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Final Report of the Safety Assessment of Methacrylic Acid[1]

Methacrylic Acid is an organic acid used at concentrations between 50 and 88 percent to pretreat the nail and maximize the adhesion between the nail and artificial nail extender. Methacrylic Acid is readily absorbed through mucous membranes of the lungs, the gastrointestinal tract, and the skin; and is distributed to all major tissues. Oral LD_{50} values for rats ranged from 277 to 2260 mg/kg; acute toxicity symptoms included severe gastric irritation, gasping, labored respiration, prostration and hematuria. In a short-term inhalation study, rats exposed to Methacrylic Acid at 1300 ppm showed nose and eye irritation and weight loss, while necropsy results and blood and urine tests were normal. Methacrylic Acid is an ocular toxicant in animals. Undiluted Methacrylic Acid is corrosive to the skin of rabbits and guinea pigs. Exposure as limited as 3 minutes can cause severe erythema and slight to moderate edema. Exposure from 15 minutes to 24 hours under occlusive patches can cause marked to severe discoloration, slight to severe subcutaneous hemorrhages, necrosis, ulcerations, severe erythema, edema and concave eschar. Methacrylic Acid was irritating and caused strong rubefaction and scab formation in a guinea pig maximization test at challenge concentrations from 10 to 100 percent. It was difficult to determine if the results were type IV hypersensitivity reactions or simple irritation. In three other studies, guinea pigs were not sensitized. Methacrylic Acid was not a reproductive/developmental toxicant in rats or mice. Methacrylic Acid was negative in *Salmonella typhimurium* mutagenicity tests using strains TA98, TA100, TA1535 and TA1537 both with and without metabolic activation, but was positive in a DNA-cell-binding assay. Case reports involving Methacrylic Acid often involve children. Effects from ingestion include drooling, gagging, and vomiting. Children exposed to Methacrylic Acid as a result of accidental spills caused first and second degree burns to the eyes, face, hands, arms, and chest. The Consumer Product Safety Commission has required child-resistant packaging for liquid household products containing more than 5 percent Methacrylic Acid (weight-to-volume) in a single package. Since Methacrylic Acid is an extremely corrosive chemical, a primary concern about its use as a cosmetic ingredient was the ability to limit exposure to the nail when pretreating the nail prior to application of an artificial nail extender. A videotape presentation demonstrated that a trained professional could use a small applicator brush to dab a limited volume of Methacrylic Acid only to the center of the nail, allowing the monomer liquid to diffuse down the nail without any exposure to the skin. There were no available data to demonstrate that an individual consumer could apply Methacrylic Acid and avoid inadvertent skin contact. In order to minimize any exposure to the acid, the Expert Panel concluded that nail primers containing Methacrylic Acid could be used safely by trained individuals instructed to ensure that there be no contact with the skin. The CIR Expert Panel recognized that there are no chronic inhalation toxicity data on Methacrylic Acid, but was concerned that inhalation of Methacrylic Acid could affect the respiratory tract. Since the inhalation exposure time is significantly increased in a commercial setting, the Panel was more concerned about the safety of the nail technician than the consumer. The Expert Panel concluded that the current NIOSH recommended exposure limit of 20 ppm would provide adequate protection.

INTRODUCTION

The organic acid Methacrylic Acid is not currently recognized as a cosmetic ingredient in the *International Cosmetic Ingredient Dictionary and Handbook* (Wenninger et al. 2000), nor were any uses of Methacrylic Acid reported to the Food and Drug Administration (FDA) in 1984 or 2001. The use of Methacrylic Acid, however, to pretreat nails prior to applying artificial fingernail enhancement products is well documented (Methacrylate Producers Association 1998; Consumer Product Safety Commission 1999).

Concerns regarding the safety of Methacrylic Acid in consumer products have been expressed by the Methacrylate Producers Association (1998). The Methacrylate Producers Association argued that the corrosive effects of Methacrylic Acid and the reports of injury in children accidentally exposed to Methacrylic Acid suggested this chemical was inappropriate for use in consumer products. The American Beauty Association (2001a) has argued that this ingredient can be used safely.

Relevant to this assessment is the Consumer Product Safety Commission (CPSC) rulemaking to require child-resistant packaging for liquid household products containing more than 5 percent Methacrylic Acid (weight-to-volume) in a single package. CPSC issued a proposed rule in 1998 (CPSC 1998a) and a final rule in 1999 (CPSC 1999) under the Poison Prevention Packaging Act of 1970.

The CPSC determined that child-resistant packaging is necessary to protect children under 5 years of age from serious personal injury and serious illness resulting from handling or ingesting a toxic amount of Methacrylic Acid. CPSC cited concerns about nail care products containing Methacrylic Acid, which were the only household products CPSC confirmed to contain Methacrylic Acid. This rule became effective on June 19, 2000 and applies to Methacrylic Acid preparations packaged on or after that date.

[1]Reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel. Report prepared by Torill Ann Yamarik and Alexander Escobar, former CIR staff. Correspondence to F. Alan Andersen, Director, CIR, 1101 17th St., NW, Suite 310, Washington, DC 20036, USA.

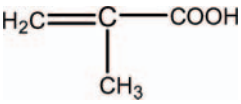

FIGURE 1
Methacrylic acid (Budavari 1989).

CHEMISTRY

Definition and Structure

Methacrylic Acid (CAS # 79-41-4) is an organic acid (see Figure 1) that polymerizes easily to form a ceramic-like mass. Its esters, methyl and polymethyl methacrylate, are used to manufacture acrylic resins and plastics (Taylor 1988).

Synonyms for Methacrylic Acid include 2-methylene alpha-acid (Registry of Toxic Effects of Chemical Substances (RTECS), 2000); 2-methylacrylic acid (RTECS 2000; Hazardous Substances Databank (HSDB), 2000); alpha-methacrylic acid (HSDB 2000; Lewis 1993a, 1993b, and 2000; Budavari 1989); 2-methylenepropionic acid (HSDB 2000; Budavari 1989); 2-methyl-2-propenoic acid (HSDB 2000); 2-methylpropionic acid (HSDB 2000; Lewis 1993b); Δ^1-methyl-1-propionic acid (Grant 1972).

Physical and Chemical Properties

The physical and chemical properties of Methacrylic Acid are presented in Table 1.

Method of Manufacture

Methacrylic Acid is derived from the reaction of acetone cyanohydrin and dilute sulfuric acid or the oxidation of isobutylene (Lewis 1993a). Methacrylic Acid is also prepared by the dehydration of alpha-hydroxyisobutyric acid, hypochlorite oxidation of methyl alpha-alkylvinyl ketone, the hydrolysis of acetone cyanohydrin followed by dehydration or oxidation of methacrolein (HSDB 2000).

Analytical Methods

Sollinger et al. (1992) used gas chromatography-mass spectrometry (GC/MS) after derivatization of Methacrylic Acid with methyl formate in the presence of a cation-exchange resin in the protonated form to determine the quantity of Methacrylic Acid in ambient air. Corkill and Crout (1982) used HPLC with a UV detector to determine the quantity of Methacrylic Acid added to blood immediately after withdrawal from the

TABLE 1
Physical and chemical properties of methacrylic acid

Property		Reference
Molecular weight	86.09	Budavari 1989; HSDB 2000; American Conference of Governmental Industrial Hygienists (ACGIH), 2000; Lewis 1993b; Assessment Technologies, Inc. 1996
Appearance/odor	Colorless crystals or colorless liquid or solid below 61°; long prisms; acrid and repulsive odor	Budavari 1989; HSDB 2000; Lewis 1993a and 1993b
Melting point	16°C	Budavari 1989; HSDB 2000; Lewis 1993a and 1993b; Assessment Technologies, Inc. 1996
Solubility	Most organic solvents, warm water, chloroform, miscible in alcohol and ether	Budavari 1989; HSDB 2000; Lewis 1993a and 1993b
Boiling point	161–163°C	HSDB 2000; Lewis 1993a and 1993b; Assessment Technologies, Inc. 1996
Density	1.0153	HSDB 2000; Grant 1972; Lewis 1993a; Assessment Technologies, Inc. 1996
pKa	4.65	HSDB 2000
pH	23 commercial products that did and did not contain Methacrylic Acid had mean pH of 3.43 $\pm$ 0.78 and 5.34 $\pm$ 2.18, respectively. The percent of Methacrylic Acid was not stated.	Woolf and Shaw 1999
Octanol/water partition coefficient	0.93	HSDB 2000; Assessment Technologies, Inc. 1996
Flashpoint	170-171°F	Lewis 1993a, 1993b, and 2000
Vapor pressure(mm Hg)	1	Assessment Technologies, Inc. 1996

patient. Prieur et al. (1995) used HPLC to determine the amount of Methacrylic Acid as an indirect food additive in packaged foods. Henriks-Eckerman and Kanerva (1997) identified the presence of Methacrylic Acid in two glue products using GC/MS.

Methacrylic Acid has been analyzed by liquid chromatography, liquid scintillation counting and nuclear magnetic resonance spectroscopy to determine its presence in blood in vitro. GC with flame ionization detection was used to detect Methacrylic Acid in blood and urine at a minimum concentration of 0.5 μg/ml. GC, thin-layer chromatography polarography (also used to determine residual monomer in the polymer), and colorimetry were also used to determine Methacrylic Acid levels in the air. Methacrylic Acid concentration was determined in industry waste water using paper chromatography. Ion chromatography with detection by UV absorption was used to detect Methacrylic Acid in the atmosphere. Methacrylic Acid was identified using mass spectra from electron impact and methane chem-ionization (HSDB 2000).

USE

Cosmetic

Methacrylic Acid is not included as a cosmetic ingredient in the *International Cosmetic Ingredient Dictionary and Handbook* (Wenninger et al. 2000). Data submitted to CIR by the Food and Drug Administration (FDA) in 2001, based on industry reports, include no uses of Methacrylic Acid. Concentration of use data submitted to the FDA in 1984 did not include Methacrylic Acid.

Nonetheless, Methacrylic Acid appears to have been used in nail cosmetics in the past and that use continues (Methacrylate Producers Association 1998). Other sources confirm this. Fisher (1973) stated that the Methacrylic Acid monomer is used in sculptured nail products. Fisher (1980) stated that the Methacrylic Acid monomer was present in one commercial nail preparation. Methacrylic Acid is a copolymer component used in nail lacquer (HSDB 2000), the principle ingredient in nail primers and is also present in at least one commercial nail preparation at a concentration of 88% (Kanerva et al. 1996). Woolf and Shaw (1998) reported that Methacrylic Acid was present in concentrations of 50–100% in 20 artificial nail primer products.

The CPSC in its rulemaking asserted that nail primers containing Methacrylic Acid are used to pretreat the nail to help nail extenders adhere (CPSC 1999). CPSC stated that concentrations of Methacrylic Acid in such primers are >50%. They indicated that most primers are labeled "for professional use only," but documented that they are readily available to consumers.

The professional use of Methacrylic Acid to prepare the nail for application of a nail extender product was demonstrated in a videotape presentation prepared by the American Beauty Association (2001c). Figure 2 presents four frames from that video.

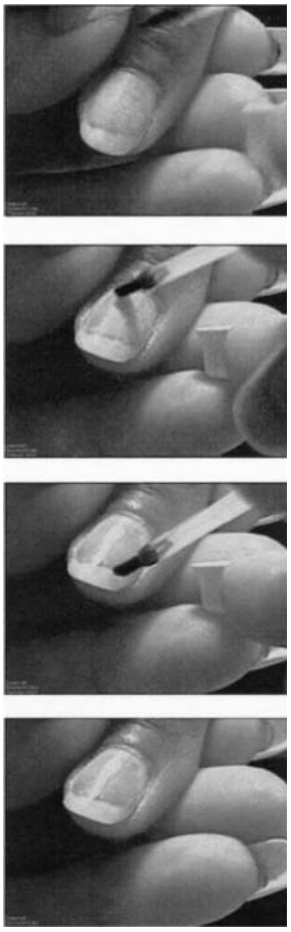

FIGURE 2
Professional application of Methacrylic Acid to one nail. Frame 1; Time 0—Nail is prepared for Methacrylic Acid application and a small amount of Methacrylic Acid is on the brush applicator. Frame 2; Time ~1 second—A small amount of Methacrylic Acid is dabbed onto center of the nail. Frame 3; Time ~2 seconds—Methacrylic Acid is brushed away from skin and allowed to diffuse toward the nail perimeter. Frame 4; Time ~3 seconds—Methacrylic Acid has been applied to nail without any skin contact.

Several key aspects of the application process were shown, including the relative ease with which a small applicator brush could be prepared with only a small quantity of Methacrylic Acid by a trained professional. The demonstration went on to show how a trained professional could touch the nail, allowing the monomer liquid to diffuse down the nail. Under those conditions, only a small quantity of Methacrylic Acid was applied to the center of the nail. There was no movement of the Methacrylic Acid to the cuticle or nail tip in the "vertical" direction and no movement in either direction to the side of the nail as shown in Figure 2. As a result, there was no exposure to the skin.

Methacrylic Acid was not listed in the Japanese Comprehensive Licensing Standards of Cosmetics by Category. Neither Methacrylic Acid nor any of its synonyms were listed in the 2000 European Economic Community Cosmetics Directive (European Economic Community 2000).

Non-Cosmetic

Methacrylic Acid is used as a polymerization component in the pharmaceutical industry to manufacture suspensions, pastes and ointments (Anonymous 1972). Methacrylic Acid copolymers are used in controlled systemic and regional drug delivery systems, including gastroresistant-enterosoluble coatings, transdermal therapeutic systems, microencapsulation, colon targeted oral drug delivery and as a drug delivery system based on a swellable polymer that responds to pH and ionic strength (Lehmann 1985; Kim and Lee 1992; Duckova et al. 1993; Bettini et al. 1995; Gordon et al. 1995; Yazici et al. 1996; Hu et al. 1997; Binder et al. 1998; Kiser et al. 1998; Wu et al. 1998; Khan et al. 1999; Negishi et al. 1999; HSDB 2000). The Methacrylic Acid content of two commercial enteric coating products contained 46-50% and 28–31% Methacrylic Acid. They dissolve at pH ranges of 4.8 to 7 and are insoluble and almost impermeable at a low pH (David et al. 1997).

Other non-cosmetic uses include the manufacture of methacrylate resins and plastics, topcoats of refrigerators and freezers and hydrogel contact lenses. Methacrylic Acid is a component of dust scrubber scale prevention agents for blast furnaces and is a constituent of enteric capsules. Methacrylic Acid is part of a mixture of compounds that make dental filling material and is an intermediate in the preparation of sodium tryopanoate (HSDB 2000). Methacrylic Acid is also used in the manufacture of shoes in Spain (Grimalt and Romaguera 1975).

Methacrylic Acid is listed by FDA for use as an indirect food additive in the Code of Federal Regulations—CFR §176.170, §177.1210, §175.300, §175.360 and §176.180 (Rothschild 1990).

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, Excretion

The CPSC has stated that Methacrylic Acid is readily absorbed through mucous membranes of the lungs and gastrointestinal tract and the skin; and is rapidly distributed to all major tissues (CPSC 1998a, 1999).

Morris (1992) stated that there are no studies which specifically address the metabolism of exogenously applied Methacrylic Acid. The available information can be derived from studies with its methyl ester, methyl methacrylate. The first step in the major metabolism pathway of methyl methacrylate is the de-esterification to Methacrylic Acid and methanol.

Male Wistar rats dosed orally with radiolabelled methyl methacrylate in corn oil revealed that endogenously generated Methacrylic Acid (0.08% of the dose) was metabolized using the pathway present in mammalian cells for the metabolism of valine, with CO_2 and water as the ultimate metabolites. See Figure 3 for the complete pathway (Bratt and Hathway 1977).

Methacrylates are metabolized via two basic pathways, hydrolysis and conjugation. Methacrylic Acid is a physiological substrate of the valine pathway and is metabolized to CO_2 by two substrates of the citric acid cycle, methylmalonyl and succinyl-CoA (Greim et al. 1995).

One proposed underlying mechanism for the toxicity of Methacrylic Acid was the nucleophilic Michael addition, the addition of a nucleophile to the activated double bond of Methacrylic Acid (Osman et al. 1988).

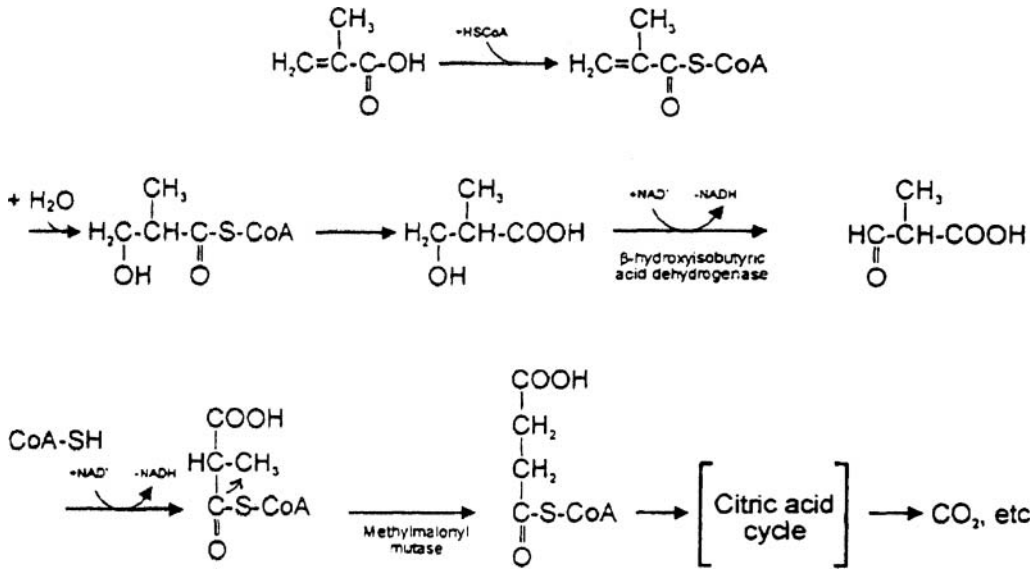

FIGURE 3
Main metabolic pathway of Methacrylic Acid in rats (Bratt and Hathway 1977).

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

In a study by Rohm and Haas (1957), a single oral dose of 2.0 ml/kg (2 g/kg) Methacrylic Acid as an aqueous solution was administered to male albino rats; severe gastric irritation was observed at necropsy.

Male albino rats (10/group) were dosed orally once with 6.5, 8.0, 10.0 or 12.0 ml/kg Methacrylic Acid. Most deaths occurred within the first 24 h of dosing, but a few ranged over the 5 day observation period. Significant weakness preceded death and at necropsy there was severe gastric irritation. The LD_{50} was reported as 2.13 ± 0.05 ml/kg (Medical College of Virginia 1957).

Haskell Laboratory (1962) dosed male rats (2/group) once orally by stomach tube with 60 to 1000, 1500, 2250 or ≥3400 mg/kg Methacrylic Acid. Two rats were dosed at 1000, 1500, 2250, and 3400 mg/kg, doses at 3400 mg/kg were with undiluted material and doses from 1000 to 2250 mg/kg were with a 10 or 30% aqueous solution. Doses below 1000 mg/kg were with a 5 or 10% aqueous solutions.

The undiluted doses were lethal at 1000 or 1500 mg/kg. The rats died in 19 h and 21 days, respectively. The minimal lethal dose for rats in the diluted series was 2250 mg/kg. Clinical signs for lethal doses above 1000 mg/kg included gasping, labored respiration, prostration and hematuria. One animal that died after a dose of 1000 mg/kg exhibited inactivity, discomfort, decreased water intake and severe weight loss. Animals that received nonlethal doses exhibited inactivity, poorly formed feces for 2–7 days, slight initial weight loss, and decreased water intake.

At necropsy, death was attributed to necrosis of the esophagus, stomach, intestines and organs adjacent to the gastrointestinal tract. Gross changes were not significant at sublethal doses. Microscopic examination of the organs revealed that Methacrylic Acid caused acute tissue destruction and degenerative changes at the primary site of contact. Microscopic changes observed at sublethal doses were less severe and dose related. The pH of undiluted and aqueous Methacrylic Acid was <1 and 2, respectively. Most of the adverse effects of the compound are attributed to its acidity. Two rats were also dosed with polymethacrylic acid; however, these observations indicated that this material was less active biologically than the monomeric acid (Haskell Laboratory 1962).

Hazleton Laboratories (1966a) dosed Sprague-Dawley rats (5/group) orally once with a neutralized mixture (29.7% active ingredients) and an unneutralized mixture (37.4% active ingredients) of Methacrylic Acid-polymethacrylic acid. The neutralized and unneutralized mixtures of Methacrylic Acid-polymethacrylic acid were administered at doses of 4.64, 10, 17.2, 21.5, 31.6 and 46.4 g/kg and 0.464, 1.0, 2.15, 4.64, 10 and 21.5 g/kg, respectively. Observations were performed immediately and at 1, 4 and 24 h and once daily thereafter for 14 days.

No toxic effects were observed at the two lowest doses of the neutralized compound. At the two highest doses transient depression, ataxia, diarrhea and weight loss were observed with death occurring sometime after 4 h. Congestion of the major organs and inflammation of the gastrointestinal (GI) tract were observed at death. No toxic effects were observed at the two lowest doses of the unneutralized compound. Transient weight loss occurred at the 2.15 g/kg dose and transient depression, labored respiration, ataxia and weight loss occurred at the three highest doses. Death occurred in all animals at 24 h at the highest dose. Congested lungs and marked inflammation of the GI tract at the highest dose was observed at death; no other major abnormalities were found at necropsy with either the neutralized or unneutralized compound. The acute oral LD_{50} for neutralized Methacrylic Acid-polymethacrylic acid was 10.5 g/kg based on the 29.7% active ingredients of this mixture. The acute oral LD_{50} for unneutralized Methacrylic Acid-polymethacrylic acid was 6.7 g/kg based on the 37.4% active ingredients of this mixture (Hazleton Laboratories 1966a).

Food and Drug Research Labs, Inc. (1977) dosed male and female Long-Evans rats (5/sex/group) orally with 10.0, 17.5, 20.0, 22.5 or 27.5 ml/kg of a compound that contained 10% Methacrylic Acid (plus 77% dicyclopentenyl methacrylate and 7.5% methanol). Animals were observed daily for 14 days. After 14 days, none of the animals in the low dose group died, 7/10 animals in the 17.5 and 20.0 ml/kg groups died and all animals in the two highest dose groups died. The following observations were found in all treated groups: ataxia, nasal discharge, salivation, diarrhea and urinary incontinence. The approximate LD_{50} was determined as 16.0 ± 1.1 ml/kg.

Greim et al. (1995) stated that the LD_{50} for rats dosed orally with Methacrylic Acid was 1320 to 2260 mg/kg.

CPSC (1998b) reported oral LD_{50} values for Methacrylic Acid in the rat, rabbit and mouse were 277 to 2260 mg/kg, 280 mg/kg and 827 to 1600 mg/kg, respectively.

According to an entry in RTECS (2000), the oral LD_{50} for Methacrylic Acid in the rat, mouse and rabbit are cited as 1060 mg/kg, 1250 mg/kg and 1200 mg/kg, respectively.

Intraperitoneal

Mir et al. (1973a) stated that the acute intraperitoneal (ip) LD_{50} for Methacrylic Acid in the mouse was 0.048 ml/kg.

Marcus et al. (1980) administered a single ip injection of 50 ml of fluid per kilogram of body weight of Methacrylic Acid to male albino mice (5/group) at concentrations of 0.6, 6, 60 or 600 ppm. Two additional groups of 2 mice/group were injected with a solution containing 60,000 or 120,000 ppm. Mice were group housed according to dose. The control group received the vehicle, cottonseed oil. Mice were observed immediately after injection and at 2, 8, 24, 48 and 72 h after injection for signs of gross toxicity. No visible signs of gross toxicity were observed at any time during the observation period in the 0.6, 6, 60 and 600 ppm groups. At 60,000 and 120,000 ppm Methacrylic Acid,

locomotion was impaired shortly after injection followed by irregular breathing patterns, convulsions and death within several minutes. These same responses were observed at 120,000 ppm and 240,000 ppm (not mentioned previously in the study). All animals died at the latter two doses.

Darvesh et al. (1999) injected (ip) albino Swiss mice (number/group not stated) of either sex with 25 ml/kg of a copolymer extract of Methacrylic Acid/2-ethylhexyl acrylate (MA/EHA) in ratios of 30:70, 40:60 or 50:50. A control group was also included in the study. Mice were examined immediately and then 4, 24, 48 and 72 h after injection. No acute toxicity was observed. The absence of toxicity was attributed to the high degree of curing and polymerization of the copolymers.

New Zealand rabbits (number/group not stated) of either sex were injected intraperitoneally with 0.2 ml/site of a copolymer extract of Methacrylic Acid/2-ethylhexyl acrylate (MA/EHA) in ratios of 30:70, 40:60 or 50:50. The rabbits received injections at five different sites of the depilated skin on each side of the spinal column. The injection sites were examined for edema, erythema and necrosis immediately and then 4, 24, 48 and 72 h after injection. No biological reactivity was observed. The absence of toxicity was attributed to the high degree of curing and excellent polymerization of the copolymers (Darvesh et al. 1999).

The ip LD_{50} in the mouse and the ip LD_{50} in the dog were given as 48 mg/kg and 95,200 ml/kg, respectively (RTECS 2000).

Dermal

The dermal LD_{50} for Methacrylic Acid in the rabbit was cited as 500 to 1000 mg/kg by Greim et al. (1995), 1243 mg/kg by CPSC (1998b), and 500 mg/kg by RTECS (2000). The LD_{50} when Methacrylic Acid was applied to guinea pig skin was cited as 1 g/kg (RTECS 2000).

Inhalation

Haskell Laboratory (1993a) assessed the sensory irritation potential of Methacrylic Acid using the method of Alarie (1981). Male Swiss Webster mice (4/group) were exposed by inhalation to 4900, 9400, 18,000, 27,000 or 42,000 ppm Methacrylic Acid for 30 min in an inhalation chamber. Most of the animals experienced a 2.5 to 3.7% weight loss after exposure to Methacrylic Acid (the time period was not stated). Respiratory rates in breaths per minute were recorded every 15 seconds during exposure and the 10 min post exposure period. Mice exposed to concentrations of $\geq$18,000 ppm had ocular discharge during or following exposures. Mice exposed to the lowest concentration tested had sporadic breathing patterns of mild sensory irritation for the first few minutes.

Sensory irritation was moderate to severe and began almost immediately after exposure and persisted throughout the 30 min exposure time and returned to normal when exposure was discontinued, at concentrations of $\geq$9,400 ppm. Decreased respiration was observed at all other exposures with increased respiratory frequency at termination of exposure. A dose-response relationship was observed between Methacrylic Acid concentration and percent decrease in respiratory rate. The concentration that caused a 50% decrease in respiratory rate (RD_{50}) was 22,000 ppm. Methacrylic Acid was considered a sensory irritant and had a low potential for causing upper respiratory tract irritation (Haskell Laboratory 1993a).

In another study by Haskell Laboratory (1993b), groups of five male and five female rats were exposed nose only via inhalation to 4.3 ± 0.27, 5.9 ± 0.91, 7.3 ± 0.57 or 8.2 ± 1.9 mg/l Methacrylic Acid for a single four hour period. No control group was included in the study. None of the animals died in the lowest concentration group, one female died in the 5.9 ± 0.91 mg/l concentration group, 2 males and females each died in the 7.3 ± 0.57 mg/l group and all animals died in the highest concentration group.

Clinical observations observed in at least one animal of each group (except the high concentration group) included alopecia, colored discharge from nose and eyes, lethargy, lung noise, irregular respiration and gasping. Males and female rats in all groups initially lost weight after exposure to Methacrylic Acid, but then gained weight and by day 15 weighed more than at start of the study. The four-hour median lethal concentration for Methacrylic Acid was 7.1 mg/l (Haskell Laboratory 1993b).

Kelly (1993) demonstrated from several single and repeat exposure inhalation studies that Methacrylic Acid is an irritant to the respiratory tract. Rats (5/sex/group) were exposed to 4.3, 5.9, 7.3 and 8.2 mg (1200, 1650, 2040 and 2290 ppm) Methacrylic Acid for 4 h. Clinical signs included marked irritation to the respiratory tract, which included nasal discharge, gasping, irregular respiration and lung noise, as well as corneal opacities.

Greim et al. (1995) stated that the 4 h inhalation exposure LC_{50} for Methacrylic Acid in rats was 7100 mg/m^3.

Morris and Frederick (1995) determined the uptake of 450 mg/l (133 ppm) Methacrylic Acid vapor in the upper respiratory tract (URT) of F344 rats using the unidirectional flow technique. URT exiting air concentrations achieved a plateau between 30 and 60 min of exposure. The mean of four animals resulted in a deposition efficiency of 95% calculated from values obtained during the 30 and 60 min time period. The average absolute deposition rate was 86 mg/min. Nasal lavage albumin and protein concentration, and nasal tissue NPSH levels were not altered by treatment with Methacrylic Acid.

In an assessment of Methacrylic Acid, the European Centre for Ecotoxicity and Toxicology of Chemicals (ECETOC) reported the results of a study that examined Methacrylic Acid vapor deposition in surgically isolated URT of anesthetized male F344 rats (ECETOC 1996). Rats were exposed to 70, 450, or 1385 mg/l (21, 133, 410 ppm) Methacrylic Acid using a unidirectional respiratory flow technique for 60 min. Control animals were exposed to humidified air. Deposition rates, from 30 to 60 min, averaged 13, 87 and 255 mg/min in the low, medium and high concentration groups, respectively. This represented

about 90% of the dose administered. No significant effect on nasal lavage albumin and protein concentration, and nasal tissue non-protein sulfhydryl levels (NPSH) were observed, indicating no irritation or direct reactivity with nucleophiles at the highest concentration of Methacrylic Acid. The investigators concluded that Methacrylic Acid will initially deposit in the mucous lining layer of the URT.

The LC_{50} values for inhalation exposure to Methacrylic Acid were reported as 1350 ppm/4 h for the rat, 3657 ppm for the mouse and 2522 ppm/1 hour for the rabbit (CPSC 1998b).

Intravenous

Male mongrel dogs (3/group) were anesthetized and given 112, 224, 562, or 1124 mM Methacrylic Acid intravenously (iv). Blood pressure, heart rate, electrocardiogram and respiration were measured. The highest dose was rapidly fatal to the dogs. Following injection of Methacrylic Acid, at all doses, an abrupt decrease in systemic pressure (36 to 79%) occurred which lasted for 2 to 4 min. The pressure increased slowly and achieved a plateau higher than control values for 10 to 15 min. Heart rate decreased at all doses compared to control values by 1 to 22%. Respiratory rate increased at all doses of Methacrylic Acid, the percent change ranging from 45 to 158%. Cardiac responses included the following: a dose-related response in which there was bradycardia, a reduced rate of impulse transmission through the A-V node, and possible acute cardiac ischemia. Higher doses produced premature ventricular contractions and incomplete A-V block (Mir et al. 1974).

Intravenous administration of 0.1 ml 100% Methacrylic Acid was lethal to dogs (CPSC 1998b).

In Vitro

Mir et al. (1973a) perfused isolated rabbit hearts in vitro with 1:100,000, 1:10,000 or 1:1000 Methacrylic Acid in Locke's solution. Methacrylic Acid was tested five times but the number of hearts used was not stated. The perfusion procedure used maintained a constant hydrostatic pressure. Each heart was perfused for a 20 min equilibration period and the test was conducted over the following 90 min. The test solution was perfused for one minute after cardiac activity had stabilized and then normal Locke's solution was perfused to permit recovery of the heart. The effect was considered irreversible if cardiac activity did not return significantly to control levels within 30 to 35 min of perfusion with normal Locke's solution.

Methacrylic Acid produced an irreversible effect (cardiac activity did not return significantly toward control levels within 30 to 35 minutes) on the isolated heart at all concentrations. The lowest concentration (1:1000) reduced the coronary flow, cardiac rate, and force of contraction by 3.8, 6.9 and 19.4% respectively. The 1:10,000 concentration reduced coronary flow, cardiac rate, and force of contraction by 5.0, 49.0 and 56.1%, respectively. The highest concentration reduced cardiac rate, force of contraction and coronary flow all by 100% because of cardiac standstill. All of the data are statistically significant with the exception of coronary flow at the 1:100,000 and 1:10,000 concentrations (Mir et al. 1973a).

Mir et al. (1973b) exposed newly isolated guinea pig ileum of either sex to Methacrylic Acid at concentrations of 1:10,000, 1:5000 or 1:2500. The number of samples used was not specified. The spontaneous activity of the intestine to Tyrode's solution was recorded and then Methacrylic Acid was added to the bath and the response recorded. Methacrylic Acid produced a concentration-dependent depressant effect upon spontaneous motility of the isolated guinea pig ileum. Additionally, a concentration-dependent antagonism of the neurogenic and myogenic stimulant effects of acetylcholine (1:10,000,000) and barium chloride (3:100,000) was observed with isolated ileum. The molar ratio of Methacrylic Acid required to produce a 50% inhibition of the acetylcholine and barium chloride responses was 5750 and 22.0, respectively. These data suggest that the inhibitory effects of Methacrylic Acid upon isolated guinea pig ileum are myogenic in origin. These effects could be terminated by washing with fresh Tyrode's solution.

Short-Term Toxicity

Oral

Hazleton Laboratories (1966b) conducted a study in which male and female Beagle dogs (3/sex/group) were orally administered a neutralized mixture of glacial Methacrylic Acid and Polymethacrylic Acid. The neutralized mixture was 23 grams of Methacrylic Acid, 100 grams of Polymethacrylic Acid, and 32 grams of 50% NaOH. The dose of the active ingredients was 0, 250, 500 and 1000 mg/kg/day daily for 90 days. The six control dogs were normal throughout the study. The 250 mg/kg group had normal behavior and appearance while on study. No signs of treatment effect were observed in any of the animals and normal body weights were maintained. The 500 mg/kg group had normal behavior and appearance; however, slight weight loss was recorded in 5/6 dogs. The high dose group had an increased frequency of emesis and diarrhea. Hematology, biochemistry and urine analyses were normal for all test animals. At gross necropsy there were no compound related organ changes. Microscopic examination did not indicate any alterations attributable to oral administration of a mixture of glacial Methacrylic Acid and polymethacrylic acid to Beagle dogs. The GI mucosa of high dose animals did not have any compound related alterations (Hazleton Laboratories 1966b).

Hazleton Laboratories (1966c) dosed albino rats (10/sex/group) orally with a mixture of 0.3, 0.7 or 1.5% glacial Methacrylic Acid and polymethacrylic acid in drinking water for 90 days. The mixture was 50% glacial Methacrylic Acid and 50% Polymethacrylic acid by weight. The polymethacrylic acid was a polymer as 23% polymethacrylic acid in water. The test mixture was reportedly 37.4% active ingredients but the author did not identify the active ingredients. A control group was also included. Calculations based on the activity of the mixture determined the concentrations delivered as 1.237,

2.886 and 6.185 mg active ingredients/ml water. At 30 and 90 days hematological studies and complete urine analyses were performed on five animals/sex/group.

No treatment-related effects were noted with regard to physical appearance, behavior, growth and food consumption in the test animals compared to controls. Water consumption was significantly decreased for the intermediate and high dose males, probably as a result of a decreased palatability because drinking water was the vehicle for the compound. No deaths occurred among the test or control animals. Hematological values were generally within normal limits; however, the total red cell count at termination was decreased in control and test groups and was significantly decreased for the high dose females. Biochemical and urine analyses for the test groups were comparable to control values. Gross and microscopic examination of tissues reported no consistent compound related changes in the organs of test animals (Hazleton Laboratories 1966c).

In a study by Rohm and Haas (1986), Methacrylic Acid was orally administered to mice. Groups of eight male ICR mice received doses of 100 ml of 4.8% Methacrylic Acid in water or 4.8, 9.6 or 19.2% Methacrylic Acid in acetone three times a week for three weeks. No treatment related clinical signs or changes in body weights were observed in the treated groups.

Subcutaneous

The implantation test was performed on New Zealand albino rabbits by aseptically implanting four copolymer strips of Methacrylic Acid/2-ethylhexyl acrylate (MA/EHA) in ratios at 30:70, 40:60 or 50:50. The strips measured 10 mm × 1 mm and were implanted on one side of the spine in the paravertebral muscle and two standard strips were implanted on the other side in a similar manner. The animals were killed 120 h later and the implant sites were examined macroscopically for hemorrhage, necrosis, discoloration, infection and encapsulation. No biological reactivity was observed. The absence of toxicity was attributed to the high degree of curing and polymerization of the copolymers (Darvesh et al. 1999).

Inhalation

Gage (1970) maintained Alderley Park rats in an exposure chamber for up to 6 h. Initial experiments used concentrations selected to produce acute effects after short exposures. Thereafter, the exposure period was extended and the concentration decreased until the animals survived 6 h exposures, 5 days/week for up to four weeks. Urine was collected overnight after the last day of exposure and on the following day the rats were killed. The experiments were performed until a concentration was reached that produced no toxic effects. At two month intervals, control rats were maintained in the chamber consistent with the exposure period.

Rats (2/sex) were exposed to a saturated solution of Methacrylic Acid for five 5 h exposure periods at 4.5 mg/l, 1300 ppm. Nose and eye irritation and weight loss were observed. Blood, urine tests and necropsy were normal. In another study, rats (4/sex) were exposed to 300 ppm Methacrylic Acid by injecting the liquid at a known rate (data not provided) into a metered stream of air by means of a controlled fluid-feed atomizer. The rats received twenty 6 h exposures of Methacrylic Acid. No toxic signs were observed and necropsy was normal. The investigators noted questionable slight renal congestion (Gage 1970).

The Chemical Industry Institute of Toxicology (CIIT) conducted a study in which male and female Sprague-Dawley rats, F344/N rats, and B6C3F1 mice (5/sex/species/group) were exposed to atmospheres that contained 0, 100, 500 or 1000 ppm Methacrylic Acid for 2 weeks, 6 h/day, 5 days/week (CIIT,1983). In general, no sex associated differences in sensitivity to the effects of Methacrylic Acid were observed. F344/N rats and B6C3F1 mice were more sensitive to the effects of Methacrylic Acid than Sprague-Dawley rats.

At the lowest concentration, no significant effects on mortality, body weight gain, clinical observations or organ weights were observed for animals in any of the three strains tested. At 100 ppm, treatment related microscopic changes in the nasal mucosa were observed in Sprague-Dawley and F344/N rats. F344/N rats had minimal to mild hyperplasia and acute inflammation of the stratified squamous epithelium of the nose and mild to minimal goblet cell hyperplasia in the respiratory epithelium lining the medial septum. In Sprague-Dawley rats, microscopic lesions were moderate hyperplasia of the stratified squamous epithelium, squamous metaplasia of the respiratory epithelium and mild to moderate goblet cell hyperplasia. B6C3F1 mice did not have microscopic changes at 100 ppm.

At 500 ppm, body weight gain and organ weights were decreased for F344/N rats and B6C3F1 mice. Clinical observations for B6C3F1 mice and F344/N rats included irregular breathing, yellow/brown stained fur, lethargy, muscle tremors, alopecia, crusty muzzle, red stained fur and crusty nose. Additionally, F344/N rats had crusty and closed eyes, while B6C3F1 mice had some squinting and ocular opacity. Body weight gain and organ weights of Sprague-Dawley rats were not statistically different from untreated controls; however, they did have clinical observations similar to the other mice and F344/N rats at this concentration.

Microscopic lesions in the nasal turbinates were observed in all strains at 500 ppm. Observations for B6C3F1 mice included slight acute necrosis with associated inflammation of the nasal mucosa; for F344/N rats, mild necrosis of nasal mucosa accompanied by acute inflammation, early squamous metaplasia of the respiratory epithelium and mild hyperkeratosis of the eyelid; and for Sprague-Dawley rats, hyperplasia and metaplasia of nasal mucosa in the respiratory epithelium and focal areas of squamous metaplasia.

The B6C3F1 mice exposed to 1000 ppm did not survive past the fourth day and the F344/N rats exposed to this level did not survive past the sixth day of the experiment.

Microscopic changes in B6C3F1 mice at the 1000 ppm exposure included severe necrosis of the mucosa and submucosa

of the nasal turbinates and minimally thickened alveolar septa. Microscopic changes for F344/N rats included acute necrosis of the nasal mucosa and submucosa, hyperplastic or metaplastic changes (one animal) and mild keratitis as indicated by small numbers of neutrophils and edema (all animals).

Sprague-Dawley rats in the 1000 ppm group had decreased body weight gain and organ weights. In addition to the same clinical signs observed in the mid-dose group, the high concentration group had lethargy, gasping, ocular opacity, poor coat quality, irritability, sneezing, prostration, swollen abdomen, and crusty/scabbed front toes. Loss of blinking response was also observed. Microscopic lesions were observed in the eyes, digits, tails, stomachs and nasal turbinates. These consisted of mild keratitis and iritis, areas of intraepidermal vesicle formation and mild neutrophilic exocytosis in skin of the forepaw digits and tip of the tail. The vesicles were located at the junction of the stratum corneum and stratum granulosum. Focal necrosis and moderate acute dermatitis were associated with these changes occasionally. Lesions in the nasal turbinates, similar to those observed in Sprague-Dawley rats at the mid-dose level, were present, but were more severe (CIIT 1983).

Subchronic Toxicity

Inhalation

In a 13 week inhalation study (daily hours of exposure not stated), rats and mice had local irritation to the upper airways at concentrations of 70.4 to 1056 mg/m^3. The NOEL was not established for rats, but for mice it was established at 352 mg/m^3 (Greim et al. 1995).

The CIIT conducted a study in which male and female Sprague-Dawley rats, F344/N rats, and B6C3F1 mice (20/sex/species/group) were exposed to atmospheres that contained 0, 20, 100 or 300 ppm Methacrylic Acid for 90 days, 6 h/day, 5 days/week (CIIT,1983). Test chambers were sampled once every two hours. Ten animals of each sex, species, strain, group were killed on the day following the fourth exposure for microscopic examination. The remaining animals were killed following 90 days of exposure.

At interim evaluation, a statistically significant decrease in body weight was observed for male and female mice and male and female F344/N rats exposed at the 300 ppm concentration compared to controls. This finding persisted only during the first eight weeks for male and female mice. F344/N male rats of the high concentration group had statistically significant decreased body weights at weeks 3, 4 and 6 to 13. F344/N female rats had no significant differences in body weights from untreated controls.

Sprague-Dawley rats had decreased body weights that were not statistically significant at the 300 ppm exposure level. Sprague-Dawley males and F344/N male and female rats exposed to 300 ppm Methacrylic Acid had sporadic statistically significant decreased food consumption compared to controls at interim evaluation. No significant differences in final food consumption occurred for mice or Sprague-Dawley rats. High dose F344/N male rats had significantly decreased final food consumption that corresponded to their decreased body weights. No significant differences from controls were observed with respect to hematology, serum chemistry or urinalysis in any of the strains/sexes studied.

At interim evaluation, F344/N rats had solitary or multiple red discolorations of the lungs. No other gross lesions were observed at this time. At study termination, male Sprague-Dawley rats had discolorations of the liver and Sprague-Dawley rats of both sexes had discoloration of the lungs. F344/N rats had no significant gross observations.

A majority of F344/N rats in the high dose group had acute inflammation of the nasal mucosa at interim evaluation. Many of these animals also had focal ulceration of the mucosa, goblet cell hyperplasia and exudate present in the lumen of the nasal cavity. Animals killed after 90 days had more severe inflammation in the nasal mucosa.

At interim evaluation, all groups of male Sprague-Dawley rats had twice the incidence of small, subpleural accumulations of lymphocytes located in the periphery of the lung compared to controls. Both sexes had an increased incidence of acute rhinitis in the mucosa of the nasal turbinate compared to the control animals. High dose animals had the most severe inflammation. At study termination, treated male and female Sprague-Dawley rats had a higher incidence of inflammation, exudate and epithelial hyperplasia of the nasal turbinates compared to controls. An increased incidence of lymphocytic hyperplasia in the mandibular lymph nodes of high dose rats of both strains was the predominant change in tissues outside the respiratory tract.

At interim evaluation, male and female mice had acute inflammation and necrosis with exudate present in the lumen of the nasal cavity, posteriorly. At study termination, only high dose male and female mice had acute rhinitis, ulceration and exudate in the nasal turbinates. Eosinophilic globules were found in cells of the mucosa in most high dose male and female mice and a few mid-dose mice.

The only treatment related change observed outside the respiratory tract was the development of cytomegaly of renal tubular epithelium in over half the high dose male mice (CIIT 1983).

Ocular Irritation

A single instillation of 0.1 ml of Methacrylic Acid into the eye of six albino rabbits resulted in severe corneal, iridial and conjunctival effects that persisted until the study was discontinued on day 7 (Rohm and Haas 1973a).

In an acute range finding study, three male New Zealand White rabbits had 0.1 ml of a compound, containing 2 to 5% Methacrylic Acid plus 88% 2-methyl-2-propenoic acid, 2-hydroxyethyl ester and 1.5% 2-propenoic acid, 2-methyl-,1,2-ethanediyl ester, applied to the conjunctival sac. Observations were made at 4, 24, 48, 72, 96 h and 7, 14 and 21 days. This

compound was corrosive to the eyes of rabbits (Rohm and Haas 1981).

In a one hour inhalation study, exposure of adult albino rats to 204 mg Methacrylic Acid (56, 916 ppm) resulted in a corrosive effect to the eyes (Rohm and Haas 1973b). In another 4 h inhalation study corneal opacity was seen in 1/10 rats exposed to 5.9 mg (1646 ppm) Methacrylic Acid. In this same study, corneal opacity and ocular discharge were observed in 1/10 animals following exposure to 8.2 mg (2037 ppm) Methacrylic Acid (Kelly 1993).

In a study reported by ECETOC (1996), Methacrylic Acid (0.1 ml) was instilled into one eye each of two New Zealand White rabbits. The lids were held together for 1 second and then the eyes were rinsed with 20 ml of tepid water four seconds after instillation. At 10 seconds, the eyes were examined using an ophthalmoscope. Corneal injury was also assessed. Methacrylic Acid caused marked ocular injury and severe corneal opacity.

Dermal Irritation

In a study by Rohm and Haas (1956), gauze patches with Methacrylic Acid (dose not specified) were applied to shaved rabbit skin for 15 or 30 min or 24 h. Severe erythema, discoloration, slight to severe subcutaneous hemorrhage and slight lichenification was observed after 15 and 30 min. One of two animals had moderate erythema while the other had severe discoloration, edema and ulcerations after 24 h. Unoccluded application of Methacrylic Acid resulted in marked discoloration, slight subcutaneous hemorrhages, edema and eschar formation 24 h and 5 days after the initial application.

Gauze pads containing Methacrylic Acid (pH 2, dose not stated) were applied to the shaved backs of eleven albino rabbits. The patches contacted the skin for 15 and 30 min and 24 h. The skin sites were examined for evidence of erythema, ulceration and edema 24 h and 5 days after the initial application of Methacrylic Acid. Methacrylic Acid was also painted on 1 square inch of skin of the backs of the rabbits. The treated areas were left uncovered and irritation was determined 24 h and 5 days after the initial application. Methacrylic Acid produced marked discoloration, slight subcutaneous hemorrhages, edema and eschar formation at all time points after the initial application (Haskell Laboratory 1977).

Severe irritation was reported in guinea pigs following dermal application of 1.5 or 10 ml of Methacrylic Acid under occlusive patches for 24 h. Daily application to the clipped backs of guinea pigs for 10 days produced necrosis (Eastman Kodak 1979).

In a range-finding study, 0.5 ml of a compound that contained 2 to 5% Methacrylic Acid plus 88% 2-methyl-2-propenoic acid, 2-hydroxyethyl ester and 1.5% 2-propenoic acid, 2-methyl-,1,2-ethanediyl ester was applied to the intact and abraded shaved skin of three male New Zealand White rabbits. The compound was applied under occlusive conditions for 24 h. The animals were observed at 24 and 72 h and 7 days. The PIS, based on the 24 and 72 h observations, was 1.3. The test substance was considered a slight irritant, primarily to damaged skin (Rohm and Haas 1981).

Rohm and Haas (1986) reported that no skin irritation or pathological changes were observed when a 4.8% aqueous solution of Methacrylic Acid or its sodium salt was applied three times weekly for three weeks to the shaved backs of groups of eight male ICR mice. The application of Methacrylic Acid in diluted acetone (4.8, 9.6 and 19.2%) three times weekly resulted in concentration-related irritation. Gross lesions observed in the skin of all treated animals included desiccation, thickening, eschar formation, reddening, firmness and hairlessness. Microscopic lesions included acanthosis, hyperparakeratosis, ulceration, epithelial necrosis and subacute dermatitis. Dermal fibrosis and keratin inclusions were seen in the skin of mice treated at the two higher doses. Subacute subcutaneous inflammation and myositis in the underlying tissues was observed in the high dose animals.

ECETOC (1996) reported a study in which Methacrylic Acid was applied to the intact and abraded skin of four New Zealand White rabbits for 24 h under occlusive conditions. Reactions were observed upon removal of the patch and again at 72 h using the Draize system. Marked dermal injury was observed, with severe erythema, edema and necrosis observed in all animals at all time points. The maximum Primary Irritation Score (PIS) was 8.0.

ECETOC (1996) also reported that application of 0.5 ml Methacrylic Acid to intact and abraded skin of 6 rabbits for 2 h resulted in severe erythema and edema at 24 and 72 h after application on both skin treatments.

The Rohm Haas Company (1997) exposed male New Zealand rabbits to 0.5 ml of undiluted Methacrylic Acid for 3 min (2 rabbits), 1 h (2 rabbits), or 4 h (1 rabbit). The latter two exposure periods were semi-occluded while the three minute site was left non-occluded.

Approximately 24 h prior to application of Methacrylic Acid, the trunk between the flank and shoulders was shaved. Methacrylic Acid was applied onto a 1 inch square gauze-lined adhesive bandage which was then applied to the shaved, intact skin. Sites were washed with tap water or soap (3 min or 1 h) which did not affect the outcome of the study. Skin irritation was evaluated at 1, 24, 48, and 72 h and at 7 and/or 14 days after patch removal. Irritation was evaluated according to the criteria of Draize.

No mortalities or clinical signs of systemic toxicity were observed during the study. On all treated sites, skin irritation in the form of concave eschar was observed which is indicative of corrosion. The 4 h exposure site had severe erythema and very slight to severe edema at all observation periods. The 3 min and 1 h sites had severe erythema and very slight to moderate edema at all observation periods. One of the rabbits treated for 1 h with Methacrylic Acid was euthanized after 24 h due to severe damage to the dermis in the form of exposed, reddened subcutaneous muscle layer. One of the 3 min exposure rabbits was euthanized after day 7 when irreversible damage was observed in the form of

concave eschar, erosion and ulceration. Methacrylic Acid was categorized as corrosive to the skin following a 4 h exposure period (Rohm and Haas Company 1997).

A study in mice reported by the CPSC (1998b) suggested that 4.8% Methacrylic Acid would act as a mild irritant to humans, even when in solution with acetone. Doubling the concentration to 9.6% Methacrylic Acid caused severe irritation equivalent to second degree burns to the skin. A concentration of 19.2% resulted in visible destruction to the skin epithelium and injury to all layers of the skin bordering on corrosive.

Darvesh et al. (1999) performed a dermal irritation patch test with the same MA/EHA copolymer extracts. Copolymer films and standard films measuring 1 cm^2 were placed on the depilated skin of each side of the spine at five different sites of New Zealand rabbits. The films were covered with a gauze patch and secured with adhesive tape. They were removed 24 h later. The application sites were examined for erythema, edema and necrosis immediately and again at 4, 24, 48 and 72 h after the removal of the films. No biological reactivity was observed and the absence of toxicity was attributed to the high degree of curing and polymerization of the copolymers.

Dermal Sensitization

The BP Group Occup. Health Center (1981) conducted a dermal sensitization study. Two weeks after topical induction with hydroxyethyl methacrylate and Methacrylic Acid (dose not stated), guinea pigs were challenged for the first time. Methacrylic Acid test and control groups were challenged with 2.5 and 5% solutions of Methacrylic Acid. One week after the first challenge, the Methacrylic Acid test and control groups were rechallenged with 5 and 10% Methacrylic Acid. Additionally, hydroxyethyl methacrylate test and control groups were rechallenged with 5 and 10% Methacrylic Acid. Skin reactions were evaluated at 48 and 72 h after both challenge phases.

Eight animals treated with hydroxyethyl methacrylate (total number not stated) reacted to the challenge with 10% Methacrylic Acid. However, some evidence of irritancy in the control animals was observed at this concentration. The incidence of skin reactions was greater in the control group than the test group (Methacrylic Acid). The authors stated that the results did not support the theory that the free Methacrylic Acid content of hydroxyethyl methacrylate is responsible for its sensitizing potential; however, individuals sensitized to hydroxyethyl methacrylate might cross-react when exposed to Methacrylic Acid. No additional information was available (BP Group Occup. Health Center 1981).

Five guinea pigs were not sensitized to Methacrylic Acid when induced by injection into the footpad and challenged one week later by a patch test on the back. No additional information was available (Clayton and Clayton 1982).

Parker and Turk (1983) injected the footpads of female Hartley guinea pigs four times with an emulsion of 2 mg/ml Methacrylic Acid in ethanol:saline (1:4) in Freund's complete adjuvant (FCA). An additional 0.1 ml of the emulsion was injected into the nape of the neck. The animals received a total of 1 mg of Methacrylic Acid. Seven days later, and weekly thereafter for up to 12 weeks, 0.02 ml of a solution in acetone:olive oil (4:1) was dropped onto the shaved flank of the animals, using a different site for each application. Methacrylic Acid did not induce contact sensitization using this protocol.

In a study by Moore (1993) the potential for Methacrylic Acid to induce delayed contact hypersensitivity in groups of 20 male Hartley guinea pigs was assessed using the Buehler method. A sample (0.4 ml) of a 20% solution of Methacrylic Acid in deionized water was applied to the shaved left flank of the animals for 6 h using occlusive dressing. A 15% solution was used for subsequent applications (weekly for 2 weeks) since eschar formation was observed within 72 h of applying the 20% solution. The site was scored for irritation after the dressing was removed from the application site. The animals were not treated for 14 days and then were challenged by application to the clipped right flank using the same procedure. The site was examined for dermal irritation and/or signs of sensitization about 24, 48 and 72 h after removal of the challenge application.

No signs of sensitization were observed following the challenge. Negative and positive control groups were included in the study and gave the expected responses (Moore 1993).

Greim et al. (1995) stated that sensitization tests for Methacrylic Acid were negative, but provided no study details.

Katsuno et al. (1996) performed a guinea pig maximization test using female Hartley guinea pigs (5 animals/group). Sensitization concentrations for Methacrylic Acid were 0.02, 0.1, 0.2, 0.5, 1.0 and 5.0%. Dichloronitrobenzene and distilled water were used as the positive and negative control, respectively. Induction was performed in two stages. In the first stage, 50 μl of Methacrylic Acid was injected into a shaved area on the back, near the neck. An aqueous mixture of Freund's complete adjuvant (FCA), Methacrylic Acid or Methacrylic Acid plus FCA was injected at two sites. The guinea pigs were pretreated with 10% sodium lauryl sulfate in petrolatum for 24 h during the second stage of induction which occurred two weeks later. Next, a filter paper patch soaked in 200 μl of the test substance was placed on the shaved back of the guinea pig. The patch remained in place for 48 h. Methacrylic Acid, 100 μl undiluted, was applied topically on day 22 as the challenge test. The hair on the flank was shaved and Methacrylic Acid was applied to the skin by the closed-patch testing technique. The challenge site was evaluated 24 h after removal of the patch. The results from the sensitization experiments determined that a 0.2% concentration of Methacrylic Acid was to be used in the elicitation test. The challenge concentrations were 10, 25, 50 and 100% (5 animals/group) and were applied to four points on each animal. Skin reactions were evaluated after 24 and 48 h.

All concentrations of Methacrylic Acid caused strong rubefaction and scab formation. The investigators had difficulty determining if these were type IV hypersensitivity reactions or simple irritation. All guinea pigs had significant responses, 7/7

on the scale used. Elicitation tests indicated that as the concentration of Methacrylic Acid increased, the response increased. Methacrylic Acid produced rubefaction at all concentrations tested (Katsuno et al. 1996).

Cytotoxicity

Darvesh et al. (1999) conducted a red blood cell hemolysis test using rabbit blood. Five grams of the copolymer MA/EHA in ratios of 30:70, 40:60 or 50:50 and standard film was added to 0.2 ml of blood. Samples were incubated at 37°C for 60 min. A positive control was included. Under experimental conditions, less than 5% hemolysis is considered insignificant. In this test, hemolysis was <2%, which indicated a lack of hemolytic activity. The absence of effect was attributed to the high degree of curing and polymerization of the copolymers.

These authors also conducted other in vitro tests with the same MA/EHA copolymer. In the agar diffusion test, 2% agar was placed on top of the monolayer of L-929 mammalian fibroblast cell line cells and two pieces of copolymer film were placed on the agar surface. The monolayer was examined microscopically 24 h later. The direct contact test was also performed, in which one piece of copolymer film and one pieced of standard film were placed directly on top of the monolayer and microscopically examined after 24 h and the elution test, in which 2 g of copolymer/ml of tissue culture medium was extracted for 24 h. The medium in petri dishes having a monolayer was replaced by the extract and the monolayer was examined microscopically after 48 h.

No biological reactivity was observed in either test. The absence of toxicity was attributed to the high degree of curing and polymerization of the copolymers (Darvesh et al. 1999).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

The 90-day CIIT (1983) inhalation study in rats and mice (see Inhalation section) reported no gross or microscopic changes in the oviducts, ovaries, uteri and mammary glands of females or in the testes, epididymes, seminal vesicles, mammary glands and prostate of males in the high concentration group. No indication of toxic effects on the reproductive systems were observed.

Rogers et al. (1986) exposed ten day rat embryos in vitro for 24 to 26 h to 0, 103 μg/ml, 129 μg/ml, 155 μg/ml, and 181 μg/ml of Methacrylic Acid. The number of embryos exposed at each level were 65, 14, 23, 50, and 51, respectively.

At 129, 155 and 181 μg/ml a significantly increased percentage of malformations were observed compared to controls. At these same concentrations, significant decreases in percent viable, crown-rump length, number of somites and protein content per embryo were observed. Methacrylic Acid treated embryos also had abnormal development characterized by abnormal neurulation, dilated neural tube, open neural tube and/or failure of neural tube to expand. Some embryos had hypoplasia of the prosencephalon, generalized edema, malpositioned heart, abnormal flexion and dilated otic vesicles. An increase in Methacrylic Acid induced cell death of the central nervous system and adjacent mesenchyme was also observed (Rogers et al. 1986).

Saillenfait et al. (1999) exposed female Sprague-Dawley rats (22–23/group) to 50, 100, 200 or 300 ppm Methacrylic Acid via inhalation 6 h/day on days 6 to 20 of gestation. Day 0 of gestation was the day vaginal smears were confirmed sperm-positive. Control animals were exposed concurrently to filtered room air in a chamber identical to the treatment groups. Exposure occurred in 200 L glass/stainless steel inhalation chambers with an adjustable laminar air flow of 6 to 20 m^3/h. Food and water were withheld during exposures. Concentrations of Methacrylic Acid were determined three times, at regular intervals, during each 6 h exposure period. Food consumption was measured for the gestation day intervals 6 to 13 and 13 to 21. Maternal body weight was recorded on gestation days 0, 6, 13 and 21 and females were killed on day 21.

All animals survived the exposure period. Significantly decreased maternal weight gain and food consumption were observed throughout the exposure period to the highest concentration of Methacrylic Acid. Absolute weight gain was significantly reduced at the 300 ppm exposure level.

No significant changes in the number of implantations, live fetuses, incidence of non-live implants and resorptions, or in fetal body weights were observed across the groups. Treatment-related effects were not observed. The incidences of fetuses with external, visceral and skeletal variations did not differ between the control and treated groups (Saillenfait et al. 1999).

GENOTOXICITY

Kubinski et al. (1981) performed a DNA-cell-binding (DCB) assay in which 50 μM Methacrylic Acid was combined with *E. coli* cells, 1 μg of radioactive DNA, lysozome and liver extract for 30 and 60 min. The lysozome and liver extract were added in combination and separately. The positive control used methanesulfonate and the negative control used only cells and DNA. A positive outcome was measured by binding (the formation of complexes between nucleic acids and proteins and other nucleic acid molecules in the presence of active carcinogens) of more than 1% over the controls. Methacrylic Acid had positive test results. The percent binding was not stated.

Querens et al. (1981) reported that Methacrylic Acid did not show any mutagenic activity in an Ames mutagenicity assay.

Mutagenicity tests were conducted on Methacrylic Acid using *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537. Positive and negative controls were used. Tests were carried out in the presence and absence of S9 activation (from rats and hamsters induced with Aroclor 1254). The doses used were 33.0, 100.0, 333.0, 1000.0, 3333.0 and 4000.0 μg/plate. The tests for Methacrylic Acid were negative (Haworth et al. 1983).

Greim et al. (1995) reported that an in vitro DNA binding screening test with Methacrylic Acid was positive, while an Ames test was negative, but provided no study details.

CARCINOGENICITY

Clayton and Clayton (1982) reported that Methacrylic Acid was reviewed by the International Agency for Research on Cancer (IARC) Working Group, but that a monograph was not prepared because adequate data were not available.

CLINICAL ASSESSMENT OF SAFETY

Case Reports with Patch Tests

Fisher (1980) reported that two patients, patch tested with 1% Methacrylic Acid monomer in petrolatum, produced a negative reaction despite the fact that they had previously had allergic reactions to methyl methacrylate.

Dempsey (1982) reported the case of a 20-year-old female factory worker who presented with vesiculation of her distal finger pads, erythema of the dorsum of her fingers and swelling and fissuring of the erythematous skin of her fingertips. She was closed patch tested with the following chemicals at 1% concentrations in petrolatum: (1) Methacrylic Acid; (2) Methacrylic Acid and monomer C, the tertiary ammonium salt of Methacrylic Acid, in a ratio of 1:2.5 (this represented an excess of Methacrylic Acid) and (3) Methacrylic Acid and monomer C in a ratio of 1:4 (this represented a stoichiometric neutral balance between Methacrylic Acid and amine monomers). At the 72 h reading, treatments 2 and 3 both produced erythema, edema and vesiculation and a strong 2+ reaction which was in accordance with the International Contact Dermatitis Research Group classification. All five controls were negative. The patient did not react to Methacrylic Acid, but did react to the amine monomer of Methacrylic Acid.

Two mechanics and 4 car assembly line workers were patch tested with acrylates because they had lesions on the distal region of the index fingers of both hands. Patch tests were removed at 48 h and results at 96 h with 0.1% Methacrylic Acid in pet. were negative for all six workers (Condé-Salazar et al. 1988).

A 47-year-old female cosmetician who had severe atopic dermatitis in her youth, but had been without symptoms for 20 years, developed dermatitis on her right thumb that subsequently spread to both hands and face after she started to work with photobonded nails and chemically cured nail cosmetics. Two patch testing sessions were performed on the back with 48 h occlusion. Readings were performed on days two, three and four. The patch test for Methacrylic Acid was negative (Kanerva et al. 1996).

Other Case Reports

Linden et al. (1998) reported on three cases that involved oral ingestion of Methacrylic Acid. A 21-month-old boy unintentionally ingested 3 to 5 ml of a product that contained 98% Methacrylic Acid. Profuse drooling and gagging were noted shortly thereafter. Thirty minutes later he was vomiting spontaneously and in "obvious distress." Upon examination, erythema of the lips, chin and neck and a grayish-white discoloration of the buccal mucosa, soft palate and tongue were observed. The lungs were clear. Upper GI endoscopy revealed diffuse gray discoloration of the esophagus, marked erythema of the lower esophageal sphincter and stomach and an area of deep ulceration on the lesser curvature of the stomach. Nasopharyngoscopy and bronchoscopy revealed similar discoloration and marked edema of the supraglottic area, erythema and copious secretions in the distal trachea and both mainstem bronchi and marked narrowing of the distal left mainstem bronchus. Bilateral pneumonia developed the day after admission to the hospital. Stridor and respiratory distress occurred after an attempted extubation on day 4 and required reintubation. Endoscopy, repeated 13 days after admission, showed superficial erosions of the distal esophagus and lesser curvature of the stomach. The patient was able to eat a regular diet when discharged at 28 days. The skin burns resolved without scarring. One month after discharge, upper gastrointestinal radiographs after a barium swallow showed a normal esophagus. An area of stricturing in the esophagus at the level of the aortic knob was also noted.

In the second case study, a $2^1/_2$-year-old boy accidently spilled 5 to 7 ml of a product that contained at least 98.5% Methacrylic Acid onto his face, right arm and chest. He immediately screamed and was observed rubbing and shaking his right arm. Evaluation 20 min later reported patchy erythema of the face, chest, right arm and flank. After rinsing with tepid water, blistering of the chest burn was noted. All burns healed without scarring.

The third case was a 27-year-old woman who ingested two artificial nail products, the first contained Methacrylic Acid (exact dose not stated) and methyl ethyl ketone, and the second contained ethylmethacrylate, proprietary modifiers and polymerization accelerators, which included *n*, *n*-dimethyl-*p*-toluidine. Oropharyngeal erythema was noted on examination. Upper GI endoscopy was performed 12 h after ingestion and revealed mucosal sloughing in the mouth and hypopharynx. Areas of the proximal esophagus were ulcerated and edematous with pseudomembrane formation. The distal esophagus and stomach were hyperemic. A repeat endoscopy 7 days later showed areas of persistent ulceration in the proximal esophagus (Linden et al. 1998).

The CPSC reported on data it received from the American Association of Poison Control Centers isolating nail products containing Methacrylic Acid for 1996 and 1997 (CPSC 1998a) in which there were 467 exposures (341 poisonings [which may also have included dermal exposure], 11 ocular exposures, 115 dermal exposures), with no deaths. The CPSC provided details on three incidents. (1) A 3-year-old female experienced burns to her lips and cheeks when she attempted to ingest a nail primer at a beauty salon. She also suffered an anaphylactic reaction. She was admitted to the pediatric intensive care unit for two days. By day 3 she was transferred to a regular bed and the open blisters on her cheeks were healing. An endoscopy on day 4 showed no GI burns. (2) A $1^1/_2$-year-old burned over half her chest after spilling primer on herself. The burns healed within 4 weeks with outpatient treatment at a burn center. (3) In the process of

ingesting primer, a 20-month-old female spilled primer on her face and other areas of skin. Blisters formed within 30 min. The blisters healed without scarring.

The CPSC also reported three detailed investigations of injury case reports due to Methacrylic Acid from the CPSC In-Depth Investigations data base. A 2-year-old female spilled $1^1/_2$ to 2 ounces of a nail primer that contained Methacrylic Acid on her thigh. She suffered first and second degree burns to her right thigh and both sides of her face even after immediate rinsing. She was treated and released from the hospital the same day.

A 2-year-old male spilled about 1 to $1^1/_2$ ounces of nail primer on his shirt and around his mouth and nose. His burns were treated at the hospital and endoscopy was performed because he had difficulty swallowing. He was released after four nights in the hospital.

A 12-month-old male spilled about 1 ounce of fingernail primer on his hands. Upon rubbing his mouth, he began drooling and frothing. He was taken to the hospital where his burns were treated and he was released the same day. The CPSC also stated that the FDA's Cosmetic Voluntary Registration Program contains four nail primer injury reports, one of which involved a 2 y old male who was brought to an emergency room after a nail primer splashed in his face and caused burns to the cornea and skin (CPSC 1998a).

Consumers reported injuries (during the years 1987–1993) from four different nail primers which caused dermatitis (to include rash, redness, swelling, blisters, sores, weeping, lumps, inflamation, sunburn, chemical burn, and irritation) to the leg, hand, face, or finger. Nail primers were also reported to cause pain (to include itching, stinging, burning, soreness, and tingling) to the eye or fingers (ABA 2001b).

Epidemiology

Woolf and Shaw (1997; 1998) analyzed data from the 1993–1995 Toxic Exposure Surveillance System (TESS) compiled by the American Association of Poison Control Centers according to age, injury type and outcome. Out of 71,033 calls, 759 concerned exposure to Methacrylic Acid nail products and 655 of those occurred in the home. Most of the exposures (56) involved children less than 6 years and of these, 3 children suffered moderate and major injuries, respectively, which included predominately dermal, oral and/or eye burns.

A hazard score (HS) was calculated for children younger than 6 years by summing the outcome major toxicity and death and dividing by the total poisonings. For Methacrylic Acid the HS was calculated as 8.6, comparable to antifreeze (HS = 9.6), kerosene (HS = 7.9), and ethanol containing beverages (HS = 8.0) and was much more hazardous than other cosmetics (HS = 0.2), mothballs (HS = 0.5) and oven cleaner (HS = 3.5). The conclusion was that artificial nail products containing Methacrylic Acid are hazardous to young children and require better measures to prevent injury. A recommendation was made that they be sold in child resistant containers accompanied by appropriate warnings to consumers (Woolf and Shaw 1997 and 1998).

Both Woolf and Shaw (1998) and the CPSC (1998a) describe findings from the National Electronic Injury Surveillance System (NEISS). Woolf and Shaw reported there were 769 emergency department visits for exposures to nail products from 1991 to 1993. Children under 6 years were involved in 421 of these visits and most incidents occurred in the child's home. The following is a breakdown of the total 769 reported nail product injuries: 4.2% involved artificial nail primers; 19% ingestions; 6% eye-only exposure; 59% dermal-only exposure; 6% other; 6% ocular/dermal combination exposures and 3% ingestion/ocular combinations. In the category of "other nail product" exposures, 120 of 737 exposures were rated by emergency room staff as moderate to major in severity. In all of the NEISS data, exposure to nail primers accounted for 4% of patient visits to the emergency department. The investigators suggest that this study should be interpreted with caution: the NEISS data included some overlap between the years and ingredients and brand names were not distinguished. As a result, some entries listed as "nail primers" were assumed to contain Methacrylic Acid, but perhaps did not.

The CPSC (1998a), in its proposed rule to require child-resistant packaging for Methacrylic Acid, described NEISS as a stratified probability sample of hospitals with emergency rooms in the USA and its territories. They stated that national estimates of emergency room visits by children less than 5 years old due to exposure to nail primers were 2,723 between January, 1988 and September, 1998, with hospitalization necessary in a projected 262 cases.

The Nail Manufacturers Council (NMC) reported that it received notices of adverse reactions related to Methacrylic Acid at a rate of less than 1.7 incidents per 10,000 units during 1987 to 2000 (American Beauty Association (ABA) 2001b).

Occupational Exposure

The ACGIH has recommended a TLV of 20 ppm and the National Institute for Occupational Safety and Health (NIOSH) has recommended a 20 ppm time weighted average (TWA) for up to a 10-hour workday and a 40-hour workweek. The Occupational Safety and Health Administration (OSHA) has regulated Methacrylic Acid for nervous system effects; with a skin designation in recognition of deemed absorption. The permissible exposure limit is 20 ppm as a TWA concentration *** (Dick and Ahlers 1998; ACGIH 2000; NIOSH 2001; OSHA 2005).

SUMMARY

Methacrylic Acid is an organic acid used to pretreat the nail and maximize the adhesion between the nail and artificial nail extender. The Consumer Product Safety Commission (CPSC) rule (effective June 19, 2000) requires that child-resistant packaging for liquid household products containing more than 5 percent Methacrylic Acid (weight-to-volume) in order to protect

children under 5 years of age from personal injury as a result of exposure.

Commercial nail primers containing Methacrylic Acid have concentrations between 50 and 88 percent. Most nail primers containing Methacrylic Acid are labeled "for professional use only," but there is documented evidence that they are readily available to consumers. A videotape of the application of Methacrylic Acid by a trained professional demonstrated that it is possible to avoid skin exposure in a professional setting.

Methacrylic Acid is readily absorbed through mucous membranes of the lungs and gastrointestinal tract and the skin; and is readily distributed to all major tissues.

The oral LD_{50} for rats ranged from 277 to 2260 mg/kg Methacrylic Acid. The oral LD_{50} for rabbits ranged between 280 and 1200 mg/kg Methacrylic Acid. The oral LD_{50} for mice ranged between 827 and 1600 mg/kg Methacrylic Acid. Severe gastric irritation, gasping, labored respiration, prostration and hematuria were observed in rats.

The acute intraperitoneal LD_{50} for Methacrylic Acid in mice was 48 mg/kg. The dermal LD_{50} for rabbits ranged from 500 to 1243 mg/kg. In an inhalation study using mice, the concentration of Methacrylic Acid that caused a decrease in respiratory rate by 50% was 22,000 ppm; this indicated that Methacrylic Acid has a low potential to cause sensory irritation to the upper respiratory tract. The LC_{50} values for inhalation exposure to Methacrylic Acid were reported as 1350 ppm/4 hours for the rat, 3657 ppm for the mouse, and 2522 ppm/1 hour for the rabbit. In dogs, 100% Methacrylic Acid was lethal by a 0.1 ml intravenous injection.

In a short-term oral study, mice administered 100 ml of 19.2% Methacrylic Acid three times a week for three weeks had no treatment related clinical signs or changes in body weights were observed. In a short-term inhalation study, rats exposed to Methacrylic Acid for five, 5 hour exposure periods at 4.5 mg/l (1300 ppm), showed nose and eye irritation, and weight loss. Necropsy, and blood and urine tests were normal.

In a short-term inhalation study, rats exposed to 300 ppm Methacrylic Acid for twenty, 6 hour exposure periods exhibited no toxic signs other than slight renal congestion.

Rats and mice were exposed to 0 to 1000 ppm of Methacrylic Acid (6 h/day, 5 days/week). No treatment-related effects were seen in mice at 100 ppm; all rats had minimal to mild hyperplasia and acute inflamation of the stratified squamous epithelium of the nose and mild goblet cell hyperplasia. At 500 ppm, rats and mice had decreased body weight gain and organ weights were decreased. Clinical observations included lethargy, gasping, ocular opacity, poor coat quality, and irritability. Microscopic lesions were observed in the nasal turbinates (including necrosis of the nasal mucosa with associated inflammation). At 1000 ppm, all rats and mice died by the 6th day. Clinical observations were similar to the 500 ppm group. Microscopic changes included necrosis of the nasal mucosa and submucosa and mild keratitis as indicated by small number of neutrophils and edema. Lesions were observed in the eyes, digits, tails, stomachs, and nasal turbinates.

In a subchronic inhalation study, mice and 2 species of rats were exposed to atmospheres containing 0 to 300 ppm Methacrylic Acid for 90 days (6 h/day, 5 days/week). At interim sacrifice (after 4th exposure), male and female mice and F344/N rats exposed to Methacrylic Acid at 300 ppm had significantly decreased body weights; moreover, the only gross lesions in F344/N rats were solitary or multiple red discolorations of the lungs. At study termination, only male F344/N rats had significantly decreased body weights and decreased food consumption, yet F344/N rats had no significant gross observations. No significant differences were observed with respect to hematology, serum chemistry, or urinalysis in any of the strains/sexes tested. At necropsy, male Sprague-Dawley rats had discolorations of the liver and both sexes had discoloration of the lungs. At study termination a majority of F344/N rats had more severe inflammation in the nasal mucosa; treated Sprague-Dawley rats had a higher incidence of inflammation, exudate and epithelial hyperplasia of the nasal turbinates compared to controls. An increased incidence of lymphocytic hyperplasia in the mandibular lymph nodes of high dose rats of both strains was the predominant change in tissues outside the respiratory tract. Only high dose mice had acute rhinitis, ulceration and exudate in the nasal turbinates. The only treatment related change observed outside the respiratory tract was the development of cytomegaly of renal tubular epithelium in over half the high dose male mice.

Methacrylic Acid (0.1 ml) caused severe corneal, iridial, and conjunctival effects in albino rabbits that persisted until the 7th day. Methacrylic Acid (56,916 ppm) produced a corrosive effect on the eyes of albino rats in a one hour inhalation study. In a 4 hour inhalation study, corneal opacity and ocular discharge were observed in 1/10 albino rats exposed to 2037 ppm Methacrylic Acid.

Undiluted Methacrylic Acid is corrosive to the skin of rabbits and guinea pigs. Exposure as limited as 3 minutes can cause severe erythema and slight to moderate edema. Exposure from 15 minutes to 24 hours under occlusive patches can cause marked to severe discoloration, slight to severe subcutaneous hemorrhages, necrosis, ulcerations, severe erythema, edema and concave eschar. A study in mice suggested that 4.8% Methacrylic Acid would act as a mild irritant in humans, even when in solution with acetone. Doubling the concentration to 9.6% Methacrylic Acid caused severe irritation equivalent to second degree burns and at 19.2% Methacrylic Acid there was visible destruction to the skin epithelium and injury to all skin layers bordering on corrosive.

Methacrylic Acid was irritating and caused strong rubefaction and scab formation in a guinea pig maximization test at challenge concentrations from 10 to 100 percent. It was difficult to determine if the results were type IV hypersensitivity reactions or simple irritation. In three other studies, guinea pigs were not sensitized to Methacrylic Acid.

In a teratogenicity study, pregnant rats were exposed to 50 to 300 ppm Methacrylic Acid via inhalation (6 h/day) on days

6 to 20 of gestation. All animals survived the exposure period. Absolute weight gain was significantly reduced at 300 ppm. No significant changes in the number of implantations, live fetuses, incidence of non-live implants and resorptions, or in fetal body weights were observed across the groups. Treatment related effects were not observed. In another study, ten day rat embryos were exposed in vitro for 24 to 26 hours to Methacrylic Acid at concentrations of 103 to 181 μg/ml. At 129 to 181 μg/ml a significantly increased percentage of malformations were observed compared to controls. At these same concentrations, a significant decrease in percent viable, crown-rump length, number of somites and protein content per embryo was observed. An increase in Methacrylic Acid induced cell death of the central nervous system and adjacent mesenchyme.

A 90-day inhalation study in rats and mice found no gross or microscopic changes in the oviducts, ovaries, uteri and mammary glands of females, or in the testes, epididymes, seminal vesicles, mammary glands and prostate of males in the high concentration group (300 ppm). No indication of toxic effects on the reproductive systems were observed.

Methacrylic Acid was negative in *Salmonella typhimurium* mutagenicity tests using strains TA98, TA100, TA1535 and TA1537 both with and without metabolic activation. However, Methacrylic Acid was positive in a DNA-cell-binding assay.

The case literature includes reports in which patients were patch tested. Two patients that previously had an allergic reaction to methyl methacrylate produced a negative reaction when patch tested with 1% Methacrylic Acid in petrolatum. A female factory worker with vesiculation of her distal finger pads, erythema of the dorsum of her fingers and swelling and fissuring of the erythematous skin of her fingertips was closed patch tested with 1% Methacrylic Acid in petrolatum. The patient did not react to Methacrylic Acid. Two mechanics and 4 car assembly line workers were patch tested with acrylates because they had lesions on the distal region of the index fingers of both hands. Patch tests were removed at 48 h and results at 96 h with 0.1% Methacrylic Acid in petrolatum were negative. A female cosmetician who had severe atopic dermatitis in her youth, but had been without symptoms for 20 years before developing dermatitis on her right thumb that spread to her hands and face while working with photobonded nails and chemically cured nail cosmetics. Two patch testing sessions were performed using Methacrylic Acid on the back with 48 h occlusion, both tests were negative.

Case reports involving Methacrylic Acid often involve children. Effects from ingestion include drooling, gagging, and vomiting. Examination of a 21-month-old boy, revealed erythema of the lips, chin and neck and a grayish-white discoloration of the buccal mucosa, soft palate and tongue were observed. Upper GI endoscopy reported diffuse gray discoloration of the esophagus, marked erythema of the lower esophageal sphincter and stomach and an area of deep ulceration on the lesser curvature of the stomach. The patient was able to eat a regular diet when discharged at 28 days. The skin burns resolved without scarring. One month after discharge, upper gastrointestinal radiographs after a barium swallow showed a normal esophagus.

There are several case reports involving children from 1 to 3 years old that accidentally spilled Methacrylic Acid. Typical exposure ranged from 5 to 7 ml up to 2 ounces which caused first and second degree burns to the eyes, face, hands, arms, and chest which can induce blistering and erythema.

From 1987 to 1993, consumers reported injuries from four different nail primers which caused dermatitis to the leg, hand, face, or finger. Nail primers were also reported to cause pain to the eye or fingers.

The American Association of Poison Control Centers compiled data from 1993 to 1995 Toxic Exposure Surveillance System. Analysis was done according to age, injury type and outcome. Out of 71,033 calls, 759 concerned exposure to Methacrylic Acid nail products and 655 of those occurred in the home. According to the National Electronic Injury Surveillance System (NEISS) there were 769 emergency department visits for exposures to nail products from 1991 to 1993. Children under 6 years were involved in 421 of these visits and most incidents occurred in the child's home. The NEISS data included some overlap between the years and ingredients and brand names were not distinguished.

Estimates of emergency room visits by children less than 5 years old due to exposure to nail primers were 2,723 between January, 1988 and September, 1998, with hospitalization necessary in a projected 262 cases.

Industry reported that it received notices of adverse reactions related to Methacrylic Acid at a rate of less than 1.7 incidents per 10,000 units during 1987 to 2000.

The ACGIH and NIOSH have separately recommended an exposure limit of 20 ppm to Methacrylic Acid as a TWA for up to a 10-hour workday and a 40-hour workweek. The OSHA no longer regulates Methacrylic Acid for nervous system effects; in 1989 the proposed permissible exposure limit was 20 ppm as a time weighted average concentration that must not be exceeded during a workshift day of a 40 h week.

DISCUSSION

The extreme corrosivity of Methacrylic Acid was of concern to the Expert Panel. A videotape presentation demonstrated that a trained professional could use a small applicator brush to dab a limited volume of Methacrylic Acid only to the center of the nail, allowing the monomer liquid to diffuse down the nail without any exposure to the skin. The Expert Panel was satisfied that a trained professional could apply Methacrylic Acid safely, however there are no available data that demonstrate that the consumer could apply Methacrylic Acid and avoid inadvertent skin contact. In order to minimize any exposure to the acid, the Expert Panel recommended that nail primer containing Methacrylic Acid be applied only by trained individuals and that there be no contact with the skin.

While the Panel recognized that there are no UV absorption data, the Panel concluded that photochemical toxicity would not be a concern, given the use restrictions described above.

The CIR Expert Panel recognized that there are no chronic inhalation toxicity data on Methacrylic Acid, but was concerned that inhalation of Methacrylic Acid could affect the respiratory tract. Since the inhalation exposure time is significantly increased in a commercial setting, the Panel was more concerned about the safety of the nail technician than the consumer. The Expert Panel concluded that the current NIOSH recommended exposure limit of 20 ppm as a time weighted average concentration that must not be exceeded during a workshift day of a 40 h week would provide adequate protection.

There are numerous case reports of children being injured by spills of Methacrylic Acid in the home and the CPSC promulgation of a regulation requiring child-resistant packaging of Methacrylic Acid was effective June 19, 2000. The Expert Panel recognized that child-resistant packaging could reduce the number of incidents involving children. The Panel, however, was still concerned that the safe use of Methacrylic Acid as a cosmetic ingredient requires its use be restricted to a professional setting, and that the beauty industry should continue and expand efforts to ensure that Methacrylic Acid is not sold to consumers.

CONCLUSION

Based on the available animal, clinical, and other data included in this report, the CIR Expert Panel concludes that Methacrylic Acid is safe as used as a nail primer by trained professionals, but there are insufficient data for retail use by consumers.

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