.53 - 4.44	3.75 - 4.52
LOEC	1.25	1.25
NOEC	0.625	0.625
	Inhibition based on Growth rate [mg/L]	
E_rC_{50}	8.81	8.26
95 % confidence interval	7.98 - 9.72	7.62 - 8.95
LOEC	2.5	5
NOEC	1.25	2.5
NOEC and LOEC values were calculated using One Way Analysis of Variance, DUNNETT'S test and BONFERRONI t-test (α=0.05) NOEC, LOEC and EC_{50}-Values (0-72 and 0-96 h) of Hydroxyethyl acrylate (HEA) based on nominal concentrations [mg/L]		

Toxicity to Microorganisms

Using the Warburg test (DEV/L2), HEA was judged non-toxic to adapted sewage sludge at a concentration of EC_0 > 250 mg/L (BASF, 1995). For the protozoan *Tetrahymena pyriformis*, a 50% impairment of growth concentration (IGC_{50}) of HEA was reported as the log (IGC_{50}^{-1}) = 0.69 mM which is equivalent to 23.7 mg/L (Shultz, 1997).

4.2 Terrestrial Effects

No data are available.

4.3 Other Environmental Effects

No data are available.

4.4 Initial Assessment for the Environment

HEA has a high toxicity to aquatic organisms. The 96-h LC_{50} for fathead minnow (*Pimephales promelas*) is 4.8 mg/l while the 48-h EC_{50} for *D. magna* is 0.78 mg/l, the most sensitive species tested. The 96 hr EC_{50} for algae based on biomass and growth rate were 4.12 and 8.26 mg/L, respectively.

5 RECOMMENDATIONS

Human Health: The chemical possesses properties indicating a hazard for human health (severe eye irritation with corneal injury which may result in permanent impairment of vision, even blindness, skin and upper respiratory tract irritation, skin sensitization, and acute toxicity from inhalation exposure). Based on exposure data presented by the Sponsor Country (relating to production in one country which accounts for 67% of global production and relating to the use pattern in the Sponsor country), this chemical is currently of low priority for further work. Countries may wish to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: The chemical possesses properties indicating a hazard for the environment (fish, invertebrate, and algae). However, the chemical is of low priority for further work for the environment because of its ready biodegradability and the limited potential for bioaccumulation.

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S I D S

Dossier

Existing Chemical	:	ID: 818-61-1
Memo	:	HEA
CAS No.	:	818-61-1

Producer related part

Company	:	The Dow Chemical Company
Creation date	:	08.08.2002

Substance related part

Company	:	The Dow Chemical Company
Creation date	:	08.08.2002
Status	:	
Memo	:	
Printing date	:	27.07.2005
Revision date	:	
Date of last update	:	30.03.2005
Number of pages	:	1
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type : manufacturer
Name : Cognis Performance Chemicals UK Ltd.
Contact person : Mr. Brian McDaid
Date : 29.12.2004
Street : Charleston Road
Town : S045 3ZG Hardley, Hythe, Southampton
Country : United Kingdom
Phone : 44 1703 245295
Telefax : 44 1703 243291
Telex :
Cedex :
Email : brian.mcdaid@cognis.com
Homepage :

26.03.2005

Type : manufacturer
Name : Degussa/Röhm GMBH & Co. KG
Contact person : Dr. Harald Müllerschön
Date : 29.12.2004
Street : Kirschenallee
Town : D-64275 Darmstadt
Country : Germany
Phone : 49 6151 184241
Telefax : 49 6151 183213
Telex :
Cedex :
Email : harald.muellerschoen@degussa.com
Homepage :

26.03.2005

Type : manufacturer
Name : The Dow Chemical Company
Contact person : Dr. John M. Waechter, Jr.
Date : 29.12.2004
Street : 1803 Building
Town : 48640 Midland, Michigan
Country : United States
Phone : 989-63-1859
Telefax : 989-638-9863
Telex : 28883
Cedex :
Email : jwaechter@dow.com
Homepage :

26.03.2005

Type : manufacturer
Name : Nippon Shokubai Co.,Ltd.
Contact person : Mr. Yuji Ito
Date : 29.12.2004
Street : Kogin Bldg. 4-1-1
Town : 541-0043 Koraibashi, Chuo-ku, Osaka
Country : Japan
Phone : 81-6-6223-9166
Telefax : 81-6-6201-3716

Telex	:	
Cedex	:	
Email	:	hkn@n.shokubai.co.jp
Homepage	:	

26.03.2005

Type	:	manufacturer
Name	:	Rohm and Haas Company
Contact person	:	Dr. James McLaughlin
Date	:	29.12.2004
Street	:	727 Norristown Road, P.O. Box 0904
Town	:	19477 Spring House, PA
Country	:	
Phone	:	(215) 641-7459
Telefax	:	(215) 619-1618
Telex	:	
Cedex	:	
Email	:	jmclaughlin@rohmhaas.com
Homepage	:	

26.03.2005

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

28.12.2004

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name	:	2-Propenoic acid, 2-hydroxyethylester
Smiles Code	:	O=C(OCCO)C=C
Molecular formula	:	C5H8O3
Molecular weight	:	116.12
Petrol class	:	

28.12.2004

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	typical for marketed substance
Substance type	:	organic
Physical status	:	liquid
Purity	:	= 96.5 - 99 % w/w
Colour	:	Pale yellow or colorless
Odour	:	Pungent, sweet

26.03.2005

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

.beta.-Hydroxyethyl acrylate

07.05.1998

2-(Acryloyloxy) ethanol

14.04.1998

2-(Acryloyloxy)ethanol

07.05.1998

2-Hydroxyethyl acrylate

07.05.1998

2-Hydroxyethyl-2-propenoate

20.10.1993

2-Propenoic acid, 2-hydroxyethyl ester (9CI)

07.05.1998

2-Propenoic acid, 2-hydroxyethylester

20.10.1993

Acrylic acid, 2-hydroxyethyl ester

07.05.1998

Acrylic acid, 2-hydroxyethyl ester (6CI, 8CI)

27.08.1996

Acrylic acid, 2-hydroxyethylester

05.11.1993

Acrylic acid: 2-hydroxyethyl ester

21.03.1995

Beta-hydroxyethyl acrylate

21.03.1995

beta-Hydroxyethylacrylate

26.03.2005

Bisomer 2HEA

27.08.1996

Bisomer HEA

24.05.1995

Ethandiol-1,2-monoacrylate

26.03.2005

Ethyleen glycol acrylaat

31.05.1998

Ethylene glycol acrylate

26.03.2005

Ethylene glycol monoacrylate

07.05.1998

HEA

21.03.1995

Hydroxyethyl acrylate

04.01.2005 (1)

Light Ester HOA

27.08.1996

Propenoic acid: 2 hydroxyethyl ester

21.03.1995

Rocryl 420

27.08.1996

Viscoat 220

26.03.2005

1.3 IMPURITIES

Purity :
CAS-No :
EC-No :
EINECS-Name : other esters
Molecular formula :
Value : < 2 % w/w

10.12.2003

Purity :
CAS-No :
EC-No :
EINECS-Name : diethylene glycol monoacrylate
Molecular formula :
Value : <= 2.1 % w/w

10.12.2003

Purity :
CAS-No : 79-10-7
EC-No : 201-177-9
EINECS-Name : acrylic acid

Molecular formula :
Value : <= 1 % w/w

10.12.2003

Purity :
CAS-No :
EC-No :
EINECS-Name : ethylene glycol
Molecular formula :
Value : ca. .25 % w/w

10.12.2003

Purity :
CAS-No : 75-21-8
EC-No : 200-849-9
EINECS-Name : ethylene oxide
Molecular formula :
Value : ca. .001 % w/w

10.12.2003

1.4 ADDITIVES

Purity type : typical for marketed substance
CAS-No :
EC-No :
EINECS-Name : methyl ether of hydroquinone
Molecular formula :
Value : = .025 - .065 % w/w
Function of additive : Inhibitor

28.12.2004

1.5 TOTAL QUANTITY

Quantity : <= - 15000 tonnes produced in 2001

Reliability : (1) valid without restriction
30.03.2005 (2)

1.6.1 LABELLING

Labelling : as in Directive 67/548/EEC
Specific limits : yes
Symbols : T, N, ,
Nota : D, D,
R-Phrases : (24) Toxic in contact with skin
(34) Causes burns
(43) May cause sensitization by skin contact
(50) Very toxic to aquatic organisms
S-Phrases : (1/2) Keep locked up and out of reach of children
(26) In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
(36/39) Wear suitable protective clothing and eye/face protection
(45) In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)
(61) Avoid release to the environment. Refer to special instructions/Safety data sets

29.03.2005

1.6.2 CLASSIFICATION

Classified : as in Directive 67/548/EEC
Class of danger : corrosive
R-Phrases : (34) Causes burns
Specific limits :

29.03.2005

Classified : as in Directive 67/548/EEC
Class of danger : dangerous for the environment
R-Phrases : (50) Very toxic to aquatic organisms
Specific limits :

29.03.2005

Classified : as in Directive 67/548/EEC
Class of danger : toxic
R-Phrases : (24) Toxic in contact with skin
Specific limits :

29.03.2005

Classified : as in Directive 67/548/EEC
Class of danger :
R-Phrases : (43) May cause sensitization by skin contact
Specific limits :

29.03.2005

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : type
Category : Non dispersive use

29.03.2005

Type of use : type
Category : Use in closed system

29.03.2005

Type of use : type
Category : Use resulting in inclusion into or onto matrix

29.03.2005

Type of use : industrial
Category : Chemical industry: used in synthesis

29.03.2005

Type of use : industrial
Category : Paints, lacquers and varnishes industry

29.03.2005

Type of use : industrial
Category : Polymers industry

29.03.2005

Type of use : industrial
Category :

29.03.2005

Type of use : use
Category : Adhesive, binding agents

29.03.2005

Type of use : use
Category : Intermediates

29.03.2005

Type of use : use
Category : Process regulators

29.03.2005

Type of use : use
Category : Viscosity adjustors

29.03.2005

Type of use : use
Category : other: Paints, lacquers, inks and varnishes.

29.03.2005

Type of use : use
Category :

29.03.2005

Type of use : use
Category : other

29.03.2005

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

Origin of substance : Synthesis
Type : Production

28.12.2004

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : MAC (NL)
Limit value : .24 mg/m3

29.03.2005 (3)

Type of limit : MAC (NL)
Limit value : .24 mg/m3

29.03.2005

Type of limit : MAK (DE)
Limit value :

Remark : Kein MAK-Wert festgelegt
29.03.2005 (4)

Type of limit : MAK (DE)
Limit value :

Remark : MAK-value does not exist.
29.03.2005 (5)

Type of limit : other
Limit value : 5 mg/m3

Remark : Swedish NGV (1993) = 5 mg/m3 8hr TWA.
29.03.2005

Type of limit : other
Limit value : 3 mg/m3

Remark : ISC work to a site standard of 3mg/m3 as recommended in many national workplace standards for Hydroxypropyl acrylate.
29.03.2005

Type of limit : other: MAC-TGG
Limit value : .24 mg/m3

29.03.2005 (6)

Type of limit : other: TWA
Limit value : 5 mg/m3

Remark : Notation: H
29.03.2005 (7)

Type of limit : other: TWA (S)
Limit value : 5 mg/m3
Short term exposure limit value
Limit value : 10 mg/m3
Time schedule :
Frequency : times

Remark : Notation: HS
29.03.2005 (8)

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

Classified by : other: BASF
Labelled by : other: BASF
Class of danger : 2 (water polluting)

29.03.2005 (9)

Classified by : other: by manufacturer
Labelled by : other: by manufacturer
Class of danger : 2 (water polluting)

29.03.2005

1.8.4 MAJOR ACCIDENT HAZARDS

Legislation : Stoerfallverordnung (DE)
Substance listed : yes
No. in Seveso directive :

Remark : Stoff-Nr.: 04c - 087
29.03.2005

1.8.5 AIR POLLUTION

Classified by : TA-Luft (DE)
Labelled by : TA-Luft (DE)
Number : 3.1.7 (organic substances)
Class of danger : II

29.03.2005

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

Remark : The substance is not produced in Europe. It is shipped by boat to Botlek (Holland), transfered to a storage tank and from the storage tank to drums. All operations are automated(closed system) resulting in no exposure.

26.03.2005

Remark : HEA used in polymer / coatings applications is not present in that form in the finished products and so no significant exposure should be possible. The biggest potential route of human exposure would be by dermal contact of liquid in the workplace where 2-HEA is manufactured or used. Inhalation of contaminated workplace air is another possible source (albeit the vapour pressure is quite low). The corrosive and sensitising potential of HEA means that opportunities for exposure are controlled tightly by manufacturers and detailed advice given to all customers.

Manufacture of HEA within ISC is based only at its Southampton site.
Source : International Speciality Chemicals Ltd. Southampton
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
23.12.2002

1.11 ADDITIONAL REMARKS

Remark : no additional remarks
13.05.1995

Remark : 2-Hydroxyethyl acrylate may be released into the environment in fugitive and stack emission or in wastewater during its production and use in the manufacture of thermosetting acrylic resins. Small amounts of the monomer has been found in some polymerised products which could lead to the leaching and volatilisation of the monomer from the polymer.
Source : Roehm GmbH Darmstadt
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
15.05.1998 (10)

Remark : 6 months at max. 30 ?C from date of delivery.
Source : Roehm GmbH Darmstadt
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
15.05.1998 (11)

1.12 LAST LITERATURE SEARCH

Type of search : External
Chapters covered : 3, 4, 5
Date of search : 22.08.2002

Remark : The search was conducted in Chemical Abstracts, Agricola, Biosis, Cancerlit, Chemlist, Chemical Safety Newsbase, Embase, HODOC, Hazardous Substance Databank, Medline, MSDS-OHS, NIOSHTIC, Toxlit, Registry of Toxic Effects of Chemical Substances, DART/ETIC, Toxline, IRIS, and genotoxicity databases on http://toxnet.nlm.nih.gov/, AQUIRE, CCRIS, BIODEG, BIOLOG.

The search also included information for Chapter 2.
29.03.2005

Type of search : Internal
Chapters covered : 3, 4, 5
Date of search : 22.08.2002

Remark : The search was conducted in Dow Technology Reports. In addition, each participating company searched internal files and provided any additional reports. This search also included information for Chapter 2.
29.03.2005

1.13 REVIEWS

2.1 MELTING POINT

Value : = -60.2 °C

Remark : Experimental value cited in DIPPR: Precise value was -60.15, rounded in value field.
Reliability : (2) valid with restrictions
Data from Handbook or collection of data.
Flag : Critical study for SIDS endpoint
25.03.2005 (12)

Value : = -30 °C
Sublimation :
Method :
Year : 2002
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (4) not assignable
Secondary literature
25.03.2005 (13)

2.2 BOILING POINT

Value : = 210 °C at 1013 hPa
Decomposition :
Method : other
Year : 1993
GLP : no data
Test substance :

Reliability : (2) valid with restrictions
Data from Reliable Handbook or compliation of data.
Flag : Critical study for SIDS endpoint
29.03.2005 (14) (15)

Value : = 192 °C at
Decomposition :
Method :
Year : 2002
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions
28.12.2004 (16)

2.3 DENSITY

Type :
Value : = 1.101 g/cm³ at 25 °C
Method :
Year : 2002
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions
20.12.2002 (16)

Type : relative density
Value : = 1.1 at 25 °C

Method : other
Year : 1993
GLP : no data
Test substance :

Remark : Water=1
26.05.1995 (15)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : = .0697 hPa at 25 °C
Decomposition :
Method :
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (1) valid without restriction
Data from Handbook or collection of data
Flag : Critical study for SIDS endpoint
28.12.2004 (17)

Value : = .173 hPa at 25 °C
Decomposition : no
Method :
Year : 2002
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : The percent error for this method is normally 6 to 10%
Result : Vapor pressure data was generated by an experimental technique utilizing differential thermal analysis. The experimental data were (pressure (mmHg) at temperature in degrees centigrade): 11.5 at 91; 29 at 108; 42 at 118; 61 at 126; 88 at 128; 116 at 134.

A vapor pressure of 0.13 mmHg at 25 degrees centigrade was calculated using the Antoine constants developed from these data which is 0.173 hPa.
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment
30.03.2005 (18)

Value : = 128.7 hPa at 135 °C
Decomposition :
Method :
Year : 2002
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (4) not assignable
Secondary literature
30.03.2005 (16)

Value : ca. .19 hPa at 25 °C
Decomposition :
Method : other (calculated)
Year : 1993
GLP : no data
Test substance :

Reliability : (4) not assignable
Secondary literature
30.03.2005 (15)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : = -.21 at 20 °C
pH value :
Method : other (measured)
Year : 1982
GLP : no data
Test substance :

Test condition : The n-octanol-water partition coefficient of 2-HEA was determined. 2-HEA was dissolved in distilled water (0.1 mM) and the water and n-octanol phases were mixed in stoppered tubes (2.5 ml water; 7.5 ml n-octanol). The tubes were shaken vigorously on a mechanical shaker for 1 h at room temperature, then cetrifuged at 2500 rev./min for 30 min. The amounts of esters in the water phase were analysed by gas-liquid chromatography.
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.
Flag : Critical study for SIDS endpoint
28.12.2004 (19)

Partition coefficient : octanol-water
Log pow : = -.25 at °C
pH value :
Method : other (calculated)
Year :
GLP : no data
Test substance :

Reliability : (2) valid with restrictions
Accepted calculation method
25.03.2005 (20)

Partition coefficient : octanol-water
Log pow : = -.13 at °C
pH value :
Method : other (measured)
Year : 1987
GLP : no data
Test substance : no data

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.
25.03.2005 (21)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : = 999999 other: g/m3 at °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C

Description : miscible
Stable : no

Reliability : (2) valid with restrictions
Data from Handbook or collection of data
Flag : Critical study for SIDS endpoint
25.03.2005 (22)

Solubility in : Water
Value : = 100 vol% at °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description : miscible
Stable :
Deg. product :
Method : other
Year : 1993
GLP : no data
Test substance :

Reliability : (4) not assignable
Secondary literature
30.03.2005 (15)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value : = 101 °C
Type : closed cup
Method : other
Year : 1993
GLP : no data
Test substance :

26.05.1995 (15)

2.8 AUTO FLAMMABILITY

Test condition : not determined
26.05.1995 (15)

2.9 FLAMMABILITY

Result : flammable
Method : other: calculation
Year :
GLP : no
Test substance :

Test condition : Lower flammability limit was estimated as 1.8 %v/v at 100 deg. C. Upper limit was estimated as 12.9 %v/v.
28.12.2004 (23) (15)

2.10 EXPLOSIVE PROPERTIES

11.05.1995

2.11 OXIDIZING PROPERTIES

Remark : no data
11.05.1995

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Memo : Henry's Law Constant

Result : O.073 Pa x m-3/mol at 20 degrees C
Reliability : (3) invalid
Documentation insufficient for assessment
Flag : Critical study for SIDS endpoint
25.03.2005 (24)

Memo : Stability and reactivity information

Remark : Stability and reactivity

Conditions to avoid:
Avoid high temperatures, ultraviolet light, and free radical initiators.

Materials to avoid:
Oxidising agents, initiators.

Hazardous polymerisation:
Hazardous polymerisation may occur if exposed to high UV light or free radical initiators.
25.03.2005 (15)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Conc. of substance	:	at 25 °C
INDIRECT PHOTOLYSIS		
Sensitizer	:	O3
Conc. of sensitizer	:	7000000000000 molecule/cm³
Rate constant	:	= .00000000000000000175 cm³/(molecule*sec)
Degradation	:	= 50 % after 6.5 day(s)
Deg. product	:	
Method	:	other (calculated)
Year	:	1987
GLP	:	no data
Test substance	:	no data
Remark	:	Brunn J. et al. (1976) J. Prakt. Chem., 318: 745-755
Result	:	Estimated atmospheric half-life for reaction of HEA with ozone at a concentration of 7 x 10E11 molecules/cm3 is 10 hours. Rate constants estimated to be 1.75 x 10E-18 cm3/molecule/sec at 25 deg. Celsius for ozone molecules. Based on slight absorption of light at wavelengths > 290 nm by ethyl acrylate and other acrylate esters. HEA may directly photolyze (see Brunn J. et al., 1976)
Reliability	:	(2) valid with restrictions Accepted calculation method.

30.03.2005 (25)

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Conc. of substance	:	at 25 °C
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	500000 molecule/cm³
Rate constant	:	= .0000000000293 cm³/(molecule*sec)
Degradation	:	= 50 % after 10 hour(s)
Deg. product	:	
Method	:	other (calculated)
Year	:	1987
GLP	:	no data
Test substance	:	no data
Remark	:	Brunn J. et al. (1976) J. Prakt. Chem., 318: 745-755
Result	:	Estimated atmospheric half-life for reaction of HEA with photochemically produced OH radical at a concentraton of 5 x10E5 radicals/cm3 is 10 hours. Rate constants estimated to be 29.3 x 10E-12 cm3/molecules/sec at 25 deg. Celsius for OH radicals. Based on slight absorption of light at wavelengths > 290 nm by ethyl acrylate and other acrylate esters. HEA may directly photolyze (see Brunn J. et al., 1976)
Reliability	:	(2) valid with restrictions Accepted calculation method.

30.03.2005 (26)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	at °C
t1/2 pH7	:	> 270 day(s) at 25 °C
t1/2 pH9	:	at °C
t1/2 pH 10.9	:	= 1.2 hour(s) at 25 °C
Degradation	:	= 93 % after 5 hour(s) at pH 11 and 25 °C
Deg. product	:	
Method	:	other: TSCA section 796.3500 Hydrolysis as a Function of pH at 25C
Year	:	1997
GLP	:	yes
Test substance	:	other TS

Method :

Hydrolysis study was conducted following the TSCA guidelines, section 796.3500 Hydrolysis as a Function of pH at 25C. Test material was added to the buffered solutions at a concentration of less than 1 mM (15 ul test material/150mL solution). Approximate nominal concentration for HEA was 110 mg/L. The concentration of HEA was at least several orders of magnitude below the water solubility (miscible in water).
Portions (10mL) of the test solutions were transferred to uniquely labeled 10-mL serum bottles and sealed with Teflon-coated rubber septa and aluminum crimp seals. The test solutions were incubated in the dark for 28 days at 25+/-1C.
Periodically, test solutions were removed for measurement of pH and the analysis of test material remaining in the solution. Single test samples were removed at each time point and analyzed in triplicate by reverse phase HPLC using UV detection. For test samples at pH 11, 20-ul portions of formic acid were added prior to analysis to adjust the sample to the pH range of 5 to 6 to minimize further hydrolysis. The following sampling schedule is described in the TSCA guidelines:

Procedure 1- If 60-70% conversion occurs within 28 days, then a minimum of six measurements will be made at regular intervals between 20 and 70% hydrolysis.

Procedure 2- If the reaction is too slow to conveniently follow the hydrolysis to a high conversion in 28 days, but is still rapid enough to attain at least 20% conversion, then the test solution should be analyzed at 15- 20 time points at regular intervals after 10% conversion is attained.

Procedure 3- If less than 20% conversion occurs after 28 days, then the concentration of test chemical after 28 days will be determined, and a half-life of >x days reported.

Effect of Methyl Ether of Hydroquinone on Hydrolysis of HEA-
Methyl ether of hydroquinone (MEHQ) is routinely added to HEA during manufacture to inhibit polymerization; therefore, the effect of MEHQ on the hydrolysis of HEA was evaluated. The hydrolysis rates at pH 11 for two different samples of HEA containing different concentrations of MEHQ were determined. The first sample of HEA contained 398 ppm MEHQ while the second sample contained 275 ppm MEHQ.

For each hydrolysis experiment, the natural logarithm of the test substance concentration was plotted as a function of time. At a constant pH, a straight line was obtained, indicating pseudo-first order kinetics. The slope of the linear regression line was equal to -Kh, where Kh was the pseudo-first order rate constant. Using the relationship T1/2=ln 2/Kh, the half-life of the hydrolysis reaction was determined. The following relationship holds for hydrolysis reactions in buffered systems:
Kh=Ka[H+]+Kb[OH-]+Kn where Ka, Kb, and Kn are the second-order rate constants for acid and base catalyzed, and neutral water hydrolysis

reactions, respectively, and Kh is the measured pseudo-first order rate constant. At a given pH, the equation contains three unknowns, Ka, Kb, and Kn; therefore, three equations are required to determine the three unknown values. This was accomplished by measuring the hydrolysis rates at pH 3, 7 and 11.

Result : Hydrolysis of HEA in Buffered Solutions at 25C

Time	pH 3		pH 7	
(days)	Ave mg/L	Std dev	Ave mg/L	Std dev
0	111.3	0.3	108.0	0.1
5	109.1	0.3	105.1	0.1
7	121.6	0.5	116.2	0.4
15	117.5	0.1	111.2	0.3
21	115.2	0.4	106.1	0.3
28	114.1	0.4	100.5	0.2

Time	pH 11	
(hrs)	Ave mg/L	Std dev
0	108.1	1.4
0.5	85.3	0.3
1	61.8	0.0
2	36.3	0.0
3.5	14.5	0.2
4	11.0	0.0
5	6.5	0.1

Results for Hydrolysis Studies for HEA

pH	K(a) (days-1)	half-life (days)	correlation coefficient (r2)
2.84	nil	-	-
7.03	0.0025	>270	-
10.87	13.72	0.051	0.9994

(a) pseudo-first-order rate constant determined at indicated pH

Calculated kA, kB and kN second order rate constants:

Ka (M-1day-1)=nil, Kb (M-1day-1)=18,500 and
Kn (day-1)=5.18X10-4

HEA hydrolyzed rapidly at pH 11, with a half-life of 0.051 days. In contrast, slow hydrolysis was observed at pH 3 and pH 7, with half-lives greater than 230 days. These results were explained by the presence of ester functional groups in HEA which are more susceptible to hydrolysis at high pH. Based on the hydrolsis rate constant determined for HEA, half-lives of 35 to 40 days would be expected at pH 8.

Effect of MEHQ inhibitor on hydrolysis- Samples of HEA containing 398 and 275 ppm MEHQ had half-lives of 1.34 and 1.30 hors, respectively. Thus, a 45% higher concentration of MEHQ resulted in only a 3% longer half-life. These results indicate that varying the MEHQ levels from 275 to 398 ppm in HEA had minimal effect on the rate of hydrolysis at pH 11. This observation was consistent with the fact that the MEHQ was diluted 10,000-fold in the test solutions, therby minimizing any possible effect on the hydrolysis reaction.

Test substance : Test material was received from The Dow Chemical Company with a reported purity of 98.52%.

Reliability : (2) valid with restrictions
Guideline study with the restriction that the test material was not characterized in accordance with GLPs.

Flag : Critical study for SIDS endpoint

30.03.2005 (27)

Type	:	abiotic
t1/2 pH4	:	at °C
t1/2 pH7	:	at °C
t1/2 pH9	:	at °C
t1/2 pH 8.1	:	= 290 day(s) at 5 °C
Deg. product	:	
Method	:	
Year	:	1997
GLP	:	yes
Test substance	:	other TS

Method : In an initial experiment (Experiment A, 28 day duration), the hydrolysis rate for HEA was determined in synthetic seawater at 25C. Based on the results of this experiment, a second study was set (Experiment B, 70 to 91 day duration) to determine the hydrolysis rates for HEA at 5, 12, and 25C in synthetic seawater buffered to pH 8.1.

Experiment A- Synthetic seawater was prepared by dissolving 40 g of Instant Ocean in water and diluting to one liter. The solution was then sterilized. A 15 uL portion of HEA was added to 150 mL of synthetic seawater to obtain a final approximate nominal concentration of 110 mg/L. The pH of the test solution was 8.15. Portions (10mL) of the test solutions were transferred to uniquely labeled 10-mL serum bottles and sealed with Teflon-coated rubber septa and aluminum crimp seals. The test solutions were incubated in the dark for 28 days at 25+/-1C. Duplicate samples were removed for the measurement of pH and analysis of HEA remaining in solution after 0, 5, 14, 21, and 28 days. Each test solution was analyzed in triplicate by reverse phase HPLC using UV detection.

Experiment B- Test solutions were prepared in the same manner as described above, except that seawater was buffered to pH 8.1 with boric acid to minimize changes in pH. Buffered seawater was prepared by dissolving 40 g Instant Ocean and 3.1 g boric acid in water and diluting to 1 liter. The pH of the solution was adjusted from 6.8 to 8.1 with 1N NaOH and sterilized. HEA was added to obtain a final approximate nominal concentration of 110 mg/L. Test solutions were incubated in the dark for up to 91 days at 25+/-1C, 12+/-1C and 5+/-1C. Duplicate test solutions were removed for the measurement of pH and the analysis of HEA remaining in solution after 0, 7, 28, 42, 56, 70, and 91 days. The experiment at 12C was terminated after day 70 because of a faulty water bath. Each test solution was analyzed in triplicate by reverse phase HPLC.

For each hydrolysis experiment, the natural logarithm of the test substance concentration was plotted as a function of time. At a constant pH, a straight line was obtained, indicating pseudo-first order kinetics. The slope of the linear regression line was equal to -Kh, where Kh was the pseudo-first order rate constant. Using the relationship T1/2=ln 2/Kh, the half-life of the hydrolysis reaction was determined.

The temperature dependence of hydrolysis reactions were described by the Arrhenius equation: y=Ae-E/RK where y is the reaction rate, E is the activation energy (cal mol-1), R is the gas constant (1.986 cal deg-1 mol-1), and K is the absolute temperature (K). A plot of the natural logarithm of the reaction rate as a function of the inverse of the absolute temperature gives a curve whose slope is equal to -E/R.

Using the reported rate constants for acid and base catalyzed and neutral water processes [Ka (M-1 day-1)= nil, Kb (M-1 day-1)= 18,500, and Kn (day-1)= 5.18X10-4, Gonsior et al, 1997, R & D report of The Dow Chemical Company] the hydrolysis half-life at pH 8.1 (25C) was estimated using the following relationships:
Kh=Ka[H+]+Kb[OH-]+Kn and T1/2=ln 2/Kh

Result : Hydrolysis of HEA in Non-Buffered Synthetic Seawater at 25C EXP-A.

Day	pH	HEA (mg/L)	Std Dev.	RSD (%)	ln (mg/L)
0	8.15	108.6	0.20	0.19	4.688
5	8.05	91.0	0.17	0.18	4.511
5	8.04	90.7	0.16	0.18	4.508
14	7.86	77.6	0.12	0.15	4.352
14	7.85	79.4	4.08	5.14	4.374
21	7.86	68.6	0.11	0.16	4.228
21	7.88	67.8	0.13	0.19	4.217
28	7.84	65.6	0.06	0.10	4.184
28	7.86	65.5	0.49	0.75	4.183

After 28 days, the concentration of HEA was reduced by 40%. However, the kinetics of hydrolysis were not pseudo-first order as indicated by a decrease in the slope of the line over time (non-linear plot). This was likely due to a decrease in pH of the test solutions from pH 8.15 to 7.85 over the 28-day experiment.

RESULTS IN BUFFERED SEAWATER

In contrast to Exp. A, the use of the borate buffer in Exp. B minimized changes in the the pH of the test solutions (pH 8.1 +/- 0.05). As a result, pseudo-first order kinetics was observed. Results and calculated half-lives are shown in the Tables below.

HEA hydrolyzed faster in seawater at 25C than would have been predicted from previous work in "regular" water (Gonsior et al, 1997). Using the reported rate constants for acid and base catalyzed and neutral water processes [Ka (M-1 day-1)= nil, Kb (M-1 day-1)= 18,500, and Kn (day-1)= 5.18X10-4, Gonsior et al, 1997, R & D report of The Dow Chemical Company] the hydrolysis half-life at pH 8.1 (25C) was estimated to be 29 days using the following relationships: Kh=Ka[H+]+Kb[OH-]+Kn and T1/2=ln 2/Kh

Hydrolysis of HEA in Buffered Synthetic Seawater (pH 8.1) at 5, 12 and 25C- Exp B.

Temp. (C)	Rate Constant (days-1) (a)	Half-Life (days)	r2 (b)
5	0.0024	290	0.8255
12	0.0068	100	0.9527
25	0.0399	17	0.9982

(a)- pseudo first order rate constant
(b)- correlation coefficient

Hydrolysis of HEA in Buffered Synthetic Seawater at 5C EXP-B.

Day	HEA (mg/L)	Std Dev.	RSD (%)	ln (mg/L)
0	106.7	0.08	0.07	4.670
0	106.3	0.49	0.46	4.667
7	109.8	3.38	3.08	4.699
7	107.8	0.08	0.07	4.680
28	102.3	0.13	0.13	4.628
28	102.3	0.06	0.06	4.628
42	100.7	0.20	0.20	4.613
42	100.6	0.09	0.09	4.611
56	97.9	0.25	0.26	4.584
56	98.7	0.23	0.23	4.592
70	85.7	0.11	0.13	4.451

70	85.6	0.03	0.04	4.449
91	90.0	0.23	0.26	4.500
91	89.1	0.19	0.21	4.490

Hydrolysis of HEA in Buffered Synthetic Seawater at 12C EXP-B.

Day	HEA (mg/L)	Std Dev.	RSD (%)	ln (mg/L)
0	106.7	0.08	0.07	4.670
0	106.3	0.49	0.46	4.667
7	109.5	8.85	8.08	4.696
7	104.1	0.14	0.13	4.645
28	92.4	1.10	1.19	4.526
28	91.3	0.06	0.07	4.514
42	85.3	0.03	0.04	4.446
42	85.2	0.08	0.10	4.445
56	79.4	0.05	0.06	4.375
56	79.3	0.05	0.06	4.373
70	64.9	0.13	0.20	4.173
70	64.9	0.13	0.20	4.172

Hydrolysis of HEA in Buffered Synthetic Seawater at 25C EXP-B.

Day	HEA (mg/L)	Std Dev.	RSD (%)	ln (mg/L)
0	106.7	0.08	0.07	4.670
0	106.3	0.49	0.46	4.667
7	82.1	0.11	0.13	4.408
7	82.5	0.05	0.06	4.413
28	37.8	0.06	0.16	3.631
28	36.9	0.04	0.12	3.608
42	20.5	0.03	0.17	3.023
42	21.6	0.05	0.24	3.070
56	12.6	0.03	0.20	2.536
56	12.5	0.01	0.04	2.528
70	6.0	0.25	4.15	1.789
70	6.2	0.01	0.20	1.818
91	3.0	0.06	1.95	1.094
91	2.9	0.06	2.01	1.071

The 17-day half-life at 25C determined in Exp. B suggests that the hydrolysis rate of HEA was accelerated by the synthetic seawater. Investigations into whether borate buffer accelerated the reaction showed that borate buffer did not affect the rate of reaction.

Pseudo-first order kinetics were observed, with measured half-lives of 290 days at 5C, 100 days at 12C, and 17 days at 25C. Based on rate constants determined in a previous study which did use seawater, a hydrolysis half-life of 29 days in "regular" water would have been expected at 25C (pH 8.1). Thus, seawater appeared to accelerate the rate of HEA hydrolysis.

Test substance : Test material was received from The Dow Chemical Company with a reported purity of 98.52%.

Reliability : (2) valid with restrictions
2d, Test material characterization was not audited for compliance with GLPs.

Flag : Critical study for SIDS endpoint

10.12.2003 (28)

Type : abiotic
t1/2 pH4 : > 28 day(s) at 40 °C
t1/2 pH7 : = 39.6 day(s) at 40 °C
t1/2 pH9 : = 15 hour(s) at 40 °C
Deg. product :

Method : OECD Guide-line 111 "Hydrolysis as a Function of pH"
Year : 1995
GLP : no
Test substance :

Reliability : (4) not assignable
15.01.2004 (29)

3.1.3 STABILITY IN SOIL

Result : Based on its biodegradability in aqueous screening tests, HEA may biodegrade in soil. Based on the hydrolyzability of ethyl acrylate, HEA may hydrolyze, especially in alkaline soils. If released into soil, HEA will be expected to exhibit a very high mobility in soil and may leach into groundwater.
30.03.2005 (30) (31) (32) (33) (34)

Remark : cited in HSDB; HEA is not mentioned in the primary literature !
Result : Using a reported log Kow of -0.21, a Koc of 18 has been calculated using a recommended regression-derived equation. The estimated Koc indicates that 2-HEA will exhibit a very high mobility in soil and is not therefore expected to adsorb significantly to soil, sediment or suspended particulate matter (HSDB). HEA may leach into goundwater.
29.03.2005 (30) (31) (32) (33) (34)

3.2.1 MONITORING DATA

Remark : no data identified from literature searched.
29.03.2005

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : fugacity model level I
Media :
Air : .016 % (Fugacity Model Level I)
Water : 99.9 % (Fugacity Model Level I)
Soil : .055 % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: Level I model version 2.11
Year : 2003

Method : Level I model version 2.11, Obtained from the Canadian Environmental Modeling Centre, Trent University, Peterborough, Ontario, Canada

Input Parameters for Level I Model:

Listed in the following order: Property: Value, Source of infomation.

Data Temperature (degC): 25, Default environmental temperature

Chemical Type: 1, Type 1 indicates chemical can partition into all environmental compartments

Molecular Mass (g/mol): 116.12, Calculated from molecular structure

Water Solubility (g/cubic m): 1.0 x 10+6 (miscible), Measured value reported in IUCLID dataset

Vapor Pressure @ 25 deg C (Pa): 6.97, from DIPPR, Complilation of Pure Chemical Properties, AIChE, New York, NY

Melting Point (0C): -60.15 deg C, from DIPPR, Complilation of Pure Chemical Properties, AIChE, New York, NY

Estimated Henry's Law Constant (H)(Pa m3/mol): 8.1 x 10-4, Calculated by Level I Fugacity Model

Log Kow Octanol-Water Partition Coefficient: -0.21, from Tanii and Hashimoto (1982) Tox. Letters 11: 125-129.

Simulated Emission (kg): 100,000, Level I Default

Result : Predicted equilibrium distribution among air, water, soil, and sediments with an emission scenario of 100,000 kg total emissions: Percentage and amount distributed to air: 1.6 x 10-2%; 16.3 kg; water: 99.9%; 1.0 x 10+5 kg; soil: 5.5 x 10-2%, 54.6 kg; sediment: 1.2 x 10-2%; 1.2 kg

Conclusion : HEA has very high water solubility, very low vapor pressure, and very low log Kow. In the absence of advective and reactive processes, these properties dictate that the material will partition exclusively to the water compartment at equilibrium.

Reliability : (2) valid with restrictions
Accepted calculation method

Flag : Critical study for SIDS endpoint

30.03.2005 (35)

Type : fugacity model level III
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other
Year : 2003

Method : Input Parameters for Level III Model:

Listed in the following order: Property: Value, Source of information.

Data Temperature (degC): 25, Default environmental temperature

Chemical Type: 1, Type 1 indicates chemical can partition into all environmental compartments

Molecular Mass (g/mol): 116.12, Calculated from molecular structure

Water Solubility (g/cubic m): 1.0 x 10+6 (miscible), Measured value reported in IUCLID dataset

Vapor Pressure @ 25 deg C (Pa): 6.97, from DIPPR, Complilation of Pure Chemical Properties, AIChE, New York, NY

Melting Point (0C): -60.15 deg C, from DIPPR, Complilation of Pure Chemical Properties, AIChE, New York, NY

Estimated Henry's Law Constant (H)(Pa m3/mol): 8.1 x 10-4, Calculated by Level I Fugacity Model

Log Kow Octanol-Water Partition Coefficient: -0.21, from Tanii and Hashimoto (1982) Tox. Letters 11: 125-129.

Reaction Half-lives (hr.) Input to Level III Model:
Air (vapor phase): 8.0

Measured half-life for indirect photolysis
Water (no susp. solids): 360*

Half-lives in water, soil, and sediment extrapolated from measured ready biodegradability reported in IUCLID dataset:
Soil: 720*, Sediment: 1440*, Suspended Sediment: **1.0 x 10+11, (Not expected to adsorb to suspended sediment).
Fish: **1.0 x 10+11, No uptake/bioaccumulation is expected
Aerosol: **1.0 x 10+11, Aerosol emissions not expected

*Half-lives extrapolated from ready biodegradability classification, according to Technical Guidance Document of the European Commission [3]. **Default value used in Level III model when reaction is expected to be negligible in this compartment

Result : Predicted distribution among air, water, soil, and sediments under various emission scenarios

Data listed as follows: Emission scenario: Percentage and amount distributed to air; water; soil; sediment; Residence Time(days); Residence time in days [without advection]
1,000 kg/hr to Air: Air: 0.1%; 4.8 x 10+2 kg; Water: 37.4%; 1.6 x 10+5 kg; Soil: 62.5%; 2.7 x 10+5 kg; Sediment: 1.4 x 10+2%; 61.5 kg; Residence time 17, [29].

1,000 kg/hr to Water: Air: 3.9 x 10-6%; 1.3 X 10-2 kg; Water: 100.0%; 3.4 x 10+5 kg; Soil: 2.1 x 10-3%; 7.4 kg; Sediment: 3.9 X 10-2%; 1.3 x 10+2 kg; Residence time: 14, [22]

1,000 kg/hr to Soil: Air: 1.4 x 10-3%; 8.3 kg; Water: 35.8%; 2.1 x 10+5 kg; Soil: 64.1%; 3.8 x10+5 kg; Sediment: 1.4 X 10-2%; 82.9 kg; Residence time 25, [32]

1,000 kg/hr simultaneously to Air, Water and Soil: Air: 3.6 x 10-2%; 4.9 x 10+2 kg; Water: 52.4%; 7.2 x 10+5 kg; Soil: 47.5%; 6.5 x10+5 kg; Sediment: 2.0 X 10-2%; 2.8 x 10+2 kg; Residence time: 19, [28]

Conclusion : This material has very high water solubility, very low vapor pressure, and very low log Kow. These properties dictate that the material has low potential to volatilize from water to air, or adsorb to soil and sediments. When released to water (the most likely emission scenario), the material will remain dissolved in water and will be removed through biodegradation and hydrolysis. When released to soil, the material will be primarily dissolved in soil pore water (groundwater), and be removed through rapid biodegradation and hydrolysis. Since this material is susceptible to destructive reactions such as indirect photolysis, biodegradation, and hydrolysis, this material is expected to be short-lived in the environment.

Reliability : (2) valid with restrictions
Accepted calculation method

Flag : Critical study for SIDS endpoint

30.03.2005 (36) (37)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	activated sludge
Concentration	:	20 mg/l related to Test substance 10 mg/l related to Test substance
Contact time	:	
Degradation	:	= 80 (±) % after 28 day(s)
Result	:	readily biodegradable
Deg. product	:	
Method	:	other: according to OECD Guide-line 301B and Directive 84/449/EEC, C.5
Year	:	1984
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	The study was conducted with 5-liter glass culture vessels that contained 3 liters of solution; the vessels were maintained in the dark at 21 degrees C +/- 1 degrees C for 28 days. Filtrate of activated sludge from a sewage treatment plant was added to the culture vessels at a final concentration of 1%. The test substance was incubated in the nutrient medium at a concentration of 10 or 20 mg/L. Concurrent controls consisted of nutrient medium alone as well as nutrient medium with 20 mg/L sodium benzoate. Degradation was measured by total inorganic carbon analysis of evolved CO2 in multiple samples from day 0 through day 28. The percentage degradation then was calculated from the total organic carbon (TOC) content of the test material; the carbon content of the test material was 52.5% based on analysis.
Result	:	2-Hydroxyethyl acrylate attained 79% biodegradation after 28 days at a concentration of 10 mg/L and 80% biodegradation at a concentration of 20 mg/L. The lag periods required before greater than 10% biodegradation occurred were approximately 6.5 and 8.2 days, at the 10 and 20 mg/l concentrations, respectively. Within ten days following these lag periods, biodegradation averaged about 72 and 75% for the 10 and 20 mg/l reactions, respectively. The sodium benzoate control attained 94% degradation which confirmed the suitability of the inoculum and test conditions. Therefore, 2-hydroxyethyl acrylate can be considered as readily biodegradable under the strict terms and conditions of the Modified Sturm Test.
Reliability	:	(1) valid without restriction GLP Guideline Study
Flag	:	Critical study for SIDS endpoint

29.03.2005 (38)

Type	:	aerobic
Inoculum	:	
Concentration	:	100 mg/l related to Test substance related to
Contact time	:	28 day(s)
Degradation	:	= 78 (±) % after 28 day(s)
Result	:	readily biodegradable
Deg. product	:	
Method	:	OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
Year	:	1992
GLP	:	yes
Test substance	:	no data
Reliability	:	(2) valid with restrictions Guideline study without detailed documentation

25.03.2005 (39)

Type : aerobic
Inoculum : other: no data
Contact time :
Degradation : = 85 (±) % after 28 day(s)
Result : other: under test conditions biodegradation observed
Deg. product :
Method : other: OECD Guide-line 301 E (Screening test)
Year : 1981
GLP : no data
Test substance : no data

Reliability : (4) not assignable
Original reference not available

29.03.2005 (40)

Type : aerobic
Inoculum : other: no data
Concentration : related to DOC (Dissolved Organic Carbon)
related to
Contact time :
Degradation : > 95 (±) % after 28 day(s)
Result : inherently biodegradable
Deg. product :
Method : other: OECD Guide-line 302 B (modif. Zahn-Wellens Test)
Year : 1981
GLP : no data
Test substance : no data

Remark : Adsorption after 3 hrs ca. 10%; DOC decrease >95% after 21 days.
Reliability : (4) not assignable
Original reference not available

29.03.2005 (40)

Type : aerobic
Inoculum : other: mixed microbial cultures of aerobic microorganisms
Concentration : related to DOC (Dissolved Organic Carbon)
related to
Contact time :
Degradation : = 61 (±) % after 5 day(s)
Result : readily biodegradable
Deg. product :
Method : other
Year : 1987
GLP : no data
Test substance : no data

Remark : Calculated ThBOD is 5.50; 5-day BOD (mmol/mmol chemical) is 3.35.
Test condition : Mixed microbial cultures capable of using 45 model organic chemicals as sole carbon and energy sources were separately isolated by an enrichment culture technique. Similarly, additional cultures were obtained that were capable of degrading 43 test chemicals. Microbial seeds for the BOD tests were prepared from the culture growth (10E5-10E6 cells/ml) in mineral salts medium containing 100 mg/l (solid) or 100 microL/L (liquid) chemical substrate. The culture was diluted 1:1 with physiological saline and incubated on a shaker for 24 h prior to its use.

HEA and 1 ml of the seed were added to 20 ml of dilution water contained in a 300-ml BOD bottle; bottles were incubated for 20 days at 21 deg. Celsius; each test was run in duplicate.

Reliability : (2) valid with restrictions
29.03.2005 (41)

3.6 BOD5, COD OR BOD5/COD RATIO

COD
Method : other: based on Hach Method Number 8000
Year : 1994
COD : = 1500 mg/g substance
GLP : no data

Method : The BOD was performed based on the methods described in Standard Methods for the Examination of Water and Wastewater, APHA, 17th Edition, 1987. The test substance was administered to the test chambers by direct addition. The tested concentration range was 2, 5, 17, 33, and 66 mg/L. The reference standard was prepared using dextrose and glutamic acid. The biological seed was Polyseed (Polybac, Bethlehem, PA).

The procedures for the COD test was based on Hach Method Number 8000. A stock solution of hydroxyethyl acrylate was prepared at a nominal concentration of 1 mg/ml in Nanopure water. Triplicate chemical oxygen demand determinations were performed on the stock solution. The reference standard was prepared using potassium hydrogen phthalate.

GLP- no data

Result : The COD was 1500 mg/g +/- 0.0 mg/g and the ThOD was 1520 mg/g. The results of the COD reference standards were within the acceptable range of 15% of nominal.

HEA did not exhibit a dissolved oxygen (DO) depletion of greater than or equal to 2.0 mg O2/L (actual was <1.0 mg/L) over the range of concentrations tested; therefore, there was insufficient DO depletion to calculate a BOD value. The absence of DO depletion may indicate inhibition of the microbial inoculum by HEA. The dilution water and glucose-glutamic acid control results were within the acceptable ranges established for the test with values of 0.15 mg O2/L and 180 mg/L, respectively.

Test substance : Test material was received from The Dow Chemical Company and is prescribed by 1.1-1.4.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

30.03.2005 (42)

Result : Calculated ThBOD is 5.50; 5-day BOD (mmol/mmol chemical) is 3.35.

Test condition : Mixed microbial cultures capable of using 45 model organic chemicals as sole carbon and energy sources were separately isolated by an enrichment culture technique. Similarly, additional cultures were obtained that were capable of degrading 43 test chemicals. Microbial seeds for the BOD tests were prepared from the culture growth (10E5-10E6 cells/ml) in mineral salts medium containing 100 mg/l (solid) or 100 microL/L (liquid) chemical substrate. The culture was diluted 1:1 with physiological saline and incubated on a shaker for 24 h prior to its use.

HEA and 1 ml of the seed were added to 20 ml of dilution water contained in a 300-ml BOD bottle; bottles were incubated for 20 days at 21 deg. Celsius; each test was run in duplicate.

30.03.2005 (43)

Result : The theoretical oxygen demand (ThOD) of HEA is 1.52 p/p. In a screening test, the biological oxygen demand (BOD) was 0.34, 0.50, and 0.72 p/p in 5, 10, and 20 days (22, 33, and 47% of ThOD), respectively.

30.03.2005 (44)

3.7 BIOACCUMULATION

Remark : It is unlikely that HEA bioaccumulates in aquatic organisms;however, there is no relevant literature available. Using the reported log Kow of -0.21, a bioconcentration factor (BCF) of 0.41 has been calculated using a recommended regression-derived equation, indicating that bioconcentration in aquatic organisms is unlikely to occur.

29.03.2005 (45) (46)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	flow through
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
NOEC	:	= 4.2 measured/nominal
LC50	:	= 4.8 measured/nominal
EC50	:	= 4.7 measured/nominal
Limit test	:	no
Analytical monitoring	:	yes
Method	:	
Year	:	1983
GLP	:	no data
Test substance	:	other TS

Method : HEA concentrations were analyzed in the water sample from the fish exposure tanks via gas-liquid chromatography. Tests were initiated by adding 20 fish per treatment and control. Death was the major test endpoint. The number of dead fish was noted every 24 hours. Observations of fish behavior and toxic sign were made at 2-8, 24, 48, 72 and 96 hours. Upon test termination, individual control fish were weighed and measured. Four surviving fish each from the control, the lowest concentration and the concentration nearest the LC50 were preserved in 10% buffered formalin and kept for histological examination (no data presented by authors). The estimated LC50 and EC50 with corresponding 95% confidence intervals were calculated using the corrected average of the analyzed tank concentrations and the Trimmed Spearman-Karber Method (Hamilton et al., 1977, Environ. Sci. Technol. 11:714-719).

Result : The 96 hr LC50 was 4.8 mg/L and the 96 hr EC50 was 4.7 mg/L (conf. lim: 4.5-4.8). All fish died within 24 hours following exposure to the 16 mg/L concentration. Affected fish lost schooling behavior and swam near the tank surface in a corkscrew/spiral pattern. They were hyperactive and overreactive to external stimuli, were darkly colored and deformed, had edema, and lost equilibrium prior to death.

The NOEC = 4.2 mg/L. This study followed ASTM (1980) guidelines using a flow-through design. Nominal exposure concentrations ranged from 2.7 to 16 mg/L and analyses at 96 hours ranged from 3.18 to 16.1 mg/L. Mortality occurred in the three highest concentrations (5.92, 9.14 and 16.1 mg/L, measured). The LC50 was determined based on analytical values.

Test condition : Water

Temperature: 24.5 deg. C
Dissolved oxygen: 7.1 mg/l
Hardness: 44 mg/l CaCO3
Alkalinity: 49.8 mg/l CaCO3
Tank volume: 2 liter
Additions: 18 V/D
pH: 7.69

Fish

Age: 28 days
Mean length: 18.5 mm (SD 2.417)
Mean weight: 0.110 gram (SD 0.0427)
Loading: 1.100 grams/L

HEA CONCENTRATION
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nominal conc. : 0.0, 2.7, 4.2, 6.5, 10, or 16 mg/l
measured conc.: <0.5, 3.18, 3.92, 5.92, 9.14, or 16.1 mg/l

Test substance : Source- Scientific Polymer Products, Inc.
Purity- >97% by gas liquid chromatography

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

Flag : Critical study for SIDS endpoint

28.03.2005 (47)

Type : flow through
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : = 4.8 measured/nominal
Limit test : no
Analytical monitoring : yes
Method :
Year : 1988
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Exposures were conducted in a similar manner as desribed in Geiger et al., 1985, Center for Lake Superior Environmental Studies, University of Wisconsin, Superior, WI.,2:14-16. In general, biological and chemical procedures followed American Society for Testing and Materials recommendations (ASTM, 1980, Standard Practice for Conducting Acute Toxicity Tests with Fishes, Macroinvertebrates and Amphibians. ASTM Committee E-35.). Water chemistry methods were those recommended by the American Public Health Association (APHA et al., 1980, 15th Edition American Public Health Association, Washington, DC.).

Chemical analysis of samples was conducted by gas chromatography.

During exposures, fish were observed daily at 8, 24, 48, 72, and 96 hr. Abnormal behavior and morphological changes were recorded.

Calculated and measured log p values were taken from the MedChem CLOG P and STARLIST programs of the Medicinal Chemistry Project at Pomona College, Claremont, CA. LC50 values were calculated using the average tank concentrations and a computerized Trimmed Spearman-Karber Method (Hamilton et al., 1977, Environ. Sci. Technol. 11:714-719).

Result : The 96 hr LC50 for HEA was 4.80 mg/L. 2-HEA showed behavioral and morphological signs in fish indicative of a neurotoxicant (Drummond et al., 1986, Poston, T.M. and Purdy, R. (eds) 9th Aquatic Toxicology, ASTM STP 921, Philadelphia, PA., American Society for Testing and Materials, Philadelphia, pp 415-435). In addition, 2-HEA caused fish to become hyperactive,overreactive to outside stimuli, and exhibit scoliosis and lordosis deformities.

Test condition :

Water

Temperature: 24.6 +/- 0.4 C
Dissolved oxygen: 6.71 +/- 0.57 mg/l
Hardness: 45.3 +/- 1.0 mg/l CaCO3
Alkalinity: 47.0 +/- 3.2 mg/l CaCO3
pH: 7.62 +/- 0.12

Fish

Age: 28-34 days
Mean length: 20.9 mm (SD 2.0)

Mean weight: 0.134 gram (SD 0.03

Test substance : The purity was >97% from Scientific Polymer Products, Inc. (Ontario, New York). (Note- Small amounts (50-600 mg/L) of either hydroquinone or methyl ester hydroquinone were present to prevent polymerization; however, the inhibitors were removed prior to testing.)

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

29.12.2004 (48)

Type : flow through
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : = 4.8 measured/nominal
Limit test : no
Analytical monitoring : no data
Method : other: according to ASTM Committee E-35
Year : 1980
GLP : no data
Test substance : no data

Test condition : The fathead minnows used during the exposures ranged in age from 28-34 days; Aerated and filtered Lake Superior water was used; Water quality was measured every day;

Water quality (mean values):
- pH = 7.62
- temperature = 24.6 deg. C
- dissolved O2 = 6.72 mg/l
- alkalinity = 47.0 mg CaCO3/l
- hardness = 45.0 mg CaCO3/l

During exposure, fish were observed daily at 8, 24, 48, 72, and 96 h; Abnormal behavioral and morphological changes wererecorded;

Test substance : 2-HEA had a purity > 97%; stock solution was prepared and not renewed; hydroquinone or methyl ester hydroquinone was added to prevent polymerization

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

30.03.2005 (49) (50)

Type : flow through
Species : Cyprinodon variegatus (Fish, estuary, marine)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : = 17.5 measured/nominal
Limit test : no
Analytical monitoring : yes
Method :
Year :
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Test fish were collected from the Surfside Beach salt marsh area. The average length and weight of the sheepshead minnow during the testing program was 3.6 cm and 2.3 grams.

Stock solutions of HEA were dissoved in 50 gallons of seawater, mixed in polyethylene drums and pumped to a proportional dilutor. Five fish were exposed at each concentration in the preliminary screening, while 10

individuals per concentration were used in the full scale tests to determine the 96-hour LC50. The propotional factor between concentrations was 0.5. Samples were extracted with diethyl ether and verified by gas chromatography.

Dissolved oxygen, pH, temperature, and chlorides were measured throughout the testing program according to Standard Methods for the Examination of Water and Wastewater (1971), 13th Edition, Washington, D.C., American Health Association, American Water Works Association, and Water Pollution Control Federation. Log-probit paper was used to calculate percent mortality versus concentration.

Result : The LC50 for HEA is 17.5 ppm or 17.5 mg/L.
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

29.12.2004 (51)

Type : static
Species : Leuciscus idus (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
NOEC : = 4.64
LC100 : = 10
Limit test : no
Analytical monitoring : no data
Method : other: according to DIN 38 412
Year : 1982
GLP : no data
Test substance : other TS: purity about 96.5%

Test condition : Positive control of animals conducted with chloroacetamide (LC50 after 48 hr about 24 mg/l); Tested 2-HEA concentrations were 2.15, 4.64, 10.0 or 21.5 mg/l.

water quality: total hardness ca. 2.5 mmol/l
(housing) acid capacity ca. 5.5 mmol/l
oxygen content > 60% of maximum saturation
pH about 8.0
temperature about 21 deg. C

water quality: reconstituted freshwater according to DIN
(test) DIN 38 412 (1982)
total hardness: 2.5 mmol/l
acid capacity : 0.8 mmol/l
ratio Ca/Mg : 4:1
ratio Na/K : 10:1
pH : 7.9
temperature : 20 deg. C

Determination or calculation of the median lethal concentration (LC50) and, if possible, the LC5 and the LC95 using the probit analysis after hours (nominal conc.): 1, 24, 48, 72, 96
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

30.03.2005 (52)

Type : static
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 72 hour(s)
Unit : mg/l
LC100 : = 20

maximum safe level	:	= 5
Limit test	:	no
Analytical monitoring	:	no data
Method	:	other
Year	:	1975
GLP	:	no
Test substance	:	no data
Reliability	:	(3) invalid Documentation insufficient for assessment

29.03.2005 (53)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	= .78 measured/nominal
Analytical monitoring	:	no data
Method	:	other: according to OECD Guide-line 202, part 1 and Directive 84/449/EEC, C2
Year	:	1992
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Exposure to the test material resulted in immobilization in the daphnia in the 0.56, 1.0, 1.8, 3.2, 5.6 and 10 mg/L test groups. On the other hand, exposure to the test material at concentrations of 0.10, 0.18 and 0.32 mg/L did not result in immobilization. Also, exposure to the untreated control solutions did not result in immobilzation. The 48-hour median effective nominal concentration (EC50) of 2-hydroxyethyl acrylate in Daphnia magna was 0.78 mg/L with 95% confidence limits of 0.64 - 0.95 mg/L. The no-observed-effect concentration was 0.32 mg/L.
Test condition	:	Subsequent to a range-finding study, 2 replicate groups of 10 daphnia were exposed to an aqueous solution of the test material at nominal concentrations of 0.10, 0.18, 0.32, 0.56, 1.0, 1.8, 3.2, 5.6 and 10 mg/L. Additional duplicate groups of 10 daphnia were included as untreated controls. The daphnia were exposed under static conditions in glass jars that contained 200 ml of the test media. The daphnia were observed for immobilization at 24 and 48 hours of exposure. The temperature, pH and oxygen concentration of the test solutions were monitored throughout the study. The pH of the water in controls was 8.0 at 0 hr and 7.9 at 48 hr in both replicates; at all HEA concentrations the pH ranged from 8.1 to 8.2 at 0 hr and from 7.9 and 8.1 at 48 hr. The water temperature was constant at 22 degrees C. HEA is expected to be stable under these conditions.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

29.03.2005 (54)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Selenastrum capricornutum (Algae)
Endpoint	:	other: biomass and growth rate
Exposure period	:	96 hour(s)
Unit	:	mg/l
Limit test	:	
Analytical monitoring	:	no
Method	:	EPA OPPTS 850.5400
Year	:	2003
GLP	:	yes

Test substance : other TS

Method : Also conducted according to OECD Test Guideline 201.

The pH-value in the control replicates increased not higher than 1.0 unit; from 7.49 to 8.48, water temperature was 24 +/- 2 degrees C; HEA is expected to be stable under these conditions based on hydrolysis studies.

Remark : Selenastrum capriornutum is now known as Pseudokirchneriella subcapitata

Result : Based on nominal concentrations:
Inhibition of Biomass (area under the curve):
EbC50 (72h) = 3.96 mg/L (95% CI = 3.53 - 4.44 mg/L)
EbC50 (96h) = 4.12 mg/L (95% CI = 3.75 - 4.52 mg/L)
NOEC (72h) = 0.625 mg/L
LOEC (72h) = 1.25 mg/L
NOEC (96h) = 0.625 mg/L
LOEC (96h) = 1.25 mg/L
Inhibition of Growth:
ErC50 (72h) = 8.81 mg/L (95% CI = 7.98 - 9.72 mg/L)
ErC50 (96h) = 8.26 mg/L (95% CI = 7.62 - 8.95 mg/L)
NOEC (72h) = 1.25 mg/L
LOEC (72h) = 2.5 mg/L
NOEC (96h) = 2.5 mg/L
LOEC (96h) = 5.0 mg/L

For the preliminary test, inhibition based on biomass was 98, 100 and 100% of control at 10, 100 and 1000 mg/L, respectively. Corresponding inhibition based on growth rate was 72, 100 and 100%.

Microscopic evaluation of the cells at the end of the incubation period revealed no morphological abnormalities. Environmental conditions (pH, water temperature) met the guideline requirements.

The following table provides a summary of cell density, area under growth curves and growth rate for the definitive test:

Nominal Conc.	Average Cell Counts (x 10,000)				Inhibition of Biomass	Rate-Related Inhibition
(mg/L)	24 h	48 h	72 h	96 h	(%)	(%)
0	8.3	46	201	453		
0.625	7.6	48	202	389	6.1	1.9
1.25	7.2	43	170	395	13.4	1.5
2.5	7.3	29	138	362	27	2.62
5	5.6	19	111	252	46	11.1
10	4.2	5.5	7.5	6.4	96	68

Test condition : Performance of the test: Static procedure

Exposure duration: 96 hours

Replicates: Three replicates for each concentration level, 6 per control.

Test container: Sterile erlenmeyer flasks, volume 250 mL, covered with cotton wool plugs.

Test volume: 100 mL

Test medium: Threefold concentrated medium according to OECD guideline (AAP medium).

Preculture: A three day old preculture was used as inoculum. Incubation was performed in 500 mL erlenmeyer flasks with test medium under the same environmental conditions as described for the definitive test. For the

start of the test the preculture was diluted test medium to receive an initial cell concentration of approximatley 1 x 10+4 cells/mL in the replicates. All algae were from the same source and had not been used in any previous studies.

Application: At the test start fluorescence was measured after application of hte test item. Application was carried our by adding appropriate volumes of the stock solution to the test replicates.

Temperature: Nominally 24 +/- 2 degrees C

Agitation: Test coantainers were placed on a rotary shaker and oscillated at approximately 100 rpm.

Light intensity: 66.5 microE x m-2 +/- 10%

Light regime: 24 h/d light

Recovery of algae: After 96 h 5 mL alga suspension from the nominal concentration 10 mg/L and from the control were transferred to 100 mL untreated test medium and allowed to grow for further 3 - 4 d to determine whether the effect of the test item was reversible. The test medium and growing conditions were the same as used in the main test.

TYPE AND FREQUENCY MEASUREMENT: Cell density was measured via Chlorophyll-a-fluorescence, exitation at 435 nm, emission at 685 nm. Each replicate was measured 6-fold. The cell density was measured at the beginning of the test and every 24 h. Filtrated culture medium was used as ground signal. The pH-value at the beginning of the test was measured out of
one additional replicate of each concentration and control. At the end it was measured from a pool of all replicates. The water temperature was recorded hourly during the test. The room temperature was measured continuously by a hygrothermograph. Light intensity was measured prior to test start. Microscopic evaluation of the cells at the start and at the end of the incubation was determined. Also any unusual cell shapes, colour differences, differences in chloroplast morphology, flocculations, adherence of algae to test containers or aggregation of alga cell were observed.

A preliminary test at concentrations of 2-HEA at 0, 1, 10, 100 and 1000 mg/L (2 replicates/concentration) was conducted in which biomass and growth rate were monitored at 0, 24, 48, 72 and 96 hours. Based on the results of the preliminary study, the definitive 96 hour static EC50 test was conducted with nominal concentrations of 0, 0.625, 1.25, 2.5, 5, and 10 mg/L.

Test substance : The test substance was 99.23% 2-HEA.
Reliability : (1) valid without restriction
GLP Guideline Study, valid without restriction
Flag : Critical study for SIDS endpoint
30.03.2005

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type : Aquatic
Species : Tetrahymena pyriformis (Protozoa)
Exposure period : 40 hour(s)
Unit : mg/l
Analytical monitoring : no data
Method : other: TETRATOX, the T. pyriformis population growth impairment assay
Year : 1997

GLP : no data
Test substance : no data

Method : The 50% impairment growth concentration (IGC50) was calculated for the freshwater ciliate Tetrahymena pyriformis (strain GL-C). Cultures were reared in 50 ml of a semi-defined medium in 250 ml Erlenmeyer flasks. Definitive test treatments consisted of a minimum of 5 different concentrations of each test material. Duplicate flasks were inoculated to an initial density of approximately 2500 cells/ml with log-growth phase ciliates. Following 40 hours of incubation at 27C +/- 1C, population density was measured spectrophotometrically and 50% effect levels determined.

The 50% impairment growth concentration (IGC50) for Tetrahymena pyriformis was determined and compared to the LC50 value determined in the 96-hour fathead minnow (Pimephales promelas) lethality assay [Center for Lake Superior Environmental Studies (CLSESe): Acute toxicities of Organic Chemicals to Fathead Minnows (Pimephales promelas), Vol. I-V, Superior, Wisconsin:University of Wisconsin 1985-1990]. A mathematical relationship was described.

Result : For HEA, the log (IGC50 exp -1) for Tetrahymena pyriformis was reported as 0.69 mM and the log (LC50 exp -1) for Pimephales promelas was 1.38 mM. These are equivalent to 23.7 mg/L and 4.84 mg/L, respectively.

The relationship between the population growth impairment to Tetrahymena pyriformis and the lethality to Pimephales promelas was described by:
log(IGC50)= 0.77 log (LC50)-0.40; r2=0.750; s=0.546; F=744.
There was a favorable similarity in toxic potency.

The observed toxicity of HEA was significantly higher than predicted by narcosis models and was thought to be bioreactive. Bioreactivity is considered to be the ability of a chemical to have a positive stereoelectronic interaction with a biological system.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

30.03.2005 (55)

Type : Aquatic
Species : other bacteria: Abwassermikroorganismen
Exposure period :
Unit : mg/l
EC0 : > 250
Analytical monitoring : no data
Method : other: modified Warburg-Method
Year : 1995
GLP : no data
Test substance : no data

29.03.2005 (56)

4.5.1 CHRONIC TOXICITY TO FISH

Remark : No data identified from literature searched.
29.03.2005

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Remark : No data identified from literature searched.

29.03.2005

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

Remark : No data identified from literature searched.
29.03.2005

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

Remark : No data identified from literature searched.
29.03.2005

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

Remark : No data identified from literature searched.
29.03.2005

4.7 BIOLOGICAL EFFECTS MONITORING

Remark : No data identified from literature searched.
05.04.1995

4.8 BIOTRANSFORMATION AND KINETICS

Remark : No data identified from literature searched.
29.03.2005

4.9 ADDITIONAL REMARKS

Remark : no additional remarks
13.05.1995

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In Vitro/in vivo	:	In vivo
Type	:	Toxicokinetics
Species	:	Rat
Number of animals		
Males	:	4
Females	:	
Doses		
Males	:	
Females	:	
Vehicle	:	
Method	:	
Year	:	
GLP	:	yes
Test substance	:	other TS

Method : The disposition of 14C-HEA was determined following a single dose administration via the oral, intraperitoneal, dermal, and inhalation routes of exposure. Four male Fischer 344 rats (approx. 200g) were utilized per dose and route of exposure. Doses selected for the oral and IP studies were 2.5 and 50 mg/kg, respectively, which were prepared in distilled deionized water. The radiotracer was diluted with non-radiolabeled HEA to obtain a target radioactivity and concentration of 20 uCi and 1.75 and 36.7 mg/ml of dosing solution. The dose applied dermally was 12.5 mg/kg and each animal received approximately 15-20 uCi of activity. The dermal site was clipped of hair and a frame was attached to the skin with adhesive. The dermal dosing solution prepared in water was then applied to the skin and immediately covered with a piece of Teflon film. The dosed area was then wrapped with tape. The nose-only inhalation exposure concentration was 8 ppm 14C-HEA for a 6 hour period under dynamic flow-through conditions. Exposure HEA concentrations and radioactivity were monitored over the exposure period.

After administration or termination of exposure to 14C-HEA, rats from all groups were housed in metabolism cages. Urine and cage rinse was collected at 0-12, 12-24 and 24-48 hr, post-dosing or post-exposure. Feces were collected at 24 hr intervals for up to 48 hr post-dosing or post-exposure. Expired organics and 14CO2 were collected at 0.25,0.5,1,2,4,8, and 12 hr post administration and then at 12 hr intervals thereafter. All of the above sample were analyzed for radioactivity. Urine and feces were also collected from individual rats during the inhalation exposure. In addition, the combined 14CO2 released into the inhalation chamber from the expired air of all 4 rats was trapped and analyzed after scrubbing 14C-HEA from the chamber exhaust. Selected samples of urine were analyzed by HPLC to determine 14C metabolic profiles.

Blood concentration-time profiles were obtained from separate groups of animals so that expired 14CO2 would not be lost while blood was collected from the animals in the metabolism cages. Blood samples for the 14C-plasma and red blood cell time course were collected at 0.25,0.5,1,2,4,6,8,12,16,24,30 and 48 hr after the administration of 14C-HEA by the oral, IP and dermal routes. During the inhalation exposure, blood samples were collected at 0.25,0.5,1,2,4 and 6 hr, and 0.5,1,2,4,8,20,30 and 48 hr post inhalation exposure. Plasma and red blood cells were analyzed for radioactivity.

The rats were sacrificed 48 hr after administration or exposure to 14C-HEA, and the radioactivity remaining in samples of blood, skin, and the carcass was quantified. For the dermal route of administration, the

radioactivity associated with the skin at the dose site and all bandage material was also determined.

The half-lives for the CO2 excretion and the plasma radioactivity were determined from the slope of the line by regression analysis of the excretion time-course obtained from each treatment group. Statistical analysis of the data was limited to the calculation of means and standard deviations were appropriate. Pharmacokinetic analysis (calculation of half-lives, AUC's etc.) were carried out using standard methodologies.

Result : Once systemically available, 2-HEA was rapidly metabolized and eliminated from the body. The in vitro half-life of HEA in rat blood was approximately 100 seconds. In vivo, greater than 70% of the administered dose of [14C]-HEA was excreted by 12 hours post-dosing or post-exposure as urinary metabolites and as [14C]-CO2 in the expired air for the oral, i.p. and inhalation routes.

Following the 2.5 mg/kg dose via the oral and IP routes, 43-47% of the dose was excreted in urine and 35-36% as expired 14CO2. At 50 mg/kg dose via the oral and IP routes, there was some evidence of saturation kinetics, with 33-36% excreted in the urine and 40-45% expired as 14CO2. The rate of absorption of HEA appeared to be route-dependent and was complete within 4 hours or less when given by oral or i.p. routes.

Following dermal administration of a dose of 12.5 mg/kg, 66% of the applied dose was slowly absorbed within 48 hours with the remaining 33% being associated with the application site. Once absorbed, 27% was excreted in the urine and 27% was expired as 14CO2.

Following inhalation exposure to 8 ppm HEA for 6 hours, 39% of the radioactivity recovered at 48 hr was eliminated
in the urine as metabolites of HEA and 41% was expired as 14CO2.

For all routes 9-16% of the dose or recovered radioactivity was found in the tissues and carcass and less than 3% in the feces. The half-lives of elimination of radioactivity in the urine and expired 14CO2 were approximately 14 hours and 17 hours, respectively. The half-life of elimination of radioactivity in the plasma was determined to be approximately 26 hours and did not represent parent chemical. No qualitative differences in urinary metabolites between routes were observed, indicating no marked route-dependent differences in the metabolic fate of HEA.

Test substance : Uniformly labeled 14C-HEA had a specific activity of 6.3 mCi/mmol and a radiochemical purity of 100% as determined by HPLC. Radiochemical purity was evaluated throughout the study and ranged from 100% to 87% (lower purity for inhalation study only).

Non-radiolabeled HEA had a molar purity of 98.3% as determined by GC and IR.

Reliability : (1) valid without restriction
A GLP study that meets generally accepted scientific standards and is described in sufficient detail.

30.03.2005 (57)

In Vitro/in vivo : In vivo
Type : Metabolism
Species : rat
Number of animals
Males :
Females :
Doses
Males : 42, 104, 208, or 333 mg/kg bw
Females :

Vehicle :
Route of administration : i.p.
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st.:
2nd.:
3rd.:
Toxic behaviour :
Deg. product :

Result : GSH was depleted in a dose-dependent manner; TOTP had no effect on hepatic GSH levels; inhibition of carboxylesterase with TOTP pretreatement enhanced the depletion of GSH by HEA;

Time course of glutathione (GSH) depletion:
- treatment with 25% of oral LD50
- animals were killed for examination at 15, 60, and 120 minutes post-treatement

Dose response relationship for GSH depletion:
- injection of 42, 104, 208, or 333 mg HEA/kg i.p. with or without pretreatment with carboxyl esterase inhibitor (TOTP,125 mg/kg i.p.; 18 hours prior to 2-HEA)
- animals were killed for examination 1 hour post-treatment

Source : Dow Benelux N.V. (Botlek) XA Botlek RT
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (2) valid with restrictions
04.01.2005 (58)

5.1.1 ACUTE ORAL TOXICITY

Type : LD50
Value : = 548 mg/kg bw
Species : rat
Strain : Sprague-Dawley
Sex : male/female
Number of animals : 16
Vehicle : other:aqueous solution
Doses : Doses (mg/kg): 266.7, 400, 600, 900, by gavage
Method : other: Litchfield and Wilcoxin (1949). "A Simplified Method of Evaluating Dose-Effect Experiments." J. Pharm. & Exp. Ther. 96, 99.
Year :
GLP : no
Test substance : other TS

Method : TEST ORGANISMS
-Source: Sprague Dawley rats, source unknown
-Age: Unknown ("young")
-Weight at study: 154-168 grams
-Controls: None
ADMINISTRATION:
-Doses (mg/kg): 266.7, 400, 600, 900, by gavage, Animals were fasted for 16 hours prior to dosing.
-Doses per time period: Single
-Volume Administered: 10% (w/v)
-Post dose observation period: 14 days
EXAMINATIONS: A necropsy exam was conducted on all animals.
Result : MORTALITY:
-Time of death: 600 mg/kg (6-22 hours); 900 mg/kg (6-22 hours)

-Number of deaths at each dose: 266.7 mg/kg (0/4); 400 mg/kg (0/4); 600 mg/kg (3/4); 900 mg/kg (4/4)
CLINICAL SIGNS:
-266.7 mg/kg hypoactivity, rough fur (onset, 30 min, duration 6-22 hr)
-400 mg/kg hypoactivity & rough fur (onset, 30 min, duration 2 days) labored breathing (onset, 1 hr, duration 6-22 hr) -600 mg/kg hypoactivity & rough fur (onset, 30 min, duration 4 days);labored breathing & muscular weakness (onset, 1 hr, duration 2 days)
-900 mg/kg hypoactivity & rough fur (onset, 30 min, duration until death); labored breathing & muscular weakness (onset, 1 hr, duration until death)
NECROPSY FINDINGS:
-Hemorrhages in the gastrointestinal tracts, no gross pathology observations were noted in animals at the end of the 14 day observation period.
POTENTIAL TARGET ORGANS:
-Not specified
SEX-SPECIFIC DIFFERENCES:
-None observed

Test substance : No purity data. Test material was received from Celanese Corporation.
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.
Flag : Critical study for SIDS endpoint
30.03.2005 (59)

Type : LD50
Value : = 540 mg/kg bw
Species : rat
Strain :
Sex :
Number of animals : 5
Vehicle :
Doses :
Method : other
Year : 1962
GLP : no
Test substance : no data

Method : A 10% aqueous solution was administered; 2-HEA
Result : Three of 3 rats receiving 1000 mg/kg and one of 2 rats
Test substance : No purity data or analysis of test material available.
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.
30.03.2005 (60)

Type : LD50
Value : = 650 mg/kg bw
Species : rat
Strain : Wistar
Sex : male
Number of animals : 10
Vehicle :
Doses :
Method : other
Year : 1966
GLP : no
Test substance : no data

Method : Wistar derived male rats were used. 2-HEA was administered undiluted at 0.5 or 1.0 ml/kg by stomach intubation. Five animals per group were tested.

Test substance	:	No purity of test material or analysis available.
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well documented and acceptable for assessment.

30.03.2005 (61)

Type	:	LD50
Value	:	= 810 mg/kg bw
Species	:	rat
Strain	:	other:albino
Sex	:	
Number of animals	:	50
Vehicle	:	
Doses	:	500, 700, 1100, 1300 and 500 mg/kg bw
Method	:	
Year	:	1979
GLP	:	yes
Test substance	:	other TS
Result	:	The acute oral LD50 was 810 mg/kg. The dosages ranged from 500-1500 mg/kg. The tested formulation was rated as slightly toxic. All animals survived and showed no effects at the low dose (500 mg/kg). All the animals that died did so in the initial 24 hours after treatment. At the 700 mg/kg dose, 2 out of 10 died. The effects noted were decreased eyelid tone, decreased corneal reflex, and loss of righting reflex. At 1100 mg/kg, 8 out of 10 died. Additionally, clonic convulsions were cited. At the 1300-1500 mg/kg, 10 out of 10 died, with muscle incoordination additionally cited. We do not know (1) the number of animals per dose that experienced these symptoms, or (2) the duration of the symptoms.
Test substance	:	No purity of test material or analysis available.
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well documented and acceptable for assessment.

30.03.2005 (62)

Type	:	LD50
Value	:	ca. 1040 mg/kg bw
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	water
Doses	:	2-16% solutions
Method	:	
Year	:	1973
GLP	:	no
Test substance	:	no data
Result	:	Symptoms: Dyspnea, slight apathy, reduction in body weight at the end of the experiment.
Reliability	:	(3) invalid Documentation insufficient for assessment

29.03.2005 (52)

Type	:	LD50
Value	:	= 1070 mg/kg bw
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	

Method :
Year : 1951
GLP : no
Test substance : no data

Remark : These data not consistent with other more recently conducted studies.
Result : Neat HEA was administered by gastric intubation to groups of five rats at concentrations differing by a factor of 2 in a geometric series. The method of moving average for calculation the LD50 was applied to the 14-day mortality data.
Test substance : No purity or test material analysis available.
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

30.03.2005 (63)

Type : LD50
Value : = 601 mg/kg bw
Species : mouse
Strain : other: ddY
Sex : male
Number of animals : 16
Vehicle : no data
Doses :
Method :
Year : 1981
GLP : no data
Test substance : other TS

Method : Male ddY mice (24-27g) were used for determining the acute oral toxicity of 2-HEA. The LD50 was assayed according to Weil (1952), using 4 animals per dose level and 4 different doses. The acute oral LD50 was expressed as the mean (95% confidence interval).

Weil, C.S. (1952). Tables for Convenient Calculation of Median Effective Dose (LD50 or ED50) and Instructions in Their Use. Biometrics, 8 (1952), 249-263.
Result : 5.177 mmol/kg (4.325-6.200) or 601 mg/kg (502-720)
Test substance : No purity data. The test material was received from Yokyo Kasei Co.
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

30.03.2005 (64)

5.1.2 ACUTE INHALATION TOXICITY

Type : other: saturated vapor exposures
Value : = 394 ppm
Species : rat
Strain :
Sex :
Number of animals : 6
Vehicle : other: none
Doses : single exposures to concentrated vapor (1.87 mg/L)
Exposure time : 4 hour(s)
Method :
Year : 1966
GLP : no
Test substance : no data

Result : Signs and/or symptoms:

Ocular irritation, diarrhea, extremities irritated Six animals were tested. Concentrated vapor was generated ina gas washing bottle by passing dried air at 2.5 l/min through a fritted glass disc. Mean vapor concentration was calculated from the loss in weight of the liquid or estimated from the vapor pressure at the actual temperature of the chemical during aeration. Tested concentration was 1.87 mg/kg or 394 ppm.

A 4 hour exposure resulted in death for 1 of 6 animals exposed.

Test substance : No purity data of test material or analysis available.
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

30.03.2005 (65)

Type : other: LC0 and ca. LC100
Value :
Species : rat
Strain :
Sex : female
Number of animals : 3
Vehicle : other: none
Doses : saturated atmosphere with HEA at room temperature or heated to 100 deg C
Exposure time : 7 hour(s)
Method :
Year : 1962
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Result : LC0: Five rats exposed to a saturated atmosphere of room temperature HEA for 7 hrs appeared normal during exposure; 0.6 grams used during exposure with 480 L airflow = 1.25 mg/L or 264 ppm; liver and kidney effects reported at gross pathologic examination are difficult to assess due to few animals, the lack of detail regarding the nature of the observations, and absence of controls.

LC0 = 264 ppm

LC100: When HEA was heated to ca. 100 deg. C, all 5 rats died within 5 hours of exposure; 3.36 grams used during the 5 hour exposure, assuming equivalent airflow the room temperature experiments the concentration was 10.58 mg/L or 2231 ppm.

LC100 = 2231 ppm

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

30.03.2005 (66)

Type : other: ca. LC100
Value : = 500 ppm
Species : rat
Strain : Sherman
Sex : male/female
Number of animals : 6
Vehicle : other: none
Doses : 500 ppm
Exposure time : 4 hour(s)
Method :
Year : 1951
GLP : no
Test substance : no data

Result	:	Groups of 6 albino Sherman rats (male and female) were exposed for 4 hours and observed for 14 days. Five of 6 rats died when exposed to HEA (500 ppm = 2370 mg/m3).
Test substance	:	No test material purity or analysis available.
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well documented and acceptable for assessment.

30.03.2005 (63)

Type	:	LC0
Value	:	
Species	:	rat
Strain	:	Sherman
Sex	:	male/female
Number of animals	:	12
Vehicle	:	other:none
Doses	:	saturated vapor
Exposure time	:	1 hour(s)
Method	:	
Year	:	1951
GLP	:	no
Test substance	:	no data

Method	:	Groups of 6 albino Sherman rats (male and female) were exposed to HEA as a saturated vapor (no concentration reported for 1 hour and observed for 14 days. No deaths occurred.
Test substance	:	No test material purity or analysis available.
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well documented and acceptable for assessment.

30.03.2005 (67)

Type	:	LC0
Value	:	
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	12
Vehicle	:	other: none
Doses	:	saturated atmosphere
Exposure time	:	8 hour(s)
Method	:	
Year	:	1973
GLP	:	no
Test substance	:	no data

Result	:	All animals (n=12) survived a 8-hour exposure to a saturated atmosphere of HEA at 20 deg. C; symptoms were dyspnea and severe irritation of the mucous membranes.
Reliability	:	(3) invalid Documentation insufficient for assessment

29.03.2005 (52)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	= 154 mg/kg bw
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male/female

Number of animals : 20
Vehicle : other: none
Doses : 63, 130, 160, 200, 250 mg/kg/bw
Method :
Year : 1981
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : The acute percutaneous absorption potential was evaluated by treating 2 male and 2 female rabbits per dose level with the undiluted test material. Following dosing to the intact skin (not abraded) the site of application was occluded with plastic wrap and left in place for 24 hours. At 24 hours post-dosing the occlusion was removed and the dose site washed with mild soap and water to remove any unabsorbed test material.

Result : The acute percutaneous absorption LD50 was 154 mg/kg (131-174 mg/kg, 95% confidence interval) when calculated by the moving average method of analysis. Rabbits were treated with 63, 130, 160, 200 or 250 mg/kg of the test material. Topical responses observed on the application sites of 10 test animals 25 hours post-treatment included marked redness (10/10), marked swelling (10/10) and slight (4/10) or moderate necrosis (3/10). The following in-life signs of toxicity were observed in test rabbits (dose groups affected are in parentheses): lethargy (all), decreased activity (63, 160 and 200 mg/kg), loss of appetite (63 and 160 mg/kg) and rapid shallow breathing (250 mg/kg). In rabbits surviving the 2 week post-treatment interval there were some skin lesions noted at necropsy. However, there were no systemic treatment related changes seen upon gross examination.

Mortality

Dose group (mg/kg bw)	No. Dead/ No. Dosed
63	0/4
130	0/4
160	3/4
200	4/4
250	4/4

Reliability : (1) valid without restriction
GLP study, meets generally accepted scientific standards and is described in sufficient detail.
Flag : Critical study for SIDS endpoint
30.03.2005 (68)

Type : LD50
Value : = 154 mg/kg bw
Species : rabbit
Strain : New Zealand white
Sex : male
Number of animals : 8
Vehicle : other: none
Doses : 0.1 and 0.2 ml/kg
Method :
Year : 1966
GLP : no
Test substance : no data

Method : New Zealand male albino rabbits were immobilized during the 24-hour contact period with the compound retained under impervious sheeting on the clipped intact skin of the trunk. Thereafter, excess fluid was removed to prevent ingestion. Maximum dosage that can be retained was 20 ml/kg. Groups of 4 animals were used; tested concentrations were 0.10 ml/kg and 0.20 ml/kg; HEA was tested undiluted.

Conversion of the LD50 from the reported value of 0.14 ml/kg bw yields 154 mg/kg bw. (Density = 1.1 mg/ml)

Test substance : No purity data or analysis of test material available.
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

30.03.2005 (65)

Type : LD50
Value : = 250 mg/kg bw
Species : rabbit
Strain : no data
Sex : male
Number of animals : 12
Vehicle : other: none
Doses : 110, 220, 440, 880 mg/kg bw
Method :
Year : 1975
GLP : no
Test substance : other TS

Remark : Fewer doses used in lower dose range than in the critical study.
Result : Severe erythema and edema followed by eschar formation. At 14 days, the skin beneath the eschar was cracked and fissured and had both sanious and ichorus pus.

Lethality within 6-48 hours post-treatment was observed in 0/3, 1/3, 3/3 and 3/3 in the 110, 220, 440, and 880 mg/kg dose groups, respectively.
Test condition : 2-HEA was applied undiluted to the closely shaven skin of three male rabbits per dose group and held under an impervious cuff in a continuous 24-hr long exposure. The doses applied were 110, 220, 440 or 880 mg/kg body weight.
Test substance : Purity not specified
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

30.03.2005 (69)

Type : LD50
Value : = 298 mg/kg bw
Species : rabbit
Strain : other: albino
Sex : male/female
Number of animals : 28
Vehicle : other: none
Doses : 118.5, 177.8, 266.7, 400, 600, 900, 3000 mg/kg bw
Method :
Year : 1974
GLP : no
Test substance : other TS

Method : HEA was applied to the clipped skin undiluted and occluded. 24 hours post-dosing the occlusion was removed and the test material removed. Surviving animals were held for a 14-day observation period.
Result : Mortality

Dose group (mg/kg bw)	No. Dead/ No. Dosed
118.5	0/4
177.8	2/4
266.7	1/4
400	2/4

600 4/4
900 4/4
3000 4/4

Inconsistent response observed from 177.8 to 266.7 mg/kg bw. LD50 calculated to be 298 mg/kg body weight; 95% confidence limits 220 to 402 mg/kg b

Test substance : No purity data. Test material was received from Celanese Corporation.
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

30.03.2005 (59)

Type : LD50
Value : > 1000 mg/kg bw
Species : rat
Strain : Wistar
Sex : male/female
Number of animals : 15
Vehicle : other: olive oil
Doses : 400 mg/kg bw (undiluted); 1000 mg/kg bw in olive oil
Method : OECD Guide-line 402 "Acute dermal Toxicity"
Year : 1999
GLP : yes
Test substance : other TS

Result : Five rats of each sex received a dermal dose of 400 mg 2-HEA/kg body weight applied to the clipped skin without any vehicle (undiluted). No lethality was observed.

Five male rats received a dermal dose of 1000 mg HEA/kg body weight in olive oil vehicle (concentration of 25 g/100 ml) at an administration volume of 4 ml/kg. No female rats were dose for animal welfare reasons since necrosis of the skin was observed in males. No lethality was observed in males treated with 1000 mg/kg.

Test substance : Test substance purity was 99.1 area % 2-HEA when analyzed by gas chromatography.
Reliability : (1) valid without restriction
GLP guideline study

29.12.2004 (70)

Type : LD50
Value : > 63 mg/kg bw
Species : rabbit
Strain :
Sex :
Number of animals : 12
Vehicle : water
Doses : 16, 32, 63, 126, 252, 500 mg/kg bw
Method :
Year : 1962
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Result : An early range-finding study showed that doses of 16, 32, and 63 mg/kg (administered as a 3.16% aqueous solution of HEA) was not lethal, while 126a, 252, or 500 mg/kg (administered as a 25.5% aqueous solution of HEA) was lethal to 2 out of 2 rabbits per group. Duration of dermal exposures was 24 hours, occluded.
Reliability : (3) invalid
Results are superseded by later more definitive studies, specifically Carreon et al., 1981.

29.03.2005 (71)

Type	:	LD50
Value	:	= 1100 mg/kg bw
Species	:	rabbit
Strain	:	
Sex	:	
Number of animals	:	6
Vehicle	:	other: none
Doses	:	
Method	:	
Year	:	1951
GLP	:	no
Test substance	:	no data

Method : The neat material was applied under covered contact to the clipped skin of six rabbits using the one-day rubber cuff application of the FDA (Draize J.H. et al. J. Pharmacol. Exp. Ther., 82, 37ff, 1944). The animals were then observed for 14 days.

Reliability : (3) invalid
Results inconsistent with other well documented studies.

29.03.2005 (67)

Type	:	LD100
Value	:	= 3000 mg/kg bw
Species	:	rabbit
Strain	:	other: not specified
Sex	:	male
Number of animals	:	8
Vehicle	:	other: none
Doses	:	
Method	:	
Year	:	
GLP	:	yes
Test substance	:	other TS

Method : Test condition: 8 males were used. All animals were shaved 24 hours prior to test material application. 0.5 ml of the test material was introduced under each of four 1 inch square gauze patches. The patches were applied to two intact and two abraded skin sites on each animal. The application sites were clipped free of hair and the abrasions were made so as to penetrate the stratum corneum but not the dermis. Each test site was covered by a gauze pad over which a rubber dam was wrapped to avoid evaporation and keep the test material in contact with the skin for a 24 hour period. At the end of this period the wrapping was removed and the skin wiped to remove any residual test material.

Test substance : The product BX-2204 contained HEA, methylenebisacrylamide and water.

Reliability : (3) invalid
Unsuitable test system the product contained significant quantities of materials other than 2-HEA

29.12.2004 (72)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type	:	LC50
Value	:	= 620 mg/kg bw
Species	:	rat
Strain	:	other: albino
Sex	:	female
Number of animals	:	15

Vehicle	:	other: none
Doses	:	
Route of admin.	:	i.p.
Exposure time	:	
Method	:	
Year	:	1966
GLP	:	no
Test substance	:	no data

Method	:	Five female albino rats per group were tested. Undiluted HEA was injected at 1.0, 0.5, or 0.25 ml/kg. At the concentration of 1 ml/kg all animals died within 24 hours.
Test substance	:	No purity available
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well documented and acceptable for assessment.

30.03.2005 (65)

Type	:	LC50
Value	:	ca. 495 mg/kg bw
Species	:	mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Route of admin.	:	i.p.
Exposure time	:	
Method	:	other
Year	:	1973
GLP	:	no
Test substance	:	no data

Reliability	:	(2) valid with restrictions

29.03.2005 (52)

Type	:	LD100
Value	:	= 250 mg/kg bw
Species	:	rabbit
Strain	:	other: albino
Sex	:	male
Number of animals	:	4
Vehicle	:	
Doses	:	0.0625 and 0.5 ml/kg bw
Route of admin.	:	i.p.
Exposure time	:	
Method	:	other
Year	:	1966
GLP	:	no
Test substance	:	no data

Result	:	Two male albino rabbits were used per group. Undiluted HEA was injected at 0.25 or 0.0625 ml/kg. At 0.25 ml/kg all animals died within 2 hours. At 0.0625 ml/kg 1 of 2 animals died within 24 hours.
Reliability	:	(2) valid with restrictions

29.03.2005

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	undiluted

Exposure	:	Occlusive
Exposure time	:	24 hour(s)
Number of animals	:	6
Vehicle	:	other: none
PDII	:	8
Result	:	highly irritating
Classification	:	irritating
Method	:	
Year	:	1981
GLP	:	no data
Test substance	:	no data

Method	:	Primary skin irritancy was assessed using albino rabbits. The test material was applied in 0.25 ml aliquots to areas of abraded and non-abraded shaved dorsal skin and the sites were covered for 24 hours with occlusive bandage. After removal of patches the remaining test material was washed off with water and the site scored using the "Draize" scoring system and again scored at 72 hours. The Draize score for primary irritation was 8 our a possible highest score of 8.
Result	:	HEA was found to be a severe irritant producing necrosis, subcutaneous haemorrhage and pitting oedema over a wide area of skin. Histological examination of one area of skin revealed epidermal necrosis together with areas of damage and haemorrhage extending deeply into the deep dermis and hypodermis.
Test substance	:	No purity available
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well documented and acceptable for assessment.
Flag	:	Critical study for SIDS endpoint

30.03.2005 (73)

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Occlusive
Exposure time	:	24 hour(s)
Number of animals	:	6
Vehicle	:	other: none
PDII	:	8
Result	:	highly irritating
Classification	:	irritating
Method	:	
Year	:	1974
GLP	:	no
Test substance	:	other TS

Method	:	Albino rabbits were exposed to 0.5 ml of undiluted HEA at abraded and intact skin sites for 24 hours under occluded conditions. After 24 hours the occlusive plastic and test material was removed. Draize scores of the skin at the sites of application were given at 24 and 72 hours.
Result	:	The Draize score for primary irritation was 8 our of a possible highest score of 8.
Test substance	:	No purity data. Test material was received from Celanese Corporation.
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well documented and acceptable for assessment.

30.03.2005 (59)

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	no data
Exposure time	:	24 hour(s)
Number of animals	:	10

Vehicle	:	other: none
PDII	:	
Result	:	highly irritating
Classification	:	irritating
Method	:	
Year	:	1966
GLP	:	no
Test substance	:	other TS

Method	:	HEA was applied in 0.01 ml amounts to clipped intact skin of 5 rabbit bellies/group either undiluted or in a dilution of 10% in acetone. Ten grades were recognized based on appearance of moderate or marked capillary injection, erythema, edema, necrosis within 24 hours.
Result	:	The undiluted material caused marked necrosis on one animal, moderate edema on 3 others and moderate erythema on a fifth. A 10% solution in acetone produced moderate to marked capillary injection on 5 animals (Grade 6).
Test substance	:	Inhibited with 50 ppm hydroquinone.
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well documented and acceptable for assessment.

30.03.2005 (65)

Species	:	rabbit
Concentration	:	other: undiluted and 10% aqueous solution
Exposure	:	Semiocclusive
Exposure time	:	24 hour(s)
Number of animals	:	2
Vehicle	:	water
PDII	:	
Result	:	highly irritating
Classification	:	irritating
Method	:	
Year	:	1962
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Result	:	The undiluted liquid caused slight redness and moderate swelling when in contact with the skin of a rabbit for 15-60 minutes, moderate redness with extensive swelling (edema) and a burn upon contact for 24 hours. Six-hour contact of a 10% aqueous solution with the skin of a rabbit produced moderate redness, swelling and slight burns which healed with a scab and scaliness.
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well documented and acceptable for assessment.

30.03.2005 (74)

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	no data
Exposure time	:	24 hour(s)
Number of animals	:	5
Vehicle	:	other: none
PDII	:	
Result	:	irritating
Classification	:	
Method	:	
Year	:	1951
GLP	:	no
Test substance	:	no data

Result	:	0.01 ml of the neat material was applied to the clipped belly skin of a group of five rabbits for 24 hours. Strong capillary injection (Grade 3 on a scale of 1-10) was recorded.
Test substance	:	No purity data available.
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well documented and acceptable for assessment.

30.03.2005 (67)

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	
Exposure time	:	20 hour(s)
Number of animals	:	
Vehicle	:	
PDII	:	
Result	:	irritating
Classification	:	
Method	:	
Year	:	1973
GLP	:	no
Test substance	:	no data
Method	:	HEA was applied undiluted to the back for 1, 5, 15 minutes and 20 hours and to the ear for 20 hours; readings were done after 24 hours and 8 days.
Result	:	Application up to 15 minutes produced slight redness and edema after 24 hours and slight desquamation after 8 days. Application for 20 hours onto the back produced slight to moderate necrosis after 24 hours and 8 days, respectively; application to the ear produced moderate necrosis and severe edema after 24 hours and moderate necrosis after 8 days.
Test substance	:	No purity data available.
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well documented and acceptable for assessment.

30.03.2005 (75)

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Occlusive
Exposure time	:	4 hour(s)
Number of animals	:	6
Vehicle	:	
PDII	:	
Result	:	moderately irritating
Classification	:	irritating
Method	:	other: DOT Title 49 Section 173.240, US Code of Federal Regulations.
Year	:	1973
GLP	:	no
Test substance	:	no data
Result	:	Non-corrosive by this test
Reliability	:	(2) valid with restrictions Comparable to guideline study with acceptable restrictions; no purity information on test material.

30.03.2005 (76)

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Occlusive
Exposure time	:	4 hour(s)

Number of animals	:	6
Vehicle	:	other: none
PDII	:	
Result	:	moderately irritating
Classification	:	irritating
Method	:	other: DOT Test for Corrosivity: US Code of Federal Register Regulations, Title 49, Section 173.240, Appendix A.
Year	:	1981
GLP	:	no data
Test substance	:	no data

Method	:	DOT Test for Corrosivity: US Code of Federal Register Regulations, Title 49, Section 173.240, Appendix A.
Result	:	A 4 hour dermal exposure to 2-HEA resulted in moderate redness, severe swelling, and superifical necrosis (2/6 rabbits). The test material was not considered corrosive by this test.
Reliability	:	(2) valid with restrictions Comparable to guideline study with acceptable restrictions; no purity information on test material.

30.03.2005 (77)

Species	:	guinea pig
Concentration	:	5 %
Exposure	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	other: acetone-polyethylene glycol 400 (70:30)
PDII	:	
Result	:	irritating
Classification	:	
Method	:	
Year	:	1992
GLP	:	no data
Test substance	:	other TS

Result	:	In a pre-sensitization test, guinea-pigs were tested for primary skin irritation. HEA was diluted to the required concentration in acetone-polyethylene glycol 400 (70:30). Intradermal injection of 0.25% HEA was slightly irritating, topical application of 5% was mildly irritating and 1% was found to be the maximum non-irritant topical concentration. see also chapter 5.3 Sensitization
Test substance	:	Purity not stated.
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well documented and acceptable for assessment.

30.03.2005 (78)

Species	:	rabbit
Concentration	:	
Exposure	:	Occlusive
Exposure time	:	24 hour(s)
Number of animals	:	6
Vehicle	:	
PDII	:	
Result	:	slightly irritating
Classification	:	
Method	:	other
Year	:	1979
GLP	:	yes
Test substance	:	other TS

Method	:	Test condition: 6 males were used. All animals were shaved 24 hours prior to test material application. 0.5 ml of the test article was introduced under each of four 1 inch square gauze patches. The patches were applied to two intact and two abraded skin sites on each animal. The application sites were clipped free of hair and the abrasions were made so as to penetrate the stratum corneum but not the dermis. Each test site was covered by a gauze pad over which a rubber dam was wrapped to avoid evaporation and keep the test article in contact with the skin for a 24 hour period. At the end of this period the wrapping was removed and the skin wiped to remove any residual test material.
Result	:	A total of 2 ml of product was applied to four application sites in the primary dermal irritation study. All six animals died within 24 hours after treatment. Based on animal weights, the dose was between 570-1000 mg/kg. Necropsied animals showed gastrointestinal hemorrhage, ulceration and hemorrhaging of the vermis a region within the brain.
Test substance	:	The product BX-2204 contained HEA, methylenebisacrylamide and water.
Reliability	:	(3) invalid Not reliable since the test material was a mixture, not pure HEA.

29.03.2005

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 ml
Exposure time	:	
Comment	:	not rinsed
Number of animals	:	6
Vehicle	:	
Result	:	highly irritating
Classification	:	
Method	:	Draize Test
Year	:	1974
GLP	:	no
Test substance	:	other TS
Method	:	Draize, J. H., Woodard, G. and Calvery, H.O. (1944) Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. J. Pharmacol. Exp. Therapeut. 82: 377.
Result	:	AVERAGE SCORES: Cornea: 1 min = 20.0, 1 hr = 20.0, 24 hr = 20.0, 72 hr = 50.0, 7 d = 53.3, 14 d = 70.0 (Out of a maximum score of 80) Iris: 1 min = 5.0, 1 hr = 5.0, 24 hr = 10.0, 72 hr = 10.0, 7 d = 10.0, 14 d = 10.0 (Out of a maximum score of 10) Conjunctiva: 1 min = 12.0, 1 hr = 18.0, 24 hr = 20.0, 72 hr = 20.0, 7 d = 19.0, 14 d = 16.7 (Out of a maximum score of 20) Overall average irritation scores: (Out of a maximum score of 110) 1 min = 37.0, 1 hr = 43.0, 24 hr = 50.0, 72 hr = 80.0, 7 d = 82.3, 14 d = 96.7 DESCRIPTION OF LESIONS: Epithelial sloughing of the cornea was noted in some animals as soon as 1 minute after instillation. The following effects were noted in some animals at or past 72 hours postexposure: blister, corrosion and/or ulceration of the cornea.

REVERSIBILITY: No information available, from the description of the lesions damage to the eye may be permanent.

Test condition : TEST ANIMALS:
Strain: New Zealand Albino rabbits
Sex: Unspecified
Source: Unspecified
Age: Unspecified
Weight at study initiation: Unspecified
Number of animals: Six
Controls: No

ADMINISTRATION/EXPOSURE:
Preparation of test substance: none, undiluted material
Amount of substance instilled: 0.1 ml of undiluted HEA
Vehicle: None
Postexposure period: 14 days
Eyes were unwashed following administration with undiluted HEA.

EXAMINATIONS:
Opthalmoscopic examination: No
Scoring system: As described by Draize, 110 points maximum score

Test substance : No purity data. Test material was received from Celanese Corporation.
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.
Flag : Critical study for SIDS endpoint
30.03.2005 (59)

Species : rabbit
Concentration :
Dose :
Exposure time :
Comment :
Number of animals :
Vehicle : other: propylene glycol
Result : highly irritating
Classification :
Method :
Year : 1966
GLP : no
Test substance : no data

Result : Severe corneal necrosis and eyelid irritation resulted from instillation of 0.005 ml amounts undiluted and from an excess (0.5 ml) of a 5% solution in propylene glycol. An excess of a 1% solution caused minor corneal injury. Grade
9.

Single instillations of 0.005, or 0.5 ml undiluted or of 0.5ml of 5% or 1% dilutions in propylene glycol were made into conjunctival sac of 5 rabbits/group. Read within one hour unstained and after fluorescein at 24 hours, with ten gradesrecognized. Trace or no injury from 0.5 ml undiluted = Grade1.

Test substance : No purity data
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.
30.03.2005 (65)

Species : rabbit
Concentration :

Dose	:	
Exposure time	:	
Comment	:	
Number of animals	:	
Vehicle	:	
Result	:	highly irritating
Classification	:	
Method	:	other
Year	:	1962
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Result : Undiluted and a 10% aqueous solution of HEA was instilled directly into the conjunctival sacs of New Zealand Albino rabbits. Within about 30 seconds of treatment one eye of each animal was washed with flowing water the other treated eye was left unwashed.

One hour after treatment with undiluted material the washed and unwashed eye showed extensive inflammation of the conjunctival membranes with corneal opacity over 50% of the eye. The response was essentially unchanged 2 and 7 days later, suggesting some permanent impairment of vision was likely.

Treatment with the 10% aqueous solution caused some slight irritation which persisted in the unwashed eye for 2 days; in addition the 10% solution produced moderate pain and slight conjunctivitis which did heal in a week. The washed eye showed no sign of irritation one hour post-instillation.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

30.03.2005 (79)

Species	:	rabbit
Concentration	:	undiluted
Dose	:	
Exposure time	:	
Comment	:	
Number of animals	:	
Vehicle	:	
Result	:	highly irritating
Classification	:	
Method	:	other
Year	:	1951
GLP	:	no
Test substance	:	no data

Result : 0.005 ml of the neat material was applied to the center of the cornea for 18-24 hours. Severe injury (Grade 5 reaction on a scale of 1-10), as seen by necrosis only after staining and covering about 75% of the corneal surface or by a more severe necrosis covering a smaller area, was noted. 0.02 ml gave a numerical score on eye injury of over 5.0.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

30.03.2005 (67)

Species	:	rabbit
Concentration	:	undiluted
Dose	:	
Exposure time	:	
Comment	:	

Number of animals	:	
Vehicle	:	
Result	:	
Classification	:	
Method	:	other
Year	:	1973
GLP	:	no
Test substance	:	no data

Method : HEA was applied undiluted to the eye (NaCl as control substance); application method not stated; readings after 1, 24 hours and 8 days.

Result : HEA produced slight to moderate redness, moderate to severe edema and slight to moderate opacity of the eyes.

Reliability : (3) invalid
Documentation insufficient for assessment

29.03.2005 (75)

5.3 SENSITIZATION

Type	:	Mouse local lymphnode assay
Species	:	mouse
Concentration	:	1st: Challenge 10 % 2nd: Challenge 25 % 3rd: Challenge 50 %
Number of animals	:	12
Vehicle	:	other: acetone:olive oil, 4:1, v/v
Result	:	sensitizing
Classification	:	sensitizing
Method	:	other: according to Basketter et al. (1991), Toxicology Methods 1, 30-43
Year	:	1992
GLP	:	no data
Test substance	:	other TS

Method : The murine local lymph node assay was conducted as described by Basketter et al., 1991, Toxicology Methods 1, 30-43.

Male and female CBA/Ca mice 8-12 weeks old were used. HEA was assayed at three consecutive concentrations (10, 25 and 50%).

Groups of four mice were treated by a daily topical application of 25uL of each concentration on the dorsal surface of each ear for 3 consecutive days. Control animals were treated with the vehicle which was acetone-olive oil (4:1, v/v). Four to five days after the first topical application, all mice were injected i.v. through the tail vein with 250 uL phosphate buffered saline containing labelled methyl thymidine. After 5 hr the mice were killed by CO2 and the draining auricular lymph nodes were excised and pooled for each experimental group. Labelled methyl thymidine incorporation into lymph nodes was measured by beta-scintillation counting. A chemical was regarded as a sensitizer in the lymph node assay if at least one concentration of the chemical resulted in a three-fold or greater increase in H3TdR incorporation compared with control values. In addition, the data had to be compatible with a biological dose response although an allowance was made, especially at high doses, for either local toxicity or immunological suppression.

Radiolabeled thymidine[3H]methyl thymidine (sp. act. 2.0 Ci/mmol0 was purchased from Amersham International plc (Bucks, UK).

Result : Following adminstration of 10, 25 or 50% HEA to mice the ratios of test to control lymphocyte proliferation (T/C) were 9.0, 8.2 and no data, respectively. Therefore HEA was classified as positive in the local lymph

node assay.

Test substance : The test material was received from Fluka AG (Glossop, Derbyshire, UK). No specific value for purity; however, the authors state that the vast majority of the chemical tested were more than 98% pure.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

Flag : Critical study for SIDS endpoint

29.03.2005 (80)

Type : Mouse local lymphnode assay
Species : mouse
Number of animals :
Vehicle :
Result : sensitizing
Classification :
Method : other: according to Basketter et al. (1991)
Year : 1991
GLP : no data
Test substance : no data

Method : CBA/Ca mice were used. 2-HEA was assayed at four consecutive concentrations (5%, 10%, 25%, 50%). Groups of four mice were treated by a daily topical applicaton of 25 microL of each concentration on the dorsal surface of each ear for 3 consecutive days. Control animals were treated with acetone-olive oil (4:1, v/v) or propylene glycol. Five days after the first topical application, all mice were injected i.v. through the tail vein with 250 microL phosphate buffered saline containing labelled methyl thymidine. After 5 hr the mice were killed by CO2 and the draining auricular lymph nodes were excised and pooled for each experimental group. Labelled methyl thymidine incorporation into lymph nodes was measured by beta-scintillation counting.

Result : 2-HEA elicited positive local lymph node assay response in all laboratories. Inter-laboratory study of 4 laboratories

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

29.03.2005 (81)

Type : Guinea pig maximization test
Species : guinea pig
Number of animals :
Vehicle :
Result : sensitizing
Classification :
Method : other: according to Magnusson and Kligmann (1970)
Year : 1970
GLP : no
Test substance : other TS: purity >98%

Method : The guinea-pig maximization test was carried out similar to that described by Magnusson and Kligman (1970), Allergic Contact Dermatitis in the Guinea Pig, Edited by Charles C. Thomas. Springfield, IL. Albino Dunkin-Hartley guinea-pigs weighing approximately 350 g were used. The animals were treated by a series of six intradermal injections of 0.25% HEA in 0.9% NaCl (aided by acetone as needed) in the shoulder region to induce sensitization. After 6-8 days, sensitization was boosted by a 48-hr occluded patch containing 5% HEA in acetone:polyethylene glycol 400 (70:30, v/v) placed over the injection site. Twelve to fourteen days later, the animals were challenged with the maximum non-irritant concentration of 1.0% HEA in acetone:polyethylene glycol 400 (70:30, v/v) on one flank by a 24-hr occluded patch. Challenge sites were scored for erythema (scale 0-3) and

oedema 24 and 48 hr after removal of the patches.

Result : Positive response (% of animals) at 24 and/or 48 hr: 70%
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

29.03.2005 (82)

Type : Guinea pig maximization test
Species : guinea pig
Concentration : 1st: Induction .25 % intracutaneous
2nd: Induction 5 % open epicutaneous
3rd: Challenge 1 % occlusive epicutaneous
Number of animals :
Vehicle :
Result : sensitizing
Classification :
Method : other: according to Magnusson & Kligman (1970)
Year : 1970
GLP : no data
Test substance : no data

Method : Albino Dunkin-Hartley guinea-pigs were used (n=10/group). The animals were sensitized by a series of intradermal injections of a sligthly irritant concentration of HEA in combination with Freund's complete adjuvant in the shoulder region. After 6-8 days, sensitization was boosted by a 48-hr occluded patch placed over the injection site. Control guinea pigs (n=4) were treated similarly, but with vehicle alone. 12-14 days later, the animals were challenged on one clipped and razored flank by a 24-hr occluded patch at the maximum non-irritant concentration. The potential of HEA to cause skin sensitization was determined by visual assessment of erythema at the challenge sites, 24 and 48 h after removal of challenge patches. The sensitization potential was expressed as the percentage of test animals exhibiting a reaction significantly greater than in control animals.
Result : Positive response (% of animals) at 24 and/or 48 hr: 75%
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

29.03.2005 (78)

Type : Guinea pig maximization test
Species : guinea pig
Concentration : 1st: Induction 5 % intracutaneous
2nd: Induction 10 % occlusive epicutaneous
3rd: Challenge 5 % occlusive epicutaneous
Number of animals : 50
Vehicle : other: propylene glycol (intradermal) and 97% ethanol (topical)
Result : sensitizing
Classification : sensitizing
Method :
Year : 1982
GLP : yes
Test substance : other TS

Method : This study was performed using procedures based on the method of Magnusson, B. and Kligman, A.M. in "The Identification of Contact Allergens by Animal Assay, the guinea pig maximization test, Journal of Investigative Dermatology, 52:268-276 and in Allergic Contact Dermatitis in the Guinea Pig, Identification of Contact Allergens, Thomas, Springfield, Illinois, 1970.

Male (300-460 g) and female (300-428g) Hartley albino guinea pigs, were used. For the intradermal induction phase, a row of three injections were made on each side for a total of six injections. The injections consisted of two sites with 0.1 ml of Freund's Complete Adjuvant (FCA)/water emulsion, two sites with 0.1 ml of test or control material and two sites with 0.1 ml of test or control material in FCA emulsion. One week after the intradermal phase the topical application was performed. 2-HEA was applied to a 2X4 cm filter paper to saturation. The filter paper was then placed on the test site, secured with tape and covered with impermeable plastic which was secured with an elastic adhesive bandage. Vehicle without test material and the positive control material was applied in the same manner. The patches were left on for 48 hours, removed and the skin wiped free of excess material. Two weeks after the topical application, the challenge phase was administered. Patches were applied to the flanks as before except a 2X2 cm filter papaer was used and stayed on the animal for 24 hours. In order to differentiate irritation from sensitization, six animals (untreated) were subjected to the same challenge procedures as the animals which were dosed during the induction phase. Approximately 21 hours after removing the patch, the challenge area was gently clipped. Readings for erythema, edema and other evidence of dermal irritation were made on all animals 24 and 48 hours after removal of the patches.

Result : HEA exhibited an extreme potential to produce dermal sensitization in guinea pigs. All ten animals treated with 5% HEA exhibited dermal responses at challenge.

No significant dermal responses were seen in the six irritation control animals; therefore, confirming that the concentration of HEA used was non-irritating. Seven of ten animals treated with the positive control exhibited a clear dermal response at challenge to a non-irritating concentration. The ethanol vehicle control group exhibited no dermal responses at challenge.

Test substance : No purity data. Test material was received from Union Carbide Corporation.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

29.03.2005 (83)

Type : Buehler Test
Species : guinea pig
Concentration : 1st: Induction 10 % occlusive epicutaneous
2nd: Challenge 10 % occlusive epicutaneous
3rd:
Number of animals : 10
Vehicle : water
Result : sensitizing
Classification : sensitizing
Method :
Year : 1974
GLP : no
Test substance : no data

Method : Each animal was insulted with a single, closed patch containing the maximim non-irritating concentration of the test material for a total of nine times. A Webril pad containing 0.5 ml of 10% HEA in water was applied to the midline of the shaved animal. The Webril pad was occluded with an Elastoplast coverlet and the animal was placed in a restrainer for five hours. Two weeks after the last exposure, the test animals and four control animals were challenged with duplicate patches. The application sites were graded for irritation 24 and 48 hours after the initial insult and 24 and 48 hours after challenge. Any reaction among the test animals at challenge that was greater than that noted after the initial insult or greater than that noted among the control animals at challenge was considered evidence of

sensitization.

Result : The results of the skin sensitization test indicated that HEA was a sensitizer. Nine of ten animals treated with 10% HEA exhibited dermal responses at challenge.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

29.03.2005 (84)

Type : Buehler Test
Species : guinea pig
Concentration : 1st: Induction 50 %
2nd: Challenge 25 %
3rd:
Number of animals : 20
Vehicle : other: acetone
Result : sensitizing
Classification : sensitizing
Method :
Year : 1977
GLP : no
Test substance : other TS

Method : The guinea pigs were of the Hartley strain, purchased from Dutchland Laboratories and weighed between 350 and 500 grams. Treatment days for the induction phase were 1, 3, 8, 10, 14, and 16. On day 42, 0.5 ml of the challenge dose was applied to the shaven area of both treated and previously untreated animals for a six hour exposure. The application sites were occluded as during the induction phase. Test sites were scored according to the Draize system 24 and 48 hours post-exposure.

Result : HEA was considered a skin sensitizer. At 24 hours post-exposure, very slight to slight erythema was observed in all ten animals sensitized with HEA and slight erythema persisted in four of the animals through 48 hours. Very slight erythema was observed at 24 and 48 hours in five of the unsensitized animals treated with the challenge dose.

Test substance : No purity data. Test material was received from Rohm and Haas Company.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

29.03.2005 (85)

Type : Guinea pig maximization test
Species : guinea pig
Number of animals :
Vehicle :
Result : sensitizing
Classification :
Method :
Year : 1967
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Result : Guinea pig sensitization tests showed HEA to be a skin sensitizer. The sample of the inhibited HEA used failed to cause skin sensitization in the 10 animals on test. Uninhibited HEA (0.5% w/v) in Dowanol* DPM/Tween80 (9:1) induced sensitization in 10 out of 10 guinea pigs. (1)

A 2.0% solution of inhibited HEA in Dowanol* DPM/Tween80 (9:1), Dowanol* EEA glycol ether or as buffered aqueous solution (pH7.4) was tested. HEA in DPM/Tween and as aqueous solution caused a skin sensitization response in 4

out of 10 animals and in 1 out of 10 animals, respectively. HEA in EEA caused no skin sensitization in animals. (2)

A 0.5% solution of HEA (not known whether inhibited) in Dowanol* DPM/Tween80 also sensitized 10/10 animals. (3)

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

29.03.2005 (86)

Type : Guinea pig maximization test
Species : guinea pig
Number of animals : 10
Vehicle :
Result : sensitizing
Classification :
Method :
Year : 1967
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : A repeated insult patch test was conducted in 10 guinea-pigs; a 2% solution of HEA in Dowanol* DPM glycol ether and 10% Tween80 and a 20% solution of Derakane in Dowanol* DPM glycol ether and 10% Tween80 were applied to the shaved skin.

Result : No reaction after the first 2 applications. Slight to moderate redness and swelling in all guinea pigs during rest of insult. Slight redness in all pigs followed challenge. Six out of 10 guinea pigs reacted to Derakane 114 resin with slight redness following challenge.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

29.03.2005 (87)

Type : Guinea pig maximization test
Species : guinea pig
Number of animals : 12
Vehicle :
Result : sensitizing
Classification :
Method : other: according to Magnusson & Kligman (1970)
Year : 1970
GLP : no data
Test substance : no data

Method : Groups of 12 female SSc:AL guinea-pigs were tested. The temperature and humidity were kept at 20 + 20 deg C and 60 + 10% respectively. Induction on day 0 was conducted by injecting intradermally three pairs of solutions to the shaved skin (2 x 50 microL) of a suspension of FCA in sterile water (1:1); 2 x 50 microL of test substance in water; 2 x 50 microL of test substance emulsified in (1:1) FCA and water). The test substance concentration was 0.5%. On day 7, about 250 mg 10% SDS in petrolatum was applied, uncovered, for 24 hr. On day 8, 400 microL of 25% 2-HEA in petrolatum was applied, covered contact, for 48 hr. Control animals were treated in a similar manner with the test substance omitted. Challenge, on day 21, was conducted on naive skin. 25 microL of 0.3% HEA was applied using a FinnChamber for 24 hr, covered contact, and read at 48 and 72 hr.

Result : All 12 treated animals gave sensitization reactions on challenge, and none

of the controls. Cross-sensitization was seen to hydroxyethyl methacrylate, hydroxypropyl methacrylate and hydroxypropyl acrylate.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

29.03.2005 (88)

Type : other: Guinea Pig Sensitization Study
Species : guinea pig
Number of animals : 30
Vehicle : other: Dowanol PM/Tween 80 (9:1)
Result : sensitizing
Classification :
Method : other
Year : 1970
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : The sensitizing property of HEA was assessed on male and female guinea pigs using a 0.5% (w/v) of the material in a 9:1 mixture of Dowanol DPM:Tween 80. The solution was applied to a clipped and chemically depilated area on the shoulders of the animals twice a week for 3 weeks. Two weeks later the animals were challenged with the test solution by exposing the clipped skin on the flanks with the test solution and the solvent surfactant system. Negative control animals received Dowanol DPM:Tween 80 mixture twice a week for 3 weeks and were challenged after a 2 week rest period with the solvent surfactant mixture. Positive control animals received DER 331 in Dowanol DPM:Tween 80 and were likewise challenged after a 2 week rest period with DER-331 in the solvent surfactant solution, as well as with the solvent surfactant alone.

Result : HEA- 10 sensitized/10 treated
DER-331 (positive control)- 10 sensitized/10 treated
Dowanol DPM:Tween® 80(solvent control)-0 sensitized/10 treated

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

29.03.2005 (89)

Type : other: modified Maguire method
Species : guinea pig
Concentration : 1st: Induction .1 undiluted
2nd: Challenge no data
3rd:
Number of animals : 8
Vehicle : no data
Result : not sensitizing
Classification :
Method :
Year : 1981
GLP : no
Test substance : no data

Method : This article is a summary of the results of various chemical groups evaluated for their skin sensitization potential in the guinea pig. The studies were conducted over a period of years and the following method describes in general terms how they were conducted.

Most studies described in this paper were conducted on randomly bred Hartley strain male guinea pigs weighing approximately 300g.

A typical test procedure consisted of topical application of a 0.1 ml aliquot of the test material to the clipped and depilated backs of 10 guinea pigs (8

animals were used for HEA) per test material four times in 10 days. At the time of the third application, 0.2 ml of Freund's adjuvant (Bacto-Adjuvant Complete, DIFCO Laboratories, Detroit, MI) was injected intradermally at one point adjacent to the insult site. After a 2-week rest period, the guinea pigs were challenged on the flanks with the test material on one flank and a solvent (if used) on the other flank. The challenge site was evaluated for erythema and edema at 24 and 48 hours. A moderate erythema and/or edema in two or more guinea pigs was considered sufficient to classify the test material as a potential human skin sensitizer. Along with each test series, ten guinea pigs were routinely subjected to the same dosing regime with the diglycidyl ether of 2,2-di-(p,p'-hydroxyphenyl)propane (DER*331 epoxy resin), a known sensitizer to serve as a positive control.

Remark : The authors state that 0.1 ml of test material was used during the induction phase; however, they did not state how the challenge phase was conducted. The assumption is that it consisted of a topical administration of 0.1 ml of undiluted test material. In addition, since the test material was applied topically the assumption is that the dose sites were wrapped with an occlusive bandage.

Result : Not sensitizing, 0/8 (number sensitized/number tested)

Reliability : (3) invalid
Documentation not sufficient for assessment

29.03.2005 (90)

Type : other: Landsteiner guinea pig sensitization test
Species :
Number of animals :
Vehicle :
Result :
Classification :
Method : other: see reference
Year : 1974
GLP : no data
Test substance : no data

Remark : Camm albino, Hartley strain, female guinea pigs were used (20 animals/group); the scapular areas were clipped;

For intradermal and topical application, a 3% solution of HEA was made in propylene glycol. A volume of 0.05 ml was injected intradermally into the right scapular area as initial test dose. Matching propylene glycol solution was injected into the left scapular area (initial control dose).Two days later the scapular area was reclipped and 0.01 ml of 5% HEA solution in acetone was applied topically to the right scapular area (initial topical dose). The same quantity of acetone was applied to the left scapular area asthe solvent control. Reactions were read at 24 and 48 hours for all applications.

On alternate days 3 times a week, a total of 7 subsequent sensitizing doses of 0.1 ml of the propylene glycol solutions were injected intradermally into sacral skin area pretreated by topical application of 0.01 ml of a 5% HEA solution in acetone.

In addition, all 4 feet of the pigs were painted with the acetone solution 5 times, starting at the time of the first sensitizing dose. After 7 sensitizing doses the pigs were rested for 3 weeks before intradermal challenge doses were given.

Challenges: Intradermal challenge doses of 0.05 ml of the propylene glycol emulsions and the propylene glycol control were injected into the scapular area 21 days after the course of sensitizing doses, the backs of the guinea pigs having been clipped 24 hours prior to injection. Reactions of the intradermally injected sites were read at 24 and 48 hrs.

Five days after the intradermal challenge injection, a topical challenge dose of 0.01 ml of 5% HEA in acetone and the acetone control solution were than dropped onto the right lumbar and left lumbar areas respectively. The reactions were read at 24 and 48 hrs and scored. Twenty-four hours after the challenge dose, 16 out of 20 guinea pigs showed an intradermal sensitization response to HEA with a mean score of 82. A greater response was seen after 48 hours, with 19 animals reacting and a mean score of 159.

The topical challenge was given 5 days after the intradermal challenge and caused the intradermal sites to redden slightly. Seventeen of 20 animals reacted to the topical challenge in 24 hours with moderate erythema the maximum response. This reaction increased in 48 hours with 14 animals reacting, and marked capillary injection being the greatest reaction.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.

29.03.2005 (91)

Type : other: see methods
Species : guinea pig
Concentration : 1st: Induction .1 % intracutaneous
2nd: Induction 5 % open epicutaneous
3rd: Challenge .1 % intracutaneous
Number of animals : 20
Vehicle : other:propylene glycol in saline (intradermal) and acetone (topical)
Result : sensitizing
Classification : sensitizing
Method :
Year : 1974
GLP : no
Test substance : other TS

Method : Camm albino, Hartley strain, female guinea pigs were used. For the intradermal injections, an emulsion was made by preparing a 3% solution of HEA in propylene glycol which was then diluted to 0.1% with sterile saline. Vehicle controls matching concentrations of propylene glycol and saline were also prepared. For the topical solution, a 5% solution of HEA was prepared in acetone.

For the initial application, the scapular area test sites were clipped and 0.5 ml of the HEA emulsion was injected intradermally into the right scapular area. Matching vehicle control was injected into the left scapular erea. Reactions were read at 24 and 48 hours. Two days later the scapular area was reclipped, and 0.01 ml of the HEA acetone solution was applied topically to the right scapular area. The same quantity of acetone was applied to the left scapular area to serve as a vehicle control. The sites were also read at 24 and 48 hours.

For the sensitizing doses, 0.1 ml of the HEA emulsion was injected intradermally into the sacral skin area which was pretreated by topical applications of HEA in acetone, on alternate days 3 times a week. A total of 7 sensitizing doses were administered. In addition, all 4 feet of the guinea pigs were painted with the HEA acetone solution 5 times, starting at the time of the first sensitizing dose. After 7 sensitizing doses the pigs were rested for 3 weeks before intradermal challenge doses were given.

Intradermal challenge doses of 0.05 ml of the HEA emulsion and the matching control was injected into the scapular area 21 days after the course of sensitizing doses. Reactions of the injected sites were read at 24 and 48 hours. Five days after the intradermal challenge injection, a topical

challenge dose of 0.01 ml of 0.01 ml of the HEA acetone solution and the acetone vehicle control were administered to the appropriate lumbar areas. Reactions were read at 24 and 48 hours.

Result : Twenty-four hours after the challenge dose, 16 out of 20 guinea pigs showed an intradermal sensitization response to HEA. A greater response was seen after 48 hours, with 19 animals reacting.

The topical challege was given 5 days after the intradermal challenge and caused the intradermal sites to redden slightly. Seventeen out of 20 guinea pigs reacted to the topical challenge in 24 hours with moderate erythema the maximum response. This reaction lessened in 48 hours with 14 guinea pigs reacting, and marked capillary injection being the greatest reaction.

Test substance : No purity data. Test material was received from Union Carbide Corp (S. Charleston).

Reliability : (3) invalid
Unsuitable test system

29.03.2005 (92)

Type : Guinea pig maximization test
Species : guinea pig
Number of animals :
Vehicle :
Result : not sensitizing
Classification :
Method :
Year : 1983
GLP : no data
Test substance : other TS

Result : None of the 10 animals reacted to 2-HEA.

Test substance : The test material was manufactured by Pfaltz & Bauer Inc., USA. The purity was >95% as analyzed by high performance liquid chromatography.

Reliability : (3) invalid
This test used hydroxypropylmethacrylate for induction followed by challenge with HEA. Although negative results were found with HEA this test cannot be considered a valid study since HEA was not used for induction.

29.03.2005 (93)

5.4 REPEATED DOSE TOXICITY

Type : Sub-chronic
Species : rat
Sex : male/female
Strain : Long-Evans
Route of admin. : i.p.
Exposure period : 13 weeks
Frequency of treatm. : 5 days/week for 13 weeks
Post exposure period : none
Doses : control (0), 3, 20 and 60 mg/kg/day
Control group : yes, concurrent vehicle
NOAEL : = 60 mg/kg bw
Method : other: consistent with OPPTS 870.6200 or OECD 424 with the exception of no motor activity and ip administration
Year : 1991
GLP : no data
Test substance : other TS

Method : METHOD FOLLOWED:The FOB protocol was originally described in Moser et al., 1988, Fundam. Appl.Toxicol. 11, 189-206 and modifications have been reported in Moser (1991), Fundam. Appl. Toxicol. 17, 7-16.

STATISTICAL METHODS: Statistical analysis of the FOB data was conducted as described in Moser et al., 1988, Fundam. Appl. Toxicol. 11, 189-206 and Creason (1989), J. Am. Coll. Toxicol. 8:157-169. FOB results for groups were compared to one of the control saline groups which were arbitrarily selected. Continuous data was analyzed by a general linear model (GLM; SAS Institute, 1985) using each rat's time-zero value as a covariate, a grouping factor of dose, and repeated measures across time. A categorical data modeling procedure (CATMOD;SAS Institute, 1985) with repeated measures across time was used for the descriptive (categorical) and rank data. Univariate analyses were carried out at each time point only when the overall dose effect or dose X time interaction was significant. For all results, $p<0.05$ was considered significant. In addition, the final evaluation of each measure took into account the presence or absence of a dose-response relationship or a time course of effect, severity of the effect, as well as statistical significance. A statistical comparison of the two saline groups was carried out to ensure that there were no differences between them. Severity scores as described by Moser (1992), J. Am. Coll. Toxicol. 10 (6): 661-669, were calculated for each rat's data from the tests that constitute each functional domain, and were then averaged across rats in each treatment group.

Statistical analysis of the pathological data were performed using Bonferroni's procedure for multiple comparisons with a single control group.

Remark : The results from this study are consistent with previous studies which reported weight loss but no overt neurological signs (Kociba et al., 1979; Leong and Trice, 1970; McCollister et al., 1967a,b)

Result : NOAEL (neurotoxicity): 60 mg/kg

LOAEL (body weight and clinical observations): 60 mg/kg

TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:

Mortality and time to death: There were two deaths during the 13-week study. One male in the 60 mg/kg/day dose group died on day 31 and one female in a saline control group died between days 45 and 47. General necropsy did not reveal the cause of death. Health surveillance, general necropsy, parasitology and serum viral panels conducted on an extra rat in the same room was all negative.

Body weights: Decreased body weight gain in only male rats, with body weights significantly different from control at the high dose from 30 days on.

Functional observational battery (FOB):There were no real differences between the saline control groups. Overall, many of the effects of HEA were transient, of small magnitude, and in many cases not dose dependent. There was no clear dose response of gait changes that were observed throughout the study in males at all dose levels and in all females on study days 30 and 60, and on day 90 for only the 60 mg/kg/day dose group. Ataxia was observed, often with the hind feet protruding outward, along with hunched posture and tiptoe gait. There was a significant impairment of righting reflex in all HEA-treated males at 90 days; however, there was no dose-response relationship and the effect was slight. The high dose of HEA decreased hindlimb grip strength in males only at 30 days. Several of the FOB measures indicated a decrease in general activity: rearing was decreased in females given 60 mg/kg/day on days 60 and 90, decreased arousal in males given 60 mg/kg/day on day 60 and in females at the 20 and 60 mg/kg/day doses at 90 days. In summary, HEA affected gait, hindlimb grip strength, and righting reflex, and most of these effects were seen only in males. Furthermore, the changes were not consistent in terms of their dose-response and time-course characteristics.

-Unrelated measures: Some unrelated measures were also affected during the study such as: both sexes showed a transient increase in urination, a few instances of ptosis in males at days 30 and 60, a non-dose related decrease in the touch response of males and mild hypthermia in male rats given 60 mg/kg/day on day 90.

Additional observations: Rats dosed with HEA were observed with bloating of the abdominal area. It was first noticed after several weeks of dosing and progress such that at 90 days, 90% of males and 70% of females were affected. In some cases, bloating was accompanied by adominal tenderness and reddish-orange urine stains. Gross and hisopathologic examinations of the peritoneum and peritoneal sufaces of perfused rats revealed no abnormalities related to treatment.

Severity-score: Results of the severity-score analysis indicated that HEA produced transient effects at day 60 in the autonomic domain in female rats only.

Acrylamide was also used in this study as a positive control agent, and time-course and dose-related changes in gait, splay and neuropathology were demonstrated and were consistent with the literature.

Histologic examination: Liver, kidneys, bladder, diaphragm, and brain revealed no abnormalities. HEA did not produce any detectable axonal degeneration in the peripheral nervous system at any dose. In addition, rats treated with HEA showed no detectable axonal degeneration in the rootlets or within the white matter of the spinal cord.

Test condition : TEST ORGANISMS
-Age: 50 day old
-Weight at study initiation: males (mean ~275 grams) and females (mean ~175 grams)
-Number of animals: 10/sex/dose level
ADMINISTRATION/EXPOSURE
-Duration of test/exposure: 5 days/week for 13 weeks
-Type of exposure: intraperitoneal (ip)
-Vehicle: isotonic saline
-Concentration in vehicle: no data (Concentrated stock solutions were made weekly, and dilutions were made daily to produce the desired dosing concentrations.)
-Total volume applied: 1 ml/kg body weight
-Doses: saline control, 3, 20 and 60 mg/kg/day
-Stability: A sample containing 30 mg HEA/ml of saline was analyzed weekly for 8 weeks. Results showed only a 2.7% deviation from the nominal value; therefore, HEA was stable and did not polymerize under the conditions of use.
SATELLITE GROUPS AND REASONS THEY WERE ADDED: none
CLINICAL OBSERVATIONS AND FREQUENCY:
-body weights were conducted on study day 0, 30, 60 and 90
-functional observational battery (FOB): before dosing (baseline), and on test day 30 +/- 1, 60 +/- 2 days, immediately before that days dose and on the day after the last dose.
-FOB description: The FOB consisted of home-cage and open-field observations, descriptions of posture, gait and any convulsions or tremors were listed, and rank scores were assigned to removal and handling, alertness, and changes in gait or mobility. Observations of lacrimation, salivation, palpebral closure and piloerection was also scored. Urinations and defecations were counted, as were the supported and unsupported rears (i.e., using the side of the cart as a support, or not). Righting reflex, pupil constriction in response to light, and the reactions to various stimuli were evaluated. Forelimb and hindlimb grip strength was assessed using strain gauges and muscle tone was measured using the landing foot splay. Body weight and core temperature were also obtained on each rat. The

observer was blind to the treatment status of the animal.

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
-Macroscopic: none
-Microscopic: Sections of the liver, kidneys, diaphragm, and urinary bladder.
Neuropathologic evaluations from 6/sex/dose group of HEA and 3/sex/each saline control group were conducted. Cross sections at specific levels of the central neuraxis were taken. Six cross sections of the telencephalon at the prechiasmic level including the anterior commissure, the diencephalon at the infundibular level including the nucleus basalis, the mesencephalon at the level of the medialgeniculate including the substantia niagra, the metencephalon at the level of the superior olivary nucleus including the cerebellum, the medulla oblongata below the pyrimidal decussation, and the upper cervical spinal cord. In addition, the Gasserian ganglia and a lumbar dorsal root ganglion was examined. To evaluate the peripheral nervous system the following seven areas were sampled and examined histologically: 1) ventral roots, 2) dorsal roots, 3)sciatic nerve at the level of the sciatic notch, 4) sciatic nerve at the level of the midfemur, 5) tibial nerve, 6) sural nerve and 7) dorsal root ganglion. Epon sections of the cervical spinal cord were also prepared but were limited to control and high dose animals.

Test substance : 2-HEA purity was 97% (Aldrich Co., Milwaukee, WI.)

Conclusion : Although intraperitoneal administration of HEA affects weight gain and some behavioral measures, no neuropathological changes were detected after HEA exposure. The results from this study are consistent with previous studies which reported weight loss but no overt neurological signs (Kociba et al., 1979; Leong and Trice, 1970; McCollister et al., 1967a,b; R & D reports of The Dow Chemical Company).

Reliability : (1) valid without restriction
Meets generally accepted scientific standards and is described in sufficient detail.

Flag : Critical study for SIDS endpoint

26.03.2005 (94)

Type :
Species : rat
Sex : male
Strain : Sherman
Route of admin. : inhalation
Exposure period : 28 days (up to 21 exposures)
Frequency of treatm. : 7 hours/day and 5 days/week
Post exposure period : up to 14 days
Doses : Control, 5, 10 or 25 ppm
Control group : yes, concurrent no treatment
LOAEL : = 5 ppm
Method : other: dynamic exposure
Year : 1970
GLP : no
Test substance : no data

Method : METHOD FOLLOWED: dynamic airflow exposure.
STATISTICAL METHODS: Means and standard deviations and t-test for significance (Steel, R.G.D. and Torrie, J.H. (1960). Principles and Procedures of Statistics. McGraw-Hill, New York, New York.

Result : LOAEL: 5 ppm
TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
-Mortality and time to death: One animal in the 10 ppm group died after 15 exposures. In the 25 ppm group, a total of 8 animals died during the 10 exposure days and following the termination of exposures after exposure

day 10, an additional 9 animals died. Only 3 animals survived and recovered from the exposures.
-Clinical signs: The 5 ppm group showed no adverse effects. Animals in the 10 ppm group exhibited mild nasal irritation and discharge and after seven exposures, some animals acquired lung rattles. The animals in the 25 ppm group were observed with eye and nasal irritation followed by dypsnea and a bloated stomach which were indicative of an upper respiratory tract irritant. These conditions became more severe as the exposures continued.
-Organ to body weight ratios: Organ to body weight ratios of liver and kidneys were significantly higher for rats exposed to 10 ppm HEA. Similar elevation of liver to body weight ratio was also seen at 5 ppm. In contrast, heart to body weight ratios for the animals in the 5 ppm group were significantly lower.No changes occurred in the relative testes weight of HEA treated rats when compared to controls.
-Body weights: The 5 ppm group showed no adverse effects. At 10 ppm, mean body weights decreased during the five exposure days of the week but showed a rapid recovery or a gain during the two no-exposure days of the weekend. At termination, mean body weight of rats exposed to 10 ppm for 20 days was significantly lower than controls. For the 25 ppm group, body weights rapidly decreased during the exposure peroid but after the exposures were discontinued on study day 12 the surviving animals quickly gained body weight over the recovery period. No changes occurred in the relative testes weight of HEA treated rats when compared to the controls.

-Terminal organ and body weights (10 exposure group)

Nominal Concentration (ppm)	0	5	10
Body Wt. (g, Mean±SD)	365±29	354±18	316±48

Relative Organ Wt.
(g/100 g BW, Mean±SD)

Nominal Concentration (ppm)	0	5	10
Heart	0.38±0.08	0.34±0.02	0.36±0.03
Liver	2.81±0.27	2.86±0.16	2.87±0.38
Kidney	0.57±0.05	0.57±0.18	0.64±0.07
Spleen	0.18±0.03	0.17±0.02	0.18±0.02
Testes	0.89±0.06	0.95±0.08	0.96±0.35

-Terminal organ and body weights (20 exposure group)

Nominal Concentration (ppm)	0	5	10
Body Wt. (g, Mean±SD)	377±32	362±27	325±46
(t value)		2.851	

Relative Organ Wt. (g/100 g BW, Mean±SD)

Nominal Concentration (ppm)	0	5	10
Heart	0.35±0.02	0.33±0.03	0.37±0.08
(t value)		2.245	
Liver	2.56±0.16	2.84±0.09	2.85±0.30
(t value)		4.579	2.678
Kidney	0.58±0.03	0.61±0.05	0.65±0.03
(t value)		4.813	
Spleen	0.18±0.03	0.15±0.02	0.17±0.02
Testes	0.94±0.14	0.94±0.09	1.00±0.11

t-values are shown for comparisons that were significant.
t-test for significance: 95% level t=2.110 d.f.=17
99% level t=2.898 d.f.=17

-In-life Body Weights (g, Mean)

	Nominal Concentration (ppm)			
	0	5	10	25
Study days				
1	269	313	278	280
3	273	308	279	265
4			279	
5	275	310		240
7			286	
8		315		225
9	290		283	
10		317		201
11			284	
12	302	318		190a
14	303		294	201
15		320		
16	305		292	227
17		321		
18	310		284	235
19		322		
21			303	
22		330		
23	325		302	258
24		335	300	
25	327			269
26		336		
28	338		313	
29	348	347		

a- exposure terminated because of high mortality

-Pathology findings: HEA produced ulcerative keratitis and chronic-active tracheitis at 5, 10 and 25 ppm. Focal ulcerative rhinitis and chronic-active laryngitis resulted from HEA exposure at 10 and 25 ppm. Lesions at the 25 ppm level were more severe than those at 10 and 5 ppm. Bronchopneumonia and severe upper respiratory lesions were responsible for the spontaneous deaths at the 25 ppm exposure. The 14-day recovery period did not significantly reduce the number of lesions observed, except for the absence of ulcerative rhinitis.

-Gross Lesions at necropsy:

				Gross Lesions			
Conc. ppm	No. of Exposures	Days Post-Exp.	No. of rats	Focal Pneumonia	Corneal Lesions	Rhinitis	Cachexia
0	5	0	5	1	0	0	0
25	5	0	5	2	4	3	0
0	10	14	5	0	0	0	0
25	10	14	3	2	0	0	0

-Gross Lesions in Animals with Spontaneous Deaths

				Gross Lesions			
Conc. ppm	No. of Exposures	Days Post-Exp.	No. of rats	Focal Pneumonia	Corneal Lesions	Rhinitis	Cachexia
25	5-10	1-3	16	2	9	14	5
10	8	1	5	2	0	0	0
5	9	1	5	0	0	0	0
0	21	1	5	0	0	0	0
10	20	2	10	2	0	0	1
5	21	1	10	4	0	0	0
0	21	14	10	2	0	0	0
10	20	14	9a	5	0	0	0
5	21	14	9b	4	0	0	0

a- One rat died after the 14 exposure due to diffuse pneumonia.
b- One rat was euthanized after the 15th exposure due to otitis media.

-Microscopic Lesions

				Microscopic Lesions			
Conc. ppm	No. of Exp.	Days Post-Exp.	No. rats	Chronic Murine Pneumonia	Focal/acute Broncho-Pneumonia	Focal Acute Bronchitis	Chronic Tracheitis
0	5	0	5	4	0	0	5
25	5	0	5	2	1	0	2
0	10	14	5	5	0	2	5
25	10	14	3	3	1	1	2
Spontaneous Deaths							
25	5-10	1-3	9	1	5	3	2
10	8	1	5	5	0	1	3
5	9	1	5	5	0	1	4
0	21	1	5	5	0	2	2
10	20	2	10	10	1	5	5
5	21	1	10	10	1	8	6
0	21	14	10	10	2	8	9
10	20	14	9	9a	2	5	6
5	21	14	9	9b	0	4	4

Microscopic Lesions (Cont'd)

				Microscopic Lesions			
Conc. ppm	No. of Exp.	Days Post-Exp.	No. rats	Chronic Active Tracheitis	Chronic Laryngitis	Chronic Active Laryngitis	Focal Ulcerative Rhinitis
0	5	0	5	0	3	0	0
25	5	0	5	3	3	2	4
0	10	14	5	0	0	0	0
25	10	14	3	0	1	1	0
Spontaneous Deaths							
25	5-10	1-3	9	3	0	4	3
10	8	1	5	2	3	2	1
5	9	1	5	1	1	0	0
0	21	1	5	0	3	1	0
10	20	2	10	1	5	2	3
5	21	1	10	2	7	0	0
0	21	14	10	0	4	2	0
10	20	14	9	1	5	2	0
5	21	14	9	3	5	0	0

Microscopic Lesions (Cont'd)

Conc. ppm	No. of Exp.	Days Post-Exp.	No. rats	Microscopic Lesions Keratitis	Focal Myocarditis	Testicular Atrophy
0	5	0	5	0	0	0
25	5	0	5	3	1	0
0	10	14	5	0	1	0
25	10	14	3	3	0	0
Spontaneous Deaths						
25	5-10	1-3	9	8	0	0
10	8	1	5	1	0	0
5	9	1	5	1	1	0
0	21	1	5	1	1	0
10	20	2	10	4	1	1
5	21	1	10	2	1	0
0	21	14	10	0	0	0
10	20	14	9	1	0	0
5	21	14	9	0	1	0

Testicular atrophy was observed histopathologically in one of 9 rats exposed to 10 ppm HEA for 20 exposures. This was judged to be spontaneous and not related to HEA exposure and consistent with an absence of testicular effects in a chronic toxicity/carcinogenicity study conducted by the inhalation route (Rampy L.W. et al. (1978) Toxicol. Appl. Phatmacol., 45:310).

Test condition : TEST ORGANISMS
-Age: no data
-Weight at study initiation: mean values ranged from 268-314 grams
-Number of animals: 15-20 animals/group (5-10 animals/group for 10 day interim sacrifice)
ADMINISTRATION/EXPOSURE
-route: inhalation
SATELITE GROUPS AND REASONS THEY WERE ADDED: An interim sacrifice group of 5- 10 animals were exposed at the same concentrations for 7 hours/day for 10 days.
CLINICAL OBSERVATIONS AND FREQUENCY: During exposures animals were observed closely for signs of irritation and toxicity.
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
-Macroscopic: organ weight: lung, liver, spleen, kidney and testes
-Microscopic: yes
EXPOSURE CONCENTRATIONS: 4.5 +/- 1.1, 10.6 +/- 1.4 and 22.5 +/- 3.9
METHOD OF CHAMBER CONCENTRATIONS: Gas-liquid chromatography

Conclusion : The LOAEL was 5 ppm. In the 5 ppm group, only irritation of the corneas was observed. Ulcerative corneal changes, nasal irritation and decreased body weight were found in the 10 ppm group; however, the animals were able to recover weight during the un-exposed weekend. Exposures of animals to 25 ppm resulted in considerable nasal irritation and severe respiratory distress within two days. Thereafter, the animals exhibited drastic loss of body weight and died of respiratory failure. These data indicate that the respiratory system and the eyes are the only systems likely to be affected by vapor exposure. Based on these results it is suggested that when worker's exposures are prolonged and repeated, the workroom concentrations be kept below 5 ppm and that the time weighed average of all exposures not exceed 1 ppm.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment; no data on test material purity or analysis were available.

Flag : Critical study for SIDS endpoint
30.03.2005 (95)

Type : Sub-chronic
Species : dog
Sex : male/female
Strain : Beagle
Route of admin. : oral feed
Exposure period : 97 days
Frequency of treatm. : daily diet
Post exposure period : no
Doses : 0.06, 0.2, or 0.4% HEA in diet
Control group : yes
NOAEL : = .4 %
Method : other
Year : 1967
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Two dogs per sex per level were maintained for 97 days on diets containing 0.06, 0.2, or 0.4% HEA (equivalent to doses of 21, 60 and 125 and 22, 63 and 131 mg/kg body weight/day for males and females respectively). The dogs were six to seven months old at the start of the study. Body weight, hematological parameters, clinical chemistry were determined pre-dosing and at termination. Lungs, heart, liver, kidneys, spleen, brain and testes were removed and weighed at termination. Histopathological examination of the above tissues as well as the lymph node, esophagus, aorta, pancreas, uterus, ovary, urinary bladder, gall bladder, stomach skeletal muscle, large intestine, small intestine, spinal cord, pituitary gland, adrenal gland, thyroid, parathyroid and portions of peripheral nerves was carried out.
Result : No adverse effects were found in male and female dogs (two of each sex per level). There were no treatment-related changes in organ weights, histopathology or other parameters.
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.
29.03.2005 (96)

Type : Sub-chronic
Species : rat
Sex : male/female
Strain : no data
Route of admin. : oral feed
Exposure period : 100 days
Frequency of treatm. : daily feed
Post exposure period : no
Doses : 0.03, 0.1, or 0.3% in the diet
Control group : yes
NOAEL : = .3 %
LOAEL : =
Method : other
Year : 1967
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Result : Body weight loss (about 5% decrease at the top dose for females only) and some minor changes in organ weights were detected, these were judged not to be related to treatment. In addition there were no treatment-related changes in histopathology for any organ or tissue.
Test condition : Male and female rats (10 of each sex per group) were dosed by HEA mixed in the daily diet.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment.
26.03.2005 (97)

Type : Sub-chronic
Species : rat
Sex : male/female
Strain : Fischer 344
Route of admin. : i.p.
Exposure period : 90 days
Frequency of treatm. : once daily, six days per week
Post exposure period : no
Doses : 2.5, or 50 mg/kg
Control group : no
Method : other
Year : 1980
GLP : no data
Test substance : no data

Result : Groups of 5 rats/sex/dose were exposed. Low-dosed rats displayed dark-stained discharges around the eyes and nose, and occasional lacrimation and body tremors. High-dosed rats showed salivation for hours after dosing (after week 2),lacrimation (after week 6), urine stains, piloerection, and a slight incidence of sporadic "hunched" back and tiptoe walking. High-dosed males also showed a transient decrease in body weight gain (week 1-3) and decreased food consumption. Males and females of both dose groups were reported to show sciatic nerve damage including "axonal swelling, ovoids, tomaculum formation, and degeneration and corrugation of myelin". In the high-dosed group, all rats were reported to have pronounced damage in peripheral nerves.
Reliability : (3) invalid
Significant methodological deficiencies (no control). Results are superceded by later well conducted studies (Moser et al., 1992).
29.03.2005 (98)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Bacterial gene mutation assay
System of testing : bacterial
Test concentration : 0, 38, 75, 78, 150, 156, 300, 313, 600, 625, 1000, 1250, 2000, 2500, 3000, 4000 and 5000 ug/plate
Cycotoxic concentr. :
Metabolic activation : with and without
Result : positive
Method : other: plate incorporation method
Year : 1996
GLP : no data
Test substance : other TS

Method : Chemically-induced mutagenicity was performed using the four bacterial strains Salmonella typhimurium TA102 and TA2638 and Escherichia coli WP2/pKM101 and WP2 uvrA/pKM101.

Compounds were tested for mutagenicity using the plate incorporation method with or without metabolic activation, essentially as described by Maron and Ames [Maron, D.M. and B. M. Ames (1983). Revised methods for the Salmonella mutagenicity test, Mutation Res., 113, 173-215]. Each bacterial strain was inoculated from the original stock cultures into nutrient broth, especially supplemented with 2 ug/ml tetracycline for TA 102, and

cultured under conditions for growth culture. Within 2 hours of the end of the growth culture period, cultures were used for the mutagenicity assay as follows: 0.1 ml of a culture, 0.1 ml of a solution of test chemical, 0.5 ml of S9 mix and 2 ml of the amino-acid-supplemented molten soft agar were mixed uniformly and overlaid on a minimal glucose agar plate. A S9 mix was used for metabolic activation which contained 10% of S9 fraction which was prepared from livers of Sprague-Dawley rats induced by phenobarbital and 5,6-benzoflavone. The plates were incubated at 37C for 48 hours and colonies counted. Chemical were tested in at least two independent experiments using five dose levels and three plates per dose, and tests were performed in two laboratories per chemical to assess reproducability. A dose of 5000ug/plate was used as the highest dose if no toxicity was observed. Positive controls were included in each experiment.

Result : In two laboratories, 2-HEA was negative in the Salmonella typhimurium strains TA102 and TA2638 and positive in the Escherichia coli strain WP2/pKM101.

Number of revertants/plate

Dose	TA102		TA2638		WP2/pKM101		WP2 uvrA/pKM101	
ug/plate	Lab 1	Lab 2	Lab 1	Lab 2	Lab 1	Lab 2	Lab 1	Lab 2
0	481	407	61	47	92	78	119	103
38	-	400	-	-	-	-	-	-
75	-	425	-	-	-	-	-	-
78	491	-	-	-	-	-	-	-
150	-	404	-	-	-	-	-	-
156	486	-	-	-	103	-	-	-
300	-	391	-	-	-	-	-	-
313	454	-	63	47	92	-	129	-
600	310a	-	-	-	-	-	-	-
625	481	-	56	40	129	-	137	-
1000	-	-	-	-	-	78	-	85
1250	385a	-	56	38	246	-	191	-
2000	-	-	-	-	-	121	-	95
2500	-	-	53	43	247	-	388	-
3000	-	-	-	-	-	146	-	155
4000	-	-	-	-	-	151	-	194
5000	-	-	33a	36a	-	107	358	182

a- toxic not tested
All values are the average of three plates of the one experiment for each laboratory.

Test substance : No data on purity; however, the authors state that the chemicals used for testing were of the highest purity available. The test material was received from Wako Pure Chemical Industries, Ltd., Osaka, Japan.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards and is described in sufficient detail.

Flag : Critical study for SIDS endpoint

29.03.2005 (99)

Type : Ames test
System of testing : Salmonella typhimurium strains TA100
Test concentration : 10, 50, 75, 100, 250, 500, 750, 1000, 2500, 7500 nl/plate
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : other: only one strain was used
Year : 1982
GLP : no data
Test substance : other TS

Result	:	Inhibition of growth was seen at concentrations of 1000 nanoliters/plate and above with activation and 250 nanoliters/plate and above without activation. Rocryl 420 (HEA) did not demostrate mutagenic activity on strain TA100.
Test substance	:	Rocryl 420 (HEA) was 96.5% a.i. as tested by Rohm and Haas.
Reliability	:	(2) valid with restrictions Only one strain was used and authors state that additional strains would be necessary before this compound could be considered a non-mutagen.

30.12.2004 (100)

Type	:	Cytogenetic assay
System of testing	:	TK+/- 3.7.2C heterozygote of L5178Y mouse lymphoma cells
Test concentration	:	0, 15, 18, or 20 microG/ml
Cycotoxic concentr.	:	
Metabolic activation	:	without
Result	:	positive
Method	:	other: Turner N.T. et al. (1984)
Year	:	
GLP	:	no data
Test substance	:	no data
Remark	:	L5178Y/TK+/- 3.7.2C cells were treated for 4 hours with 2-HEA (0, 15, 18 or 20 microG/ml) in DMSO according to Turner et al. (1984). No more than 100 microL DMSO was addedto 10 ml culture and this concentration does not effect the cytotoxicity or mutagenicity of the culture. Cells were then centrifuged and washed and 10 microL M bromodeoxyuridine added. Cultures for micronucleus analysis were treated with 3 microg/ml cytochalasin B and harvested 12-13 hr later. Cultures for aberration analysis were incubated for 14-15 hr; 0.1 microL/ml colcemid being added for the last 2 hr. For a positive result, the response must be double that of the negative control for the experiment as well as that of the historic means for negative controls (quoted as being 4.45 + 2.11 aberations/100 cells or 9.90 + 2.47 micronuclei/1000 cells). A dose-related decrease in survival (calculated according to Clive & Spector, 1975) was seen up to a level of 15% at 20 microg/ml. This was considered adequate for examining the cytogenetic effects. The background number of total aberrations was 2/100 cells and that in the treated cultures was 99/100 cells. In the micronucleus test, a background of 13/1000 cells compared to 47/1000 in the treated culture was seen. The total mutant frequencies in the control and treated groups were 85 x 10E6 and 560 x 10E6 respectively.
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards and is described in sufficient detail.

29.03.2005 (101)

Type	:	Mouse lymphoma assay
System of testing	:	TK+/- 3.7.2C heterozygote of L5178Y mouse lymphoma cells
Test concentration	:	0, 6, 10-20 microG/ml
Cycotoxic concentr.	:	
Metabolic activation	:	without
Result	:	positive
Method	:	other: Turner N.T. et al. (1984)
Year	:	1984
GLP	:	no data
Test substance	:	no data
Result	:	A dose-related decrease in survival was seen to a level of 6% at 20 microG/ml. The background mutant frequency was 89-102 x 10E-6 survivors/100 cells. In the test system, a concentration of 18 microG/ml was considered to produce an

adequate survival rate (13%) for mutant frequency to be determined. The mutant frequency was 707 x 10E-6 survivors/100 cells, showing 2-HEA to be a mutagen. The ratio of small colonies/large colonies at this dose was 607/100 in comparison to the background ratio of 67/22; the large excess of small colonies indicating a possible cytogenic effect.
L5178Y/TK+/- 3.7.2C cells were treated for 4 hours with 2-HEA (0, 6, 10-20 microG/ml) in DMSO according to Turner etal. (1984). No more than 100 microL DMSO was added to 10 ml culture and this concentration does not effect the cytotoxicity or mutagenicity of the culture. Cells were then centrifuged, washed, resuspended in fresh medium and maintained at 37 deg.C in log-phase growth for 2 days. They were then cloned with 1 microG/ml trifluorothymidine for 9-11 days at 37 deg.C, the colonies counted and the mutant frequency calculated. A positive response was defined as onein which the quantitated mutant frequency is >2x the background mutant frequency. The response must be consistentand observed at concentrations giving > 10% cell survival.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards and is described in sufficient detail.

29.03.2005 (101)

Type : Gene mutation in Saccharomyces cerevisiae
System of testing : Saccharomyces cerevisiae D3
Test concentration : no data specified
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : other
Year : 1976
GLP : no
Test substance : no data

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards and is described in sufficient detail.

29.03.2005 (102)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Micronucleus assay
Species : mouse
Sex : male/female
Strain : NMRI
Route of admin. : gavage
Exposure period : Single administration
Doses : 0, 100, 300, 600 mg/kg bw
Result : negative
Method : OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year : 2000
GLP : yes
Test substance : other TS

Method : Groups of 10 mice (5 of each sex) were administered a single p.o. dose of the test substance orally at concentrations of 100, 300 and 600 mg/kg body weight. The test substance was prepared in carboxymethylcellulose. The volume administered was 33.3 ml/kg body weight. Two additional groups of

mice (5/sex/group) were used as the negative control and positive control. The negative control group received carboxymethylcellulose by gavage. The positive control group animals received a single i.p. injection of 10 ml/kg cyclophosphamide in 0.9% NaCl at 30 mg/kg b.w. Five males and five females from each group were sacrificed 24 hours after dosing. Forty eight hours after dosing five animals per sex from the 600 mg/kg dose level were killed. One bone marrow smear was prepared per animal from the tissue cleared from each femur. Stained smears were examined by light microscopy for incidence of micronucleated cells per 2000 polychromatic erythrocytes per animal. To describe a cytotoxic effect, the ratio of polychromatic to normochromatic erythrocytes was assessed by the examination of at least 1000 erythrocytes.

Evaluation of Results: Cells were evaluated for large (aneugenic effects) and small (clastogenic effects) micronuclei. The test substance was classified as mutagenic if it induced either a statistically significant, dose-related increase in the number of micronucleated polychromatic erythrocytes or a reproducible, statistically significant positive response for at least one of the test points.

Remark : These data on 2 Hydroxypropyl acrylate as an analog of 2 hydroxyl ethyl acrylate. It is expected that a similar result as observed in this study would result if 2 hydroxyethyl acrylate were tested in this assay.

An initial experiment to determine the toxicity of the test substance was conducted. Three male and three female mice were administered the test substance orally at 1000 mg/kg b.w. This dose resulted in only slight toxicity and was therefore chosen as the top dose. In the main experiment, two animals died within the first 6 hours of dosing at 1000 mg/kg b.w. so a dose of 600 mg/kg b.w. was chosen as the highest dose that could be used for analysis of micronuclei. All 10 mice at 1000 mg/kg b.w. died within 24 hours of dosing.

Result : The ratio of normochromatic to polychromatic erythrocytes was slightly affected by the treatment with 2-hydroxypropylacrylate at a dose of 600 mg/kg b.w (at 24 and 48 hours in male mice and at 48 hours in female mice). At this dose level, only slight toxic effects, as evidenced by reduced spontaneous reactivity, were obtained up to 6 hours after dosing. There was no increase in the frequency of micronuclei at any dose level at either 24- or 48-hours after dosing compared to the negative control group. Data are shown below:

Males

24 hours	Mean Micronuclei/2000 PCE		Mean PCE/NCE
	All (%)	Small (%)	
Negative control	3.2 (0.16)	2.8 (0.14)	1000/873.6
600 mg/kg	4.4 (0.22)	3.8 (0.19)	1000/1056.8
300 mg/kg	5.4 (0.27)	5.4 (0.27)	1000/1177.6
100 mg/kg	4.8 (0.24)	3.8 (0.19)	1000/974.6
Positive control	20.2 (1.01)	18.8 (0.94)	1000/739.6

Females

24 hours	Mean Micronuclei/2000 PCE		Mean PCE/NCE
	All (%)	Small (%)	
Negative control	3.2 (0.16)	2.8 (0.14)	1000/737.4
600 mg/kg	2.8 (0.14)	2.0 (0.10)	1000/854.6
300 mg/kg	5.2 (0.26)	4.8 (0.24)	1000/773.8
100 mg/kg	3.2 (0.16)	2.8 (0.14)	1000/918.8
Positive control	19.6 (0.98)	18.4 (0.92)	1000/688.6

	48 hours	Sex	Mean Micronuclei/2000 PCE All (%)	Small (%)	Mean PCE/NCE
	600 mg/kg	Male	2.2 (0.11)	2.0 (0.10)	1000/986.2
	600 mg/kg	Female	2.2 (0.11)	1.8 (0.09)	1000/1065.4

Test substance : other TS: 2-Hydroxypropylacrylate (purity = 97.68%)
Conclusion : It was concluded that 2-Hydroxypropyl acrylate is considered to be non-mutagenic in this micronucleus test
Reliability : (1) valid without restriction
GLP guideline study
Flag : Critical study for SIDS endpoint
29.03.2005 (103)

Type : Cytogenetic assay
Species : rat
Sex : male/female
Strain : no data
Route of admin. : inhalation
Exposure period : 18 months
Doses : 0.5, or 5 ppm (2.37 or 23.7 mg/m3)
Result : negative
Method : other
Year : 1977
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Groups of 100 male and 100 female animals were exposed to HEA vapor at 0 (controls), 0.5 or 5 ppm for 6 hours/day, 5 days/week as part of the chronic toxicity/oncogenicity study. After the first year of treatment, 4 male and 4 female rats per group were injected intraperitoneally with colchicine (0.4 mg/kg) sacrificed four hours after injection and samples of bone marrow collected. Slides of the bone marrow were prepared for the microscopic examination of chromosomes. Fifty cells per animal were scored for chromatid abberations, chromosome aberrations and abnormal cells, with the exception of female controls where 35, 43, 19 and 25 cells were scored and one female in the 5 ppm group where only 2 cells were scored.
Result : No bone marrow cytogenetic alterations were found as a result of exposure to HEA.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
29.03.2005 (104)

5.7 CARCINOGENICITY

Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : inhalation
Exposure period : 18 months
Frequency of treatm. : 6 hours/day; 5 days/week
Post exposure period : 5 months (male); 6 months (females)
Doses : 0 ppm, 0.5 ppm (2.4 mg/cubic meter), and 5.0 ppm (24 mg/cubic meter)
Result : negative
Control group : yes
Method : other
Year : 1979
GLP : no
Test substance : other TS: 96% HEA

Remark : The statistically significant increase in the incidence of fibrinoid degeneration of the vascular channels in the testes of male rats exposed to

5 ppm was known to be a local vascular manifestation of mesenteric periarteritis syndrome observed as age-related lesion in this rat strain (Sprague-Dawley, Spartan substrain). The laboratory conducting this study commonly observed this lesion in control aging rats of this strain at similar incidence as was observed in this study during it's period of use in the mid to late '70s (the incidence in historical controls in this period ranged from approximately 37 to 85% for seven chronic toxicity/oncogenecity studies).

Polyarteritis (polyarteritis or periarteritis nodosa) is the most conspicuous inflammatory lesion of the blood vessels of rats. The etiology is unknown and the indidence varies among strains and colonies (Mitsumori, K. (1990) Chapter 29 in Pathology of the Fischer Rat. Eds: Boorman et al., Academic Press, Inc. p 477). A common site in male rats are the arteries of the testicle and to a lesser extent the arteries of the spermatic cord (Burek, J.D. (1978) Pathology of the Aging Rat, CRC Press p. 87). Carlton and Engelhardt (Polyarteritis, In: Cardiovascular and Musculoskeletal Systems Eds: Jones, T.C., Mohr, U. and Hunt, R.D., Springer-Verlag, 1991, p 71) also indicate that this lesion can be present in spermatic arteries.

Result

MORTALITY AND TIME TO DEATH: The cumulative mortality for male rats exposed to 5 ppm HEA was statistically increased from controls in the 16th month of the study only. This correlated with the onset of chronic murine pneumonia which initially affected this group and subsequently spread to the other exposure and control groups. Mortality of exposed females was comparable to controls except for a statistical increase in the 17th month at 5 ppm and in the 15th month at 0.5 ppm. Overall the cumulative mortality data were not markedly different between exposed and control groups indicating an absence of a treatment-related effect with the possible exception of the initial increased mortality associated with the onset of chronic murine pneumonia in rats exposed to 5 ppm (Tables 1 & 2).

Table 1

CUMULATIVE PERCENT MORTALITY FOR MALE RATS EXPOSED TO VAPORS OF 2-HYDROXYETHYL ACRYLATE 5 DAYS/WEEK FOR 18 MONTHS FOLLOWED BY A 5 MONTH OBSERVATION PERIOD

Months on Study	Exposure Level: Control No. Dead (% Dead)	5 PPM No. Dead (% Dead)	0.5 PPM No. Dead (% Dead)
No. Rats Alive on Day 0[a]	91	91	91
1	0 (0)	0 (0)	1 (1)
2	1 (1)	0 (0)	2 (2)
3	1 (1)	0 (0)	2 (2)
4	1 (1)	1 (1)	3 (3)
5	1 (1)	1 (1)	5 (5)
6	1 (1)	1 (1)	5 (5)
7	2 (2)	1 (1)	6 (7)
8	2 (2)	1 (1)	7 (8)
9	2 (2)	1 (1)	7 (8)
10	2 (2)	1 (1)	8* (9)
11	3 (3)	1 (1)	8 (9)
12	4 (4)	2 (2)	8 (9)
13	5 (5)	5 (5)	9 (10)
14	7 (8)	7 (8)	9 (10)
15	8 (9)	11 (12)	10 (11)
16	8 (9)	28* (31)	13 (14)
17	37 (41)	42 (46)	24* (26)
18	53 (58)	44 (48)	44 (48)
19	57 (63)	48 (53)	54 (59)
20	66 (73)	49* (54)	64 (70)
21	70 (77)	56* (62)	71 (78)
22	74 (81)	60* (66)	80 (88)
23	77 (85)	70 (77)	82 (90)
Beginning of 24	77 (85)	72 (79)	82 (90)
Terminal Kill	14	19	9
12 Month Interim Kill	5	5	5
12 Month Kill for Cytogenetics	4	4	4
Total Rats In Study	100	100	100

[a] Excludes those rats used in interim kill (5/sex/dose), and used for cytogenetic examination (4/sex/dose).

* Statistically different from control data when analyzed using Fisher's Exact Probability test, $p<0.05$.

Table 2

CUMULATIVE PERCENT MORTALITY FOR FEMALE RATS EXPOSED TO VAPORS OF 2-HYDROXYETHYL ACRYLATE 5 DAYS/WEEK FOR 18 MONTHS FOLLOWED BY A 6 MONTH OBSERVATION PERIOD

Months on Study	Exposure Level: Control No. Dead (% Dead)	5 PPM No. Dead (% Dead)	0.5 PPM No. Dead (% Dead)
No. Rats Alive on Day 0[a]	91	91	91
1	0 (0)	0 (0)	1 (1)
2	0 (0)	0 (0)	1 (1)
3	0 (0)	0 (0)	1 (1)
4	0 (0)	0 (0)	1 (1)
5	0 (0)	0 (0)	1 (1)
6	0 (0)	0 (0)	1 (1)
7	0 (0)	0 (0)	1 (1)
8	2 (2)	1 (1)	1 (1)
9	3 (3)	3 (3)	2 (2)
10	3 (3)	4 (4)	3 (3)
11	4 (4)	4 (4)	5 (6)
12	4 (4)	5 (5)	7 (8)
13	4 (4)	8 (9)	9 (10)
14	5 (5)	9 (10)	12 (13)
15	5 (5)	10 (11)	13* (14)
16	5 (5)	16 (18)	16 (18)
17	16 (18)	28* (31)	21 (23)
18	23 (25)	34 (37)	27 (30)
19	28 (31)	39 (43)	35 (39)
20	37 (41)	42 (46)	41 (46)
21	43 (47)	46 (51)	46 (51)
22	53 (58)	56 (62)	59 (66)
23	62 (68)	61 (67)	65 (72)
24	70 (77)	64 (70)	70 (78)
Terminal Kill	21	27	20
12 Month Interim Kill	5	5	5
12 Month Kill for Cytogenetics	4	4	4
Total Rats In Study	100	100	99

[a] Excludes those rats used in interim kill (5/sex/dose), and used for cytogenetic examination (4/sex/dose).

* Statistically different from control data when analyzed using Fisher's Exact Probability test, $p<0.05$.

CLINICAL SIGNS: The haircoat of rats exposed to 5 ppm had a characteristic yellow staining as well as an increased incidence and severity of chronic murine pneumonia. These effects were not observed in rats exposed to 0.5 ppm.

BODY WEIGHTS: A statistically significant decrease in body weights was

observed for male rats at 0.5 and 5.0 ppm at 12 months but not at terminal sacrifice (Tables 3 and 4). The difference in body weight at 12 months was not concentration dependent; the 0.5 ppm group having a lower mean weight than the 5 ppm group.

FOOD/WATER CONSUMPTION: No data collected

OPHTHALMIC EXAMINATION: No treatment-related effect observed at necropsy using a glass microscope slide on the surface of the eye for magnification and examination of the interior of the eye.

CLINICAL CHEMISTRY: There were no significant differences between control and exposed groups in regard to blood urea nitrogen, or SGPT and AP activities either at the interim or terminal sacrifice.

HEMATOLOGY: At the interim sacrifice, no statistical differences were observed for male rats. Females at 5 ppm had statistically significant elevation of the mean hemoglobin concentration and statistically lower total leukocyte count. At the terminal sacrifice, there were no statistical differences from controls with the exception of a increase in red blood cell count in male rats exposed to 5 ppm.

URINALYSIS: No treatment-related effects were observed at either the interim or terminal sacrifice.

ORGAN WEIGHTS: At the interim sacrifice, there were no statistically significant differences in absolute organ weights; the relative brain and testes weight for males exposed to 0.5 ppm were significantly increased relative to controls secondary to a statistically significant decrease in the terminal body weights. There were no significant differences from either absolute or relative control organ weights for females exposed to HEA for twelve months, consistent with the absence of an effect on body weight in females.

At the terminal sacrifice, there were no statistically significant differences from controls in body weight, or the absolute or relative organ weights for HEA exposed rats with the exception of a decrease in the absolute weight of the brain for males at 0.5 ppm and of the heart for females exposed to 5 ppm. These observations were considered of no toxicologic significance in view of no change in the relative weight. In addition for the females, the inclusion of one "inordinately low" heart weight from one animal also had impact on the differences.

Mean organ weight data for interim and terminal sacrifices are shown in Tables 3 and 4, respectively.

Table 3. BODY WEIGHTS, ORGAN WEIGHTS, AND ORGAN/BODY WEIGHT RATIOS FOR MALE AND FEMALE RATS EXPOSED TO VAPORS OF 2-HYDROXYETHYL ACRYLATE 5 DAYS/WEEK FOR 12 MONTHS

Exposure level PPM	Sex		Body Weight g	Organ Weights (g and g/100 g Body Weight)									
				Brain		Heart		Liver		Kidneys		Testes	
				g	g/100g	g	g/100g	g	g/100g	g	g/100g	g	g/100g
0	M	Mean	621	1.97	0.32	1.64	0.26	15.14	2.42	3.95	0.63	3.87	0.62
		±S.D.	37	0.03	0.02	0.07	0.01	2.75	0.32	0.62	0.07	0.76	0.12
5.0	M	Mean	565[a]	1.93	0.34	1.59	0.28	14.98	2.64	3.77	0.66	4.08	0.72
		±S.D.	24	0.08	0.01	0.12	0.02	3.17	0.46	0.79	0.12	0.18	0.02
0.5	M	Mean	549[a]	1.98	0.36[a]	1.55	0.28	12.92	2.35	3.30	0.60	4.38	0.80[a]
		±S.D.	40	0.06	0.03	0.17	0.02	1.32	0.13	0.15	0.06	0.24	0.03
0	F	Mean	317	1.85	0.59	1.05	0.33	7.36	2.32	2.16	0.68		
		±S.D.	16	0.05	0.04	0.02	0.02	0.41	0.18	0.21	0.08		
5.0	F	Mean	342	1.80	0.53	1.13	0.33	7.87	2.30	2.31	0.68		
		±S.D.	26	0.07	0.04	0.07	0.02	0.63	0.12	0.27	0.04		
0.5	F	Mean	347	1.87	0.54	1.11	0.32	9.18	2.63	2.17	0.63		
		±S.D.	15	0.04	0.02	0.13	0.03	2.05	0.46	0.14	0.02		

[a] Statistically significant difference from control mean by analysis of variance and Dunnett's test $p < 0.05$.

Table 4. BODY WEIGHTS, ORGAN WEIGHTS, AND ORGAN/BODY WEIGHTS OF MALE AND FEMALE RATS EXPOSED TO VAPORS OF 2-HYDROXYETHYL ACRYLATE 5 DAYS/WEEK FOR 18 MONTHS FOLLOWED BY A 5 MONTH (males) or 6 MONTH (females) OBSERVATION PERIOD

Exposure level PPM	Sex		Fasted Body Weight g	Organ Weights (g and g/100 g Body Weight)									
				Brain		Heart		Liver		Kidneys		Testes	
				g	g/100g	g	g/100g	g	g/100g	g	g/100g	g	g/100g
0	M	Mean	478	1.99	0.43	1.72	0.36	16.88	3.49	5.38	1.13	3.81	0.80
		±S.D	93	0.06	0.09	0.38	0.06	4.62	0.51	1.56	0.23	0.90	0.13
5.0	M	Mean	485	1.98	0.42	1.71	0.36	16.30	3.39	4.73	0.98	3.48	0.71
		±S.D	77	0.08	0.06	0.20	0.04	2.01	0.32	0.91	0.16	1.16	0.19
0.5	M	Mean	480	1.91[a]	0.41	1.81	0.39	15.53	3.26	4.48	0.95	3.11	0.64
		±S.D	96	0.12	0.09	0.32	0.09	2.91	0.38	1.02	0.21	1.22	0.21
0	F	Mean	367	1.80	0.51	1.32	0.38	12.13	3.35	2.84	0.82		
		±S.D	81	0.07	0.10	0.12	0.09	2.31	0.52	0.44	0.26		
5.0	F	Mean	319	1.80	0.58	1.12[a]	0.36	10.21	3.23	2.57	0.82		
		±S.D	53	0.08	0.09	0.13	0.05	1.57	0.43	0.35	0.16		
0.5	F	Mean	440	1.82	0.47	1.28	0.32	12.61	2.88	2.68	0.67		
		±S.D	167	0.04	0.16	0.07	0.11	5.47	0.55	0.35	0.21		

[a] Statistically significant difference from control mean by analysis of variance and Dunnett's test, $p<0.05$
+ {[mean + T value = 2.07] [mean – T value = 1.92]}

GROSS PATHOLOGY: A statistically significant number of both male and female rats exposed to 5 ppm HEA had a distinctive grossly visible yellow staining of the haircoat that persisted into the post-exposure portion of the study. The yellow staining was judged to be a result of the contact of the HEA vapor with the haircoat and was not observed in rats exposed to 0.5 ppm HEA. Chronic murine pneumonia caused by Mycoplasma sp. was observed in all groups as evidenced by pulmonary consolidation and mucopurulent inflammation along the tracheobronchial system. This sometimes included abscess formation, pleuritis, pericarditis, rhinitis and/or tracheitis. An increase in the incidence of numerous gross or microscopically visible lesions occurring as part of or secondary to the chronic murine pneumonia was observed in both male and female rats exposed to 5 ppm HEA.

An increase was observed in the incidence of female rats having a total of 3 grossly-visible subcutaneous masses in the groups exposed to 5 or 0.5 ppm HEA. However, this was not the case with female rats of either exposure group that had 1,2,4, or 5 subcutaneous masses.

HISTOPATHOLOGY: Statistical differences between control and HEA exposed rats in the respiratory tract lesions related to chronic murine pneumonia were observed. Specifically, at 5 ppm, an increase in the incidence and severity of the lesions associated with chronic murine pneumonia was observed.

Lymphoreticular System: Statistical increases in the incidence of edema, inflammation and reactive lymphoid hyperplasia of the thoracic lymph nodes in females at 5 and 0.5 ppm, secondary to chronic murine pneumonia were observed; an increased incidence of edema in mesenteric lymph nodes was also present in females at 0.5 ppm.

Liver: At the terminal sacrifice a statistically significant increase as compared to controls was observed in the focal areas of swollen hepatocytes and focal aggregates of mononuclear cells in males exposed to 5 ppm. A statistically significant increase as compared to controls in the incidence of focal bile duct proliferation in female rats exposed to 5 ppm HEA was also observed.

Female reproductive organs: At the terminal sacrifice only, a statistically significant increase in the incidence of inflammation of the uterus of female rats exposed to 5 ppm was observed (Table 5). Incidence data are shown in the attached table from the study report (HEA histopath uterus.pdf). No other statistically significant differences for histopathologic observations of the female reproductive organs were found. Specifically, there were no histopathological effects in the ovaries of HEA exposed rats that were considered treatment-related. In addition, at the interim sacrifice, no treatment-related histopathological effects were noted in female reproductive organs of five animals evaluated immediately after 12 months of HEA exposure at 5 ppm.

Table 6

MICROSCOPIC OBSERVATIONS ON FEMALE RATS EXPOSED TO VAPORS OF 2-HYDROXYETHYL ACRYLATE

(Terminal Kill After Month 24)

Dose in ppm	0	5	0.5
Number of rats per group[a]	21	27	20
Number of rats in study	100	100	99
REPRODUCTIVE SYSTEM (Continued)			
Uterus			
Multiple areas of cystic endometrial hyperplasis	14/21/21	20/27/27	1/3/20
Sclerosing carcinoma of uterus with metastasis to lungs	0/21/21	0/27/27	1/3/20
Uterine inflammation	2/21/21	11/27/27[b]	1/3/20
Adenomatous polyp formation in uterus	4/21/21	9/27/27	0/3/20
Squamous keratinization of uterus	0/21/21	1/27/27	0/3/20
Fibrotic polyp of uterus	0/21/21	0/27/27	1/3/20
Hematogenous pigment within uterus	2/21/21	6/27/27	1/3/20
Cyst formation within endometrium	3/21/21	8/27/27	0/3/20
Uterine polyp formation	1/21/21	0/27/27	0/3/20
Adenocarcinoma of uterus	1/21/21	1/27/27	0/3/20
Abscess of uterus	1/21/21	2/27/27	0/3/20
GASTROINTESTINAL SYSTEM			
Stomach			
Dilatation of gastric pits	7/21/21	11/27/27	0/1/20

Data listed as number of observations/total number of tissues, organs, or masses examined microscopically/ number of animals examined grossly.

[a]Microscopic examination of all major organs limited to control and top dose group. Liver, kidney, lungs, nasal turbinates, thoracic lymph nodes, and all lesions grossly suggestive of tumor formation were examined from the low dose group.

[b]Statistically different from control by the Fisher Exact Probability Test, $p<0.05$.

Male reproductive organs: At the terminal sacrifice only, there was a statistically significant increase in the incidence of fibrinoid degeneration of the vascular channels (local vascular manifestation of mesenteric periarteritis syndrome observed as age-related lesion in this rat strain) in the testes of male rats exposed to 5 ppm (8/14 or 57% in controls; 17/19 or 89% in the 5 ppm group) (Table 6A). The laboratory conducting this study

commonly observed this lesion in control aging rats of this strain at similar incidence as was observed in this study during its use in the mid to late '70s (historical control values from seven chronic toxicity/oncogenicity studies ranged from 37 to 85%). Periarteritis of the mesenteric blood vessels was also common in the control and HEA exposed rats (Table 6B). No other statistically significant differences were found in the histopathologic observations of the male reproductive organs. Specifically, there was no difference between treated and control groups in spermatogenesis in the testes or in the morphology and secretory content of the male accessory sex glands. In addition, at the interim sacrifice, no treatment-related histopathological effects were noted in male reproductive organs of five animals evaluated immediately after 12 months of 2-HEA exposure at 5 ppm.

Table 6A

MICROSCOPIC OBSERVATIONS ON MALE RATS EXPOSED TO VAPORS OF 2-HYDROXYETHYL ACRYLATE

(Terminal Kill During Month 24)

Dose in ppm	0	5	0.5
Number of rats per group[a]	14	19	9
Number of rats in study	100	100	100
URINARY SYSTEM (Continued)			
Urogenital Tract			
Diffuse hyperplasia of urinary bladder mucosa	2/14/14	0/19/19	0/0/9
Organized plug within lumen of urinary bladder	3/14/14	1/19/19	0/0/9
REPRODUCTIVE SYSTEM			
Testis			
Decreased spermatogenesis, one testis	1/14/14	0/19/19	0/0/9
Decreased spermatogenesis, both testes	2/14/14	1/19/19	0/0/9
Focal atrophy of seminiferous tubules	9/14/14	7/19/19[b]	0/0/9
Vascular fibrinoid degeneration in the testes	8/14/14	17/19/19[b]	0/0/9
Focal interstitial fibrosis of testicle	3/14/14	5/19/19	0/0/9
Interstitial cell tumor of testicle	0/14/14	1/19/19	0/0/9
Diffuse testicular atrophy	1/14/14	2/19/19	0/0/9
Accessory Sex Glands			
Decreased secretory content of accessory sex glands	11/14/14	10/19/19	0/0/9
Atrophy of accessory sex glands	2/14/14	5/19/19	0/0/9

Data listed as number of observations/total number of tissues, organs, or masses examined microscopically/ number of animals examined grossly.

[a] Microscopic examination of all major organs limited to control and top dose group. Liver, kidney, lungs, nasal turbinates, thoracic lymph nodes, and all lesions grossly suggestive of tumor formation were examined from the low dose group.

[b] Statistically different from control by the Fisher Exact Probability test, $p<0.05$.

Table 6B

MICROSCOPIC OBSERVATIONS ON MALE RATS EXPOSED TO VAPORS OF 2-HYDROXYETHYL ACRYLATE

(Terminal Kill During Month 24)

Dose in ppm	0	5	0.5
Number of rats per group[a]	14	19	9
Number of rats in study	100	100	100
CARDIOVASCULAR SYSTEM			
Heart			
Focal myocardial degeneration and inflammation - slight	8/14/14	11/19/19	0/0/9
Focal myocardial degeneration and inflammation - moderate	3/14/14	5/19/19	0/0/9
Focal myocardial degeneration and inflammation - pronounced	1/14/14	0/19/19	0/0/9
Myocardial mineralization	1/14/14	0/19/19	0/0/9
Aorta			
Aortic mural mineralization	0/14/14	4/19/19	1/8/9
Thickening of endothelial lining of aorta	2/14/14	3/19/19	0/8/9
Blood Vessels			
Degeneration of myocardial blood vessels	10/14/14	14/19/19	0/0/9
Periarteritis and sclerosis of mesenteric blood vessels	6/14/14	7/19/19	2/2/9
Thrombosis and hematoma formation associated with mesenteric periarteritis	1/14/14	0/19/19	1/2/9
Mineralization of selected blood vessels	1/14/14	2/19/19	0/2/9
Hyalinization and thickening of mesenteric blood vessels	2/14/14	6/19/19	0/2/9
Congestion of myocardial vessels	1/14/14	0/19/19	0/0/9

Data listed as number of observations/total number of tissues, organs, or masses examined microscopically/ number of animals examined grossly.

[a]Microscopic examination of all major organs limited to control and top dose group. Liver, kidney, lungs, nasal turbinates, thoracic lymph nodes, and all lesions grossly suggestive of tumor formation were examined from the low dose group.

Stomach: An increase in the incidence of microscopically visible dilatation of gastric pits in male rats exposed to 5 ppm HEA was observed.

Cardiovascular system: An increase in the incidence of microscopically visible degeneration of myocardial blood vessels in female rats exposed to 5 ppm was observed (Table 7).

Table 7

MICROSCOPIC OBSERVATIONS ON FEMALE RATS EXPOSED TO VAPORS OF 2-HYDROXYETHYL ACRYLATE

(Terminal Kill After Month 24)

Dose in ppm	0	5	0.5
Number of rats per group[a]	21	27	20
Number of rats in study	100	100	99
CARDIOVASCULAR SYSTEM			
Heart			
Focal myocardial degeneration and inflammation - slight	7/21/21	12/27/27	0/1/20
Focal pericarditis	0/21/21	1/27/27	0/1/20
Aorta			
Aortic mural mineralization	1/19/21	1/27/27	0/16/20
Thickening of endothelial lining of aorta	3/19/21	7/27/27	2/16/20
Blood Vessels			
Degeneration of myocardial blood vessels	1/21/21	11/27/27[b]	0/1/20
Periarteritis and sclerosis of mesenteric blood vessels	4/21/21	2/27/27	0/1/20
Mineralization of selected blood vessels	1/21/21	0/27/27	0/20/20
Fibrosis around blood vessel in thoracic adipose tissue	1/21/21	0/27/27	0/18/20

Data listed as number of observations/total number of tissues, organs, or masses examined microscopically/ number of animals examined grossly.

[a]Microscopic examination of all major organs limited to control and top dose group. Liver, kidney, lungs, nasal turbinates, thoracic lymph nodes, and all lesions grossly suggestive of tumor formation were examined from the low dose group.

[b]Statistically different from control by the Fisher Exact Probability Test, $p<0.05$.

OTHER: CYTOGENETIC EVALUATION - Bone Marrow: There were no indications of alterations related to HEA exposure that were observed in the cytogenetic evaluation.

TIME TO TUMORS: Statistical analyses revealed no increases in the incidence of HEA exposed rats bearing benign neoplasms, malignant neoplasms or all types of neoplasms as compared to controls nor were there differences as compared to controls in the temporal occurrence of neoplasms.

Test condition : TEST ORGANISMS:
Age: not specified
Weight at study initiation: Male group means ranging from 287-300 g; Female group means ranging from 217-224 g
Number of animals: 99 or 100 animals/sex/exposure level

ADMINISTRATION/EXPOSURE:
Duration of test/exposure: 18 months
Type of exposure: Whole body
Post exposure period: Males: 5 months, Females: 6 months
Vehicle: none/not applicable
Target Exposure Concentrations: 0, 0.5 and 5 ppm vapor
Actual Analytical Mean +/- S.D. Exposure Concentrations:
0, 0.56 +/- 0.39 ppm, 3.66 +/- 1.65 ppm.

CLINICAL OBSERVATIONS AND FREQUENCY:
Body weights: All animals weighed on the following study days:
0,5,7,12,19.26,33,40,54,68,96,131,159,194,223,251,286,
314,342,377,405,433,468,496,532,552,585,620,648,675,702,723

Clinical signs: animals examined at "frequent intervals" for

mortality/morbundity

Hematology: 12 months, 5 rats/sex/exposure level; and at end of 5 or 6 month post-exposure period, 10 rats/sex/exposure level. Packed cell volume, erythrocyte count, hemoglobin concentration, total and differential leukocyte count.

Cytogenetic evaluation: 12 months, 4 rats/sex/exposure level; chromosomal aberations, breaks

Clinical Chemistry: 12 months, 5 rats/sex/exposure level, Blood urea nitrogen, alkaline phosphatase, glutamic pyruvic transaminase

Urinalysis: 12 months, 5 rats/sex/exposure level; and at end of 5- or 6-month post-exposure period, 10 rats/sex/exposure level. Specific gravity, pH, glucose, protein, ketones, bilirubin and blood.

ORGANS EXAMINED AT NECROPSY:
Macroscopic:
At 12-month interim sacrifice: all organs, weight of brain, heart, liver, kidneys, testes, 5 rats/sex/exposure level.
At terminal sacrifice: all organs, all surviving animals. The weights of brain, heart, liver, kidneys, testes were recorded at the terminal sacrifice for 9-19 animals per sex/exposure level.

Microscopic:
Control and 5 ppm, at interim and terminal sacrifice: brain, heart, liver kidneys, testes, lungs, thoracic and/or mesenteric lymph nodes, salivary glands, pancreas, adrenals, spleen, thymus, aorta, skeletal muscle, small intestine, large intestine, thyroid gland, trachea, spinal cord, peripheral nerve, pituitary gland, epididymides, urinary bladder, accessory sex glands, adipose tissue, ovaries, uterus, nasal turbinates, and any gross lesion suggestive of a pathologic process or with tumor formation.

At 0.5 ppm terminal sacrifice lungs, livers, kidneys, lymph nodes tracheas and grossly visible lesions from all surviving animals; at interim sacrifice grossly visible lesions or tissues where lesions seen at 5 ppm.

Rats dying or culled during the course of the study, complete necropsy and microscopic exam as described above (except when autolysis precluded evaluation) and the presence and absence of neoplasms recorded.

STATISTICAL METHODS:
Hematology, clinical chemistries, body weights, absolute and relative organ weights were analyzed using analysis of variance and Dunnett's Test. Cumulative mortality data were analyzed using Fisher's Exact Probability Test. In both cases, p values of less than 0.05 considered statistically significant.

Gross and microscopic pathology data were analyzed using Fisher's Exact Probability Test ($p<0.05$) as follows: Gross necropsy: the total collated data from each of the high and low exposure groups were compared with the data of the control group. Each sex was compared separately. Microscopic observations: the incidence of lesions in tissue for each sex from highest exposure group (5 ppm) was compared with the data from controls. At the terminal sacrifice, data from the lower exposure group (0.5 ppm) were analyzed statistically when the number of tissues examined was similar to the controls. The incidence rate for each type of neoplasm was compared separately for each sex between the high exposure group and controls. For the lower exposure (0.5 ppm), statistical evaluation was conducted for neoplasms in those organs upon which microscopic exam was conducted to the degree comparable to the controls and highest exposure group (liver,

kidney, lung and lymph nodes and subcutaneous masses/nodules).

To examine the possibility that neoplasms appeared earlier in treated vs. control rats the following parameters were compared for 6 month time periods using Fisher's Exact Probability Test and the Mantel-Haenzel Test with $p<0.05$:
1) Total number of rats bearing tumors, 2) Number of rats with benign tumors, 3) Number of rats with malignant neoplasms, and 4) Number of rats bearing subcutaneous masses/nodules.

Test substance : SOURCE: Texas Division of The Dow Chemical Company

PURITY: 96.3% 2-hydroxyethyl acrylate by vapor phase chromatography

IMPURITIES:

Acrylic acid	0.91%
Water	0.06%
Ethylene oxide	0.43%
Hydroxyethyl acetate	0.82%
Hydroxyethyl methacrylate	0.1%
Ethylene diacrylate	0.11%
Diethylene glycol nitroacrylate	1.11%
2-Hydroxyethyl ester of diacrylic acid	0.19%
methyl ethyl hydroquinone (ppm)	475

COMMON NAME: 2-hydroxyethyl acrylate

LOT NUMBER: TB-08153

Reanalysis 14 months from the initial analysis showed the test material to be stable.

Conclusion : The results of this study indicate that chronic inhalation of 2-HEA by rats produced only a minimal degree of toxicity at 5 ppm (haircoat staining and increased incidence and severity of chronic murine pneumonia). Female rats in the 5 ppm group at the terminal sacrifice showed an increased incidence of uterine inflammation as compared to the control animals. However, no other statistically significant differences for histopathological observations of the female reproductive organs were found, including the ovaries. An evaluation of the histopathological data from the male animals exposed to 5 ppm indicated an increased incidence of fibrinoid degeneration in the vascular channels of the testes which was a local vascular manifestation of mesenteric periarteritis syndrome observed as age-related lesion in this rat strain. This effect was also present in the control rats. In a recent review of the histopathological findings in male and female reproductive organs by the study pathologist and principal author, the fibrinoid degeneration in the testes was not considered to be a substance-specific toxic effect of HEA and the effects in the uterus were not considered indicative of a reproductive toxicity potential for 2-HEA. In summary, the NOAEL was 0.5 ppm and there was no evidence in this study that 2-HEA has the potential for reproductive toxicity or an oncogenic effect in either of the exposure groups.

Following are the tables referenced in the Results section, above.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

The number of animals per group at the start of the study was twice the number specified in current guidelines for chronic toxicity/carcinogenicity studies.

Flag : Critical study for SIDS endpoint

29.03.2005 (105)

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	Sprague-Dawley
Route of admin.	:	inhalation
Exposure period	:	6 hours/day
Frequency of treatm.	:	during days 6 to 20 of gestation
Duration of test	:	21 days
Doses	:	1, 5 or 10 ppm
Control group	:	yes, concurrent no treatment
NOAEL maternal tox.	:	= 5 ppm
NOAEL teratogen.	:	= 10 ppm
Result	:	negative
Method	:	other: consistent with OPPTS 870.3700 with minor exceptions
Year	:	1999
GLP	:	no data
Test substance	:	other TS

Result :

MATERNAL TOXIC EFFECTS BY DOSE LEVEL:
-Mortality and day of death: none
-Body weight/body weight gain: Maternal body weight gain was decreased through GD 6-21 and statistically identified as decreased from controls on GD 6-13 for animals exposed to 10 ppm HEA. In addition, decreases in absolute weight gain [(Day 21 body weight)-(gravid uterus weight)-(Day 6 body weight)] was statistically identified at 10 ppm.

Exp. Conc.	No. of Dams	BW GD 6	BW gain (g) on GD 6-13	13-21	6-21	Absolute wt gain(g)
0	21	262±18	29±9	105±15	134±17	34±15
1	19	261±16	23±13	113±34	135±36	31±6
5	22	264±18	25±6	109±20	134±21	29±14
10	21	263±21	22±7*	98±15	120±19	15±14**

*,** Significant differences from control (0 ppm) value, p<0.05, and p<0.01, respectively.

-Food consumption: A slight but statistically significant decrease in food consumption was seen at 10 ppm for the entire exposure period (GD 6-21).

Exp Conc.	No. of Dams	Food Consumption (g/dam/day) on GD 0-6	6-13	13-21	6-21
0	21	24±2	22±2	28±2	25±2
1	19	23±2	22±2	28±3	25±2
5	22	23±2	22±2	28±2	25±2
10	21	24±2	20±2**	25±2**	23±2**

** Significant difference from control (0 ppm) value, p<0.01.

-Implantations and resorptions: There were no significant changes in the numbers of implantations and live fetuses, incidence of non-live implants and resorptions.

			Litters with implants		
Exp. Conc.	No. of females	No. of litters	No. of implant sites/litter	% of non-live implants/litter	% of resorptions sites/litter

0	23	21	14.71±2.53	10.93±13.99	10.93±13.99
1	23	19	15.00±3.27	8.93±22.70	8.93±22.70
5	23	22	14.91±2.62	7.63±11.02	7.63±11.02
10	22	21	15.33±1.53	6.52±6.73	6.52±6.73

FETAL DATA:
-Fetal body weights: There were no significant changes in the fetal body weights across groups.

Litters with Live Fetuses

Exp. Conc.	No. of litters	No. of live fetuses/ litter	Average Fetal Body Weight (g)/litter All	Males	Females
0	21	13.05±2.91	5.68±0.32	5.83±0.41	5.55±0.31
1	18	14.61±2.79	5.71±0.27	5.85±0.27	5.52±0.31
5	22	13.82±2.94	5.69±0.32	5.84±0.34	5.50±0.31
10	21	14.33±1.80	5.54±0.25	5.64±0.28	5.43±0.25

Litters with live fetuses

Fetal sex ratio

Exp. Conc.	No. of litters	Ratio M:F
0	21	0.93
1	18	1.31
5	22	1.19
10	21	1.06

-Fetal malformations: The only malformation observed was a unilateral microphthalmia at 1 ppm. There were no significant changes in the incidence of external, visceral, or skeletal variations.

Incidence of Malformations and Variations in Fetuses (a)

Total No. fetuses (litters) examined

Exp. Conc.	0	1	5	10
External	274 (21)	263 (18)	304 (22)	301 (21)
Visceral	137 (21)	132 (18)	152 (22)	150 (21)
Skeletal	137 (21)	131 (18)	152 (22)	151 (21)

Malformations(b)

Exp. Conc.	0	1	5	10
Microphthalmia (unilateral				
	0	1 (1)	0	0
No. (%)fetuses with any malformations				
	0	1 (0.4)	0	0
No. (%) litters with any malformations				
	0	1 (5.5)	0	0
Mean % fetuses with any malformations/litter				
	0	0.40+/-1.68(c)	0	0
External variations				
Palate (rugae mishappen)				
	0	1 (1)	0	0
Club foot (unilateral)				
	1 (1)	0	1 (1)	2 (2)
# (%) fetuses with external variations				
	1 (0.4)	1 (0.4)	1 (0.3)	2 (0.7)
# (%) litters with external variations				
	1 (4.8)	1 (5.6)	1 (4.5)	2 (9.5)

Mean % fetuses with external variations/litter
0.37+/-1.68 0.40+/-1.68 0.28+/-1.33 0.62+/-1.97
Visceral variations
Dilated renal pelvis
0 0 2 (2) 0
Hydroureter (unilateral)
0 0 2 (2) 0
Distended ureter
5 (3) 7 (5) 19 (8) 15 (6)
(%) fetuses with visceral variations
5 (3.6) 7 (5.3) 19 (12.5) 15 (10.0)
# of litters with visceral variations
3 (14.3) 5 (27.8) 8 (36.4) 6 (28.6)
Mean % fetuses with visceral variations per litter
3.26+/-9.12 5.16+/-9.33 12.21+/-19.56 9.48+/-19.22
Skeletal variations
Skull
Parietals, incomplete ossification, slight
0 0 1 (1) 0
Hyoid, incomplete ossification
0 0 0 2 (2)
5th sternbra, incomplete ossification or unossified (d)
12 (8) 4 (3) 5 (4) 3 (3)
Rib(s)
Cervical, rudimentary
1 (1) 2 (2) 0 0
14th, supernumerary
7 (4) 6 (3) 16 (7) 6 (5)
13th, short
0 1 (1) 0 1 (1)
Thoracic and/or lumbar vertebral centra.
incomplete ossification (one to three)
10 (6) 12 (8) 18 (11) 12 (10)
(%) fetuses with skeletal variations
28 (20.4) 23 (17.6) 38 (25.0) 22 (14.6)
(%) litters with skeletal variations
11 (52.4) 12 (66.7) 16 (72.7) 13 (61.9)
Mean % fetuses with skeletal variations/litter
19.37±22.58 18.77±19.53 25.05±25.55 14.76±13.58
(%) fetuses with any variations
34 (12.4) 31 (11.8) 57 (18.7) 39 (13.0)
(%) litters with any variations
13 (61.9) 13 (72.2) 17 (77.3) 16 (76.2)
Mean % fetuses with any variations /litter
11.60±12.10 12.49±12.85 18.49±15.00 13.02±12.79

(a) The incidence of individual defect is presented as number of fetuses (number of litters). Only live fetuses were examined. A single fetus may be represented more than once in listing individual defects.
(b)One fetus in the 1 ppm group had mcrophthalmia and misshappen palate ruggae.
(c) Mean +/-SD
(d)Unossified: alizarin red S negative

Test condition : TEST ORGANISMS
-Age: Young, nulliparous females
-Weight at study initiation: 200-220g
-Number of animals: groups of 20-29 bred female rats (19-22 pregnant)
ADMINISTRATION/EXPOSURE
-Route: inhalation
-Concentrations: The analytical concentrations were 1.1+/-0.1, 5.0+/-0.6 and 10.6+/-1.4 for the 1, 5 and 10 ppm groups as measured by gas chromatography. Control animals were exposed concurrently to filtered

room air in an adjacent chamber with characteristics identical to those of the treatment groups.
-Exposures: Exposures were conducted in 200-L glass/stainless-steel inhalation chambers with dynamic and adjustable laminar air flow (6-20m3/hour). 2-hydroxyethyl acrylate was delivered with an infusion pump, a constant rate of liquid chemical from the top of a heated glass column filled with glass beads. Compressed air heated by a glass heater was introduced at the bottom of the glass column in a countercurrent fashion to the liquid flow. Concentrations were monitored continuously with a gas-chromatograph equipped with a flame ionization detector and an automatic gas-sampling valve. In addition, exposure levels were determined once during each 6-hour exposure period by collecting atmosphere samples through glass tubes packed with activated charcoal. Samples were then desorbed with dichloromethane and analyzed by gas chromatography.

SATELLITE GROUPS AND REASONS THEY WERE ADDED: none
MATING PROCEDURES: Females were housed overnight with adult males (one male:two or three females) from the same strain and supplier. The day that vaginal smears were found to be sperm-positive was considered day 0 of gestation.
PARAMETERS ASSESSED DURING STUDY:
-Body weight/body weight gain: Maternal body weights were recorded on GD 0, 6, 13 and 21.
-Food consumption: Food consumption was recorded on GD 0-6, 6-13,and 13-21.
-Clinical observations performed and frequency:
Parent: no data
Fetus: no data
-Examination of uterine content: Uteri were removed and weighed, and the number of implatation sites, resorptions, and dead and live fetuses were recorded. Uteri which had no visible implantation sites were stained with ammonium sulfide to detect very early resorptions.
-Examination of fetuses: Live fetuses were weighed, sexed, and examined for external anomalies including those of the oral cavity. Half of the live fetuses from each litter were preserved in Bouin's solution and examined for internal soft tissue changes. The other half were fixed in ethanol, eviscerated, and then processed for skeletal staining with alizarin red S for subsequent skeletal examination.
-Organs examined at necropsy:
Parent: none
Fetus: see results table
OTHER EXAMINATIONS:
STATISTICAL METHODS: Data were presented as mean +/-SD. The number of implantation sites and live fetuses and the various body weights were analyzed by one-way analysis of variance (ANOVA), followed by Dunnett's test if differences were found. The percentages of non-live implants and resorptions and the proportions of fetuses with alterations in each litter were evaluated by using the Kruskal-Wallis test, followed by the Dixon-Massey test where appropriate. Rates of pregnancy, fetal sex ratio, and percentage of litters with malformations or external, visceral, or skeletal variations were analyzed by using Fisher's test. Where applicable, least-squares analysis was carried out. For all statistical tests, the level of significance was set a priori at alpha=0.05.

Test substance : The test material was received from Rohm (Germany) with a reported purity of 95.8% by gas chromatography.

Conclusion : Exposure to 10 ppm HEA caused overt maternal toxicity. This was evidenced by a transient decrease in body weight changes, a decrease in absolute weight gain and a continuous reduction of food consumption during exposure. There were no effects in maternal toxicity in animals exposed to 5 ppm HEA. The NOAEL for maternal toxicity was 5 ppm. Although there were some evidence of maternal toxicity, no adverse developmental effects were noted. Therefore, the NOAEL for

developmental toxicity was >= 10 ppm for HEA

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

Flag : Critical study for SIDS endpoint

29.03.2005 (106)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

Type of experience : Human - Medical Data

Result : A 15-Year Study of Patch Testing to (Meth)Acrylates
A retrospective appraisal of all patch test records from the Contact Dermatitis Investigation Unit from between January 1983 and March 1998 (approximately 14,000 records) was conducted. Patch testing and scoring were performed on the back of patients using Finn Chambers on Scanpor tape, with an occlusion time of 2 days. 2-HEA was applied at a 0.5% concentration. Reactions were assessed at 2 and 4 days.

GLP- no data
2-HEA tested positive, 24 allergic/250 patients tested (9.6%).
no data
(2) valid with restrictions

Reliability : (2) valid with restrictions

04.01.2005 (107)

Type of experience : Human - Medical Data

Result : Allergy Caused by Acrylate Compounds at the FIOH 1975-1995
In the 1990's, 124 patients with a history of exposure to acrylate compounds were patch tested with conventional patch test techniques. 2-HEA was administered at a range of 0.1-0.5% (w/w).

A cosmetologist became occupationally sensitized from photobonded sculptered nails. The nail gel used for the photobonded nails contained 0.3% methyl acrylate, 2% hydroxyethyl acrylate, 0.3% tripropylene glycol acrylate and 8% tripropylene glycol diacrylate based on GC/MS analysis. Each of these components was patch tested.

GLP- no data
Twenty-three patients showed at least one positive patch test reaction (Kanerva L., Estlander T., Jolanki R. and Tarvainen K. Statistics on allergic patch test reactions caused by acrylate compounds, including data on ethyl methacrylate. Am J Contact Dermatitis 1995;6:1-4.) 2-HEA was one of three acrylate compounds most often positive and tested positive in 14 of 124 patients.

The hydroxyethyl acrylate component of the nail gel used for the photobonded nails resulted in a patch test score of 2+ when administered at a concentration of 0.32% in pet.
no data
(2) valid with restrictions

30.12.2004 (108)

Type of experience : Human - Medical Data

Result : 10 Years of Patch Testing with the (Meth)Acrylate Series
During 1985-1995, a total of 275 patients with a history of exposure to (meth)acrylates were patch tested with 0.1-0.5% 2-HEA. Patch testing and scoring were performed on the back with an occlusion time of 1 or 2 days as previously described [1)Estlander, T. (1990). Occupational skin disease in Finland. Observations made during 1974-1988 at the Institute of Occupational Health, Helsinke. Acta Dermato-venerologica 1990: (suppl 155): 1-85 and 2)Jolanki R. (1991). Occupational skin disease from epoxy compounds. Acta Dermato-venerologica 1991: (suppl 159):1-80].

GLP- no data
Of the acrylates tested, 2-HEA most often provoked an allergic patch test reaction. Sixteen patients had an allergic reaction out of 132 patients tested or 12.1%.
No data
(2) valid with restrictions

30.12.2004 (109)

Type of experience : Human - Medical Data

Result : Statistics on Allergic Patch Testing
Patch testing was performed on the back of subjects with 24- or 48-hour occlusion using conventional patch testing techniques. Patch testing was conducted on 124 patients with the large (meth)acrylate series of Chemotechnique Diagnostics. 2-HEA was administered to the back of patients at 0.1-0.5% (wt/wt). All patients had anamnestic data on acrylate exposure.
Twenty-three patients showed at least one positive patch test reaction to acrylate compounds. 2-Hydroxyethyl acrylate was one of the top three acrylate compounds most often positive with 14 testing positive to 2-HEA out of 124 patients. Authors concluded that the acrylate compounds that caused the most sensitizations probably were significant contact sensitizers in humans or have a strong tendency to cross-react with sensitizers.
no data
(2) valid with restrictions

30.12.2004 (110)

Type of experience : Human - Medical Data

Result : Occupational Allergic Contact Dermatitis Due to Acrylates in Lodz
Aim of this work was to assess the sources of occupational allergy to acrylates among patients of the Nofer Institute of Occupational Medicine, Loda, Poland.

Among 1619 patients suspected of occupational skin disease examined during the yeatrs 1990-1994, 23 were exposed to acrylates. Tests with (meth)acrylate series (Chemotechnique Diagnostics AB- 0.1% 2-HEA) were performed on 23 patients exposed to acrylates. The patch tests were applied to the back for 2 days. Readings were taken by the same physician on the 2nd and 3rd days.
Among 15 acrylate-positive tests, 2 were positive to 2-HEA and dentists were more sensitive to 2-HEA than dental technicians.
no data
(2) valid with restrictions

30.12.2004 (111)

Type of experience : Human - Medical Data

Result : Acrylate, a Hidden Allergen of Electrocardiogram Electrodes
A 53-year-old woman noted irritation at the sites where electrocardiogram patches were applied, seeming to correspond to the zones where the

electrodes were applied, and leaving fixed pigmented erythema. Patch testing was conducted with 20 allergens from the Chemotechnique (meth)acrylate series.
Positive to hydroxyethyl acrylate 0.1% pet.
no data
(2) valid with restrictions

30.12.2004 (112)

Type of experience : Human - Medical Data

Result : Finn-chamber method: Pirila V. (1975) Contact Dermatitits 1:48-52
Results:

Before 1982: no patient sensitized from patch testing with (meth)-acrylates, or own substances containing acrylates.

During 1985-1986: 12 of 24 patients tested for sensitizationto 2-HEA showed no reaction. Three of 24 patients were found to have a relevant allergic reaction and were diagnosed as having an occupational allergic contact dermatitis to acrylates. Nine patients of 24 showed slight irritation in the patch tests at 24- and 48-h readings, and sometimes at 72-96 h. Three of these were sensitized. Of the six patients who showed irritation but were not sensitized, every patient showed irritation to 2-HEA. None of them showed irritation to the tape.

Results from the 3 patients which were sensitized to 2-HEA:
- 3 showed irritant reaction at initial patch testing
- 3 showed active sensitization at the patch test sites
- Test sites became positive after 18-21 days
- 2 of 2 tested patients were positive to 2-HEA when retested
Test condition:

The Finn-chamber method with an occlusion time of 24 h was used. The tests were applied on the back with a non-occlusive porous tape or when the back was full of patch tests, they used the thighs. The tests were read on removal and 24 h, 48 h, and 96-120 h after removal (at least 3 readings). All readings were made by a dermatologist. 2-HEA was applied at a concentration of 0.5 %w/w (molality =0.043)in pet. (vehicle).
Dow Benelux N.V. (Botlek) XA Botlek RT
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
(115)

- Finn-chamber method: Pirila V. (1975) Contact Dermatitits 1: 48-52
- ICDRG: Fisher AA (1986) Contact Dermatitis (ed 3). Philadelphia, PA, Lea & Febiger
On day 21 after patch testing, the patient noticed itching papules on her back and over the next few days her patch test sites were examined. A positive patch test reaction had developed to 2-HEA. On retesting 2 months later she had positive patch test reactions to 2-HEA (most pronounced 6-21 days after patch retest).
Test condition:

A 31-year-old shift worker was tested for sensitization because occupational skin disease was suspected. Patch

testing was performed with the (meth)acrylate series (Chemotechnique) on the back with the Finn-chamber techniquewith an occlusive time of 48 hours. The tests were read at 48, 72, and 96 hours and were negative. Scoring of patch test reactions was performed according to the suggestion by ICDRG. 2-HEA was applied at a concentration of 0.1 %w/w.

30.12.2004 (113)

Type of experience : Human - Medical Data

Result : - Finn-chamber method: Pirila V. (1975) Contact Dermatitits 1: 48-52
- ICDRG: Fisher AA (1986) Contact Dermatitis (ed 3). Philadelphia, PA, Lea & Febiger
On day 21 after patch testing, the patient noticed itching papules on her back and over the next few days her patch test sites were examined. A positive patch test reaction had developed to 2-HEA. On retesting 2 months later she had positive patch test reactions to 2-HEA (most pronounced 6-21 days after patch retest).
Test condition:

A 31-year-old shift worker was tested for sensitization because occupational skin disease was suspected. Patch testing was performed with the (meth)acrylate series (Chemotechnique) on the back with the Finn-chamber technique with an occlusive time of 48 hours. The tests were read at 48, 72, and 96 hours and were negative. Scoring of patch test reactions was performed according to the suggestion by ICDRG. 2-HEA was applied at a concentration of 0.1 %w/w.
Dow Benelux N.V. (Botlek) XA Botlek RT
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA) (116)

Case report of an 81-year-old woman who received new dentures and a hearing aid. She lost gradually her sense of taste and suffered from intense rash and itching at sites of contact with the hearing aid.

Patch testing revealed multiple reactions to acrylates. 48-h reading showed positive effect for 2-HEA (0.1 %w/w). All other tests which were performed were negative (compounds not mentioned; no data about test conditions).

30.12.2004 (114)

Type of experience : Direct observation, clinical cases

Result : Case report of an 81-year-old woman who received new dentures and a hearing aid. She lost gradually her sense of taste and suffered from intense rash and itching at sites of contact with the hearing aid.

Patch testing revealed multiple reactions to acrylates. 48-h reading showed positive effect for 2-HEA (0.1 %w/w). All other tests which were performed were negative (compounds not mentioned; no data about test conditions).

30.12.2004 (115)

Type of experience : Direct observation, clinical cases

Result : Case report of 2 patients; both patients were first patch tested with the GIRDCA standard series. Later, patch testing was performed with dental allergens, in particular with the allergens contained in products used for manufacturing acrylic prostheses. The 2 patients and 6 controls were patch tested with Vertex polymerization fluid and Colorstat Opaquer paint, both at 2% and 5% in petrolatum. The patch tests also included a series of acrylic monomers commonly used for manufacturing resins that are not necessarily employed in dentistry.

The patch tests with hydroxyethyl acrylate (HEA; 0.5% in pet.) were performed with Finn-chambers for 48 h and the 2nd at 72 h, results were scored as recommended by the ICDRG; patch tests were performed on the backs of the 2 patients.

Result:

The tests carried out on the controls with Vertex SC, Vertex RS and Colorstat Opaquer were negative. The patch tests were negative for HEA.

30.12.2004 (116)

Type of experience : Direct observation, clinical cases

Result : Case report of a 51-year-old man;
standard patch tests of Grupo Esopanol Investigacion Dermatitis Contacto (GEIDC) were performed;
a special plastics and glue and (meth)acrylates chemotechnique series are performed.

The patch test for 2-hydroxyethyl acrylate (0.1% in petrolatum) was negative at 48- and 96-h.

04.01.2005 (117)

Type of experience : Human - Medical Data

Result : 2-Hydroxyethyl acrylate was used at 0.167 %w/w in petrolatum. 2-HEA was not tested on 2 patients. In 3 patients (one patient using 0.5 %w/w) reaction on patch testing was negative. In two patients the reaction to HEA was scored as ++ and +++, respectively.
Finn-chamber method: Pirila V. (1975) Contact Dermatitits 1:48-52
Seven patients with allergic contact dermatitis due to dental composite resin products have been detected.

Patch testing, (meth)acrylate series, was done on the back using Tinn-chambers, with an occlusion time of 24 h and at least 3 readings by a dermatologist. Patch tests have been scored according to the recommendations of the Finnish Contact Dermatitis Group:
- = negative
+ = erythema
++ = erythema and oedema
+++ = erythema, oedema and vessicles
++++ = bullous or ulcerative reaction

30.12.2004 (118)

Type of experience : Direct observation, clinical cases

Result : Reference 1:

Case reports of 3 out of 6 workers who were working with (meth)acrylate and developed occupational contact dermatitis. One patient (male, age 35 years) agreed to undergo a series of patch tests (Finn Chamber). 2-HEA was tested at concentration of 0.5% and 1.0% in ethanol.

The results for 2-HEA read at 48 and 72 hr showed:
- weak erythema, infiltration extending beyond application site for 0.5%
- erythema, infiltration extending beyond application site for 1.0%

Control testing:
Three individuals (2 female, 1 male) were exposed in a patch test to 2-HEA at 0.5% and 1% (v/v) in ethanol. Results, read at 24 and 48 hr, were negative.
Reference 2:
- The protective effect of gloves (several materials) were tested on 2 volunteers which developed contact dermatitis and/or toxic effects which were attributed to 1-hexadecene (1-HD) and 2-HEA.
- Latex-, vinyl- and 4H-gloves were exposed to 1-HD or 2-HEAfor several hours. An area of 1 cm2 of the unexposed side ofthe glove was in contact with the arm.
- Skin reaction was monitored at 24 hours. Positive reactions were found with Latex- and Vinyl-gloves at 4 min exposure but not with 4H-gloves at 30 min exposure through gloves to 2-HEA.
Reference 3:
- Different experimental set-ups were used to provide direct information on the degradation of gloves (vinyl-, latex, 4H) by 1-hexadecene (1-HD) and 2-HEA and permeation of these compounds through the gloves; skin of two sensitized volunteers were exposed to the unexposed sideof 4H gloves material that had been in contact with 1-HD or 2-HEA for 200 hours.
- 2-HEA dissolved the vinyl gloves but the latex gloves appeared intact; however, the distinctive smell of 2-HEA had permeated. 2-HEA elicited a faint inflammation at the 30 minsite of contact and a slightly stronger reactions at the 90 min site of contact, appearing slowly within 4 hours, but neither itching nor producing vesicles or fissures.
Reactions using latex or vinyl gloves exposed to 2-HEA were stronger.

04.01.2005 (119)

Type of experience : Direct observation, clinical cases

Result : Case report of a 35-year-old nurse; transcutaneous electrical nerve stimulation (TENS) was performed to treat low back pain; she developed florid eczema beneath the electrode pads; she was patch tested with the European standard series, a (meth)-acrylate series and some TENS accessories (Tac conductivity gel, carbon rubber electrode shavings, hydropad conductive pad, Micropore adhesive tape and glycerol).

Positive reactions were found with hydropad, 2-HEA, 2-hydroxypropyl methacrylate and ethylene glycol dimethacrylate.

04.01.2005 (120)

Type of experience : Direct observation, clinical cases
Result : 82 patients suspected of occupational acrylic sensitization were patch tested with the GIRDCA standard series and an extensive acrylate series; hydroxyethyl methacrylate was patch tested at a concentration of 5% in petrolatum; reactions were read after 2, 3, and 4 days.

No detailed data about sensitization properties of HEA were shown.

04.01.2005 (121)

Type of experience : Direct observation, clinical cases
Result : A 39-year-old woman presented with oedema, erythema and ulceration of the mucosa of the upper lip; patch testing with 2-hydroxyethyl methacrylate showed strong positive reactions

04.01.2005 (122)

Type of experience : Direct observation, clinical cases
Result : - Two laboratory technicians involved in the manufacture of soft, disposable contact lenses, experienced hand dermatitis 6 weeks and 6 months after starting work, respectively. The latter experienced systemic symptoms of fatigue, nausea and vomiting after 2 years employment, after exposure to contactlens components.
- Both were patch tested using Finn Chambers to the ICDRG standard series and to the constituents of the lenses (no more details on the patch testing regimen were given).
- In the former patient, the standard battery was negative; 2-HEA at 1% in petrolatum caused irritation after 72, 96, and 144 hours; 2-HEA at 0.1% in petrolatum caused irritationafter 96 hours and gave positive sensitization responses after 72 and 144 hours; and 2-HEA at 0.01% in petrolatum gave positive sensitization responses after 48 and 96 hours.
A weak reaction in 2-hydroxyethyl methacrylate was also recorded. The latter patient reacted to formaldehyde in the standard battery and to 2-HEA at 0.1 and 0.01% in petrolatum after 48 and 72 hours. Systemic symptoms were not reproducedon patch testing and the other components of the contact lenses were negative.

04.01.2005 (123)

Type of experience : Direct observation, other
Result : An odor threshold study has determined that humans can detect HEA at concentrations as low as 3 ppm, which causes nasal irritation, and can tolerate 10 ppm for several minutes.

Irritation to eyes and respiratory tract and skin sensitization have been reported in plant workers exposed to HEA vapors.

04.01.2005 (95)

Type of experience : Direct observation, other
Result : The odor threshold for 2-HEA was 0.01 mg/l.
30.12.2004 (124)

5.11 ADDITIONAL REMARKS

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(3) Rapport Insake Grenswarde 2-Hydroxyethylacrylaat
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Directoraat-Generaal Van De Arbeid, RA13/87

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ISBN: 3-527-27576-2

(6) SZW; De Nationale MAC-lijst 1995; P 145, De Haag (1995);
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(7) Arbejdstilsynet, At-anvisning Nr. 3.1.0.2, Directoratet for Arbejdstilsynet, Kobenhavn (1996)

(8) AFS (Arbetarskyddsstyrelsens Forfattningssamling), Hygieniska Gransvarden, AFS 1996: 2, Stockholm (1996);
ISBN: 91-7930-306-4

(9) BASF AG, Sicherheitsdatenblatt Hydroxyethylacrylat (15.09.1995)

(10) DIMDI Deutsches Institut fuer Medizinische Dokumentation und Information (09.07.1993); File: HSDB Hazardous Substances Data Bank (Last-update 30.04.1993); source: SRC

(11) Rohm GmbH, product information FA 201, 2-Hydroxyethyl acylate (July 1997)

(12) R. L. Rowley, W. V. Wilding, J. L. Oscarson, Y. Yang, N. A. Zundel, T. E. Daubert, R. P. Danner, DIPPR® Data Compilation of Pure Chemicals Properties, Design Institute for Physical Properties, AIChE, New York, NY (2004). Data from Hazardous Chemicals Data Book, Noyes Data Corporation Park Ridge, New Jersey (1980).

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(15) Safety Data Sheet, Dow Europe S.A., Rev. 2/95

(16) Dow Product Stewardship Manual (October, 2002)

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(18) Dow Product Stewardship Manual (October, 2002)

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