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Final Report on Ethyl Methacrylate[1]

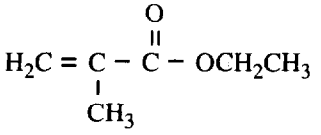
Abstract: Ethyl Methacrylate is the ester of ethyl alcohol and methacrylic acid used as the major structural monomer of artificial fingernail formulations that are cross-linked with one or more multifunctional methacrylates. Ethyl methacrylate monomer is polymerized rapidly and very little free monomer is available even during filing of the fingernails. The oral LD_{50} for rats ranged from 12.7 to 18.14 g/kg, with lesions in the respiratory system and hemoglobinuria observed in treated animals. Ocular, nasal, and respiratory tract irritation was observed in acute inhalation tests using rats. Very little toxicity was seen in subchronic studies using rabbits. Ethyl Methacrylate caused irritation and vehicle dependent sensitization in animals, but no photosensitization. Evidence of embryotoxic and teratogenic effects were observed in pregnant rats after intraperitoneal injection of Ethyl Methacrylate at a range of concentrations. Both positive and negative mutagenicity test data were found. Clinical testing showed little evidence of irritation, although case studies report allergic contact dermatitis as a result of exposure to Ethyl Methacrylate and related methacrylates with application of artificial fingernails. Occupational contact dermatitis from acrylates and methacrylates are also reported, with some evidence for cross-reactivity between the two chemical classes. Based on the sensitizing potential of this ingredient the CIR Expert Panel recommended that fingernail enhancement formulations with Ethyl Methacrylate be applied only by trained individuals and that the ingredient not be used in products intended for retail sale (currently, these products are believed to be sold only for application by a trained individual). Because of the low likelihood of significant exposure if such formulations are applied properly, the Expert Panel concluded that the ingredient is safe as used, with the caveat that skin contact should be avoided.
Key Words: Ethyl methacrylate—Embryotoxic effect—Teratogenic effect.

Ethyl Methacrylate is the ester of ethyl alcohol and methacrylic acid used in artificial fingernail enhancement products. The safety data on this ingredient are presented in this report.

CHEMISTRY

Definition and Structure

Ethyl Methacrylate (CAS No. 97-63-2) is the ester of ethyl alcohol and methacrylic acid, which has the following chemical structure (Nikitakis et al., 1991):



[1] Reviewed by the Cosmetic Ingredient Review Expert Panel.

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Other chemical names for Ethyl Methacrylate are Ethyl 2-Methyl-2-Propenoate; 2-Methyl-2-Propenoic Acid, Ethyl Ester; 2-Propenoic Acid, 2-Methyl-, Ethyl Ester; and Methacrylic Acid, Ethyl Ester (Nikitakis et al., 1991; RTECS, 1992).

Properties

Ethyl Methacrylate is a colorless liquid with a melting point below −75°C, a boiling point of 119°C, and a specific gravity of 0.911 (Hawley, 1971). It has a molecular weight of 114.14 (EPA, 1986), a refractive index (n 25/D) of 1.4116, and a flash point (OC) of 70°F (Hawley, 1971). Ethyl Methacrylate has an acrid acrylate odor and is soluble in alcohol and ether (EPA, 1985).

Ethyl Methacrylate is readily polymerized (Hawley, 1971), and is chemically reactive (Nemec and Kirch, 1981).

The extent of curing for two Ethyl Methacrylate–based commercial fingernail formulations was determined over intervals ranging from 5 min to 24 h. The formulations used were moderately cross-linked preparations that were cured in sample pans at body temperature (37°C). Differential scanning calorimetry was used to measure the exotherm created when unreacted monomer began to polymerize. Negative values were indicative of greater exotherm, and therefore larger amounts of unreacted monomer. Additionally, the formulations were allowed to cure on fingernails at room temperature (28°C) and particles produced from filing the hardened formulations were analyzed after 45 and 90 min of aging, and fingernail clippings were evaluated after 45 min.

After 5 min of curing, both formulations had significant exotherm values (−44.93 J/g and −83.05 J/g) that were used as conservative estimates of the 50% monomer conversion value. Using these values, it was calculated that the relative percentage of unreacted monomer after 1 hr at 37°C was <1.0% for both formulations. The average residual monomer content for the fingernail filings was <2% at 45 min, and <1% at 90 min. The slower polymerization observed here was attributed to the cooler temperature (28°C) at which the formulations were allowed to cure. This was also observed with the fingernail clippings, in which <1% monomer was found in both clipping samples at 45 min (Schoon, 1994*a*).

As a follow up to this study, Schoon (1994*b*) measured the unreacted monomer content of the same two fingernail samples cured at 30°C. Both samples were cured in aluminum pans at 30°C, and exotherm measurements were taken at 5 min and 1 and 4 h. Using the 5-min exotherm values as the estimated 50% monomer conversion values, residual monomer content was calculated to be 0.6% at 1 h. At 4 h, the residual monomer content fell below detection levels.

A profile of the cure temperature of the two Ethyl Methacrylate fingernail formulations was also conducted. Each formulation, stored at 23°C, was applied at 25°C to a fingernail fitted to precision fine wire thermocouples. Temperatures were recorded using an analog-to-digital data acquisition board, cold junction signal conditioner, and a 486/66 MHz computer. Immediately following the first

bead application of both products at the dorsal tip of the nail, cooling was measured. When the formulations were applied directly over the thermocouple, the temperature dropped from 35.5 to 29.2°C, which was attributed to the lower temperatures of the formulations. Two additional drops in temperature were observed when the second and third beads of each formulation were applied to the nail.

The temperature began to rise within 1 min following the final bead application. This warming trend lasted for ~3 min for one formulation and an additional 20 s for the other formulation. Maximum exotherm temperatures of 41.8 and 43.0°C were measured, which returned to a baseline temperature of 35.8°C. Five minutes after curing, the nail enhancements were filed, which produced a small amount of frictional heat. However, filing with a less abrasive "finishing" file produced an overall cooling effect, which the investigator attributed to lower generation of heat and higher thermal conductivity of the file. Temperatures returned to baseline levels once the finishing process was completed.

The mean temperature over the 40-min test period was 35.1 and 35.2°C for the two formulations. The investigator noted that table lamps were not used during this experiment, but are commonly used during salon applications. Therefore, mean temperatures recorded in this study are probably lower than would occur under normal conditions of use (Schoon, 1994*c*).

Method of Manufacture

Ethyl Methacrylate is formed by the reaction of methacrylic acid or methyl methacrylate with ethyl alcohol (Hawley, 1971).

Analytical Methods

Gas chromatography (Black, 1977) and glass capillary gas chromatography combined with mass spectrometry (Horna et al., 1986) may be used to identify Ethyl Methacrylate.

Impurities

Hydroquinone and the methyl ester of hydroquinone (as inhibitors) are typically found in commercial grades of Ethyl Methacrylate at concentrations ranging from 22 to 28 ppm and 15–20 ppm, respectively (EPA, 1985; Nemec and Kirch, 1981).

USE

Cosmetic

Ethyl Methacrylate is used as a chemical additive in cosmetic formulations (Wenninger and McEwen, 1992). Although this ingredient was not reported to the FDA as being used in 1994 (FDA, 1994), representatives of the Nail Manufactur-

ers Council reported that Ethyl Methacrylate is used in artificial fingernail enhancement products which are designed for application by trained individuals (Schoon, 1994*a*).

Typically, artificial fingernails are formed from two part formulations containing Ethyl Methacrylate as the major structural monomer and are crosslinked with one or more multifunctional methacrylates (Schoon, 1994*a*).

Ethyl Methacrylate is a substitute for methyl methacrylate, the compound originally used in sculptured fingernail products. Methyl Methacrylate was banned from use in fingernail products by the U.S. Food and Drug Administration in 1974 because of consumer complaints about onycholysis and fingernail dislocation and/or irritation (U.S. District Court Decision, 1974).

Noncosmetic

Ethyl Methacrylate is used in the production of acrylic polymers for paints and coatings and in components for the automotive, aerospace, and furniture industries. It is also used by the dental industry for dentures, plates, and cements (EPA, 1985; Freeman, 1965). Contact lenses (Refojo, 1979) and artificial fingernails (Lee and Orlowski, 1976) are also produced with Ethyl Methacrylate.

BIOLOGICAL PROPERTIES

Pharmacological Effects

Mir et al. (1973*a*) investigated the response of the isolated rabbit heart to Ethyl Methacrylate perfusion. The isolated hearts of rabbits were perfused with Ethyl Methacrylate at concentrations of 1:100,000, 1:10,000, and 1:1,000 (v/v) in Locke's solution for 1 min, followed by perfusion with Locke's solution only. Each concentration was tested five times and the heart rate, force of contraction, and coronary flow rate were quantified prior to perfusion and immediately after perfusion. Irreversible damage was reported if the cardiac parameters did not make a significant return to control levels of activity within 30–35 min. Ethyl Methacrylate, at a concentration of 1:1,000, caused cardiac standstill. A concentration of 1:10,000 reduced the cardiac rate by 17.8%, the force of contraction by 72.2%, and the coronary flow by 57.9%. These parameters were reduced by 5.8, 19.8, and 26.1%, respectively, at a 1:100,000 concentration. The effects of Ethyl Methacrylate on the isolated heart were irreversible at all three concentrations.

Ethyl Methacrylate was also tested using isolated guinea pig ileum. Actively contracting loops of ileum were isolated from guinea pigs and exposed to Ethyl Methacrylate at concentrations of 1:2,000, 1:1,000, and 1:500 (v/v) in Tyrode's solution. A force–displacement transducer electrically connected to a polygraph recorded changes in contractions when the ileum was exposed to Ethyl Methacrylate alone or in the presence of either acetylcholine (1:10,000,000) or barium chloride [3:100,000 (w/v)]. Ethyl Methacrylate alone inhibited pendular movements and relaxation of the muscle, and a dose–response relation was observed. The stimulant actions of acetylcholine and barium chloride were also antagonized

by Ethyl Methacrylate in a dose-dependent fashion. These effects were reversed when the ileum was rinsed with fresh Tyrode's solution (Mir et al., 1973*b*).

The effects of Ethyl Methacrylate on respiratory and cardiovascular function was studied in dogs. Groups of three male mongrel dogs were anesthetized with sodium pentobarbital and were given intravenous doses of 0.0171, 0.0342, and 0.3684 ml/kg Ethyl Methacrylate. A pressure transducer was attached to the carotid artery to monitor the systemic blood pressure, and another transducer was attached to the trachea to record respiratory pressure changes. Four needle electrodes were placed subdermally into each limb of the dog to record the electrocardiogram.

Ethyl Methacrylate caused a biphasic response in the blood pressure. Blood pressure abruptly fell by 31.95–58.66% for 2–4 min, and then pressure slowly rose, reaching a plateau 7.21–24.74% above the control value lasting 10–15 min. The heart rate also decreased in a dose-dependent fashion, but was not of the same magnitude; there was a 11.13–25.11% decrease. Respiratory rate was increased by 34.10–146.41% for ~20 min. The electrocardiogram had the following dose-related changes: bradycardia, a reduction in the rate of impulse transmission through the A-V node, and indications of acute cardiac ischemia. The larger doses also caused premature ventricular contractions and incomplete A-V block (Mir et al., 1974).

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

Tanii and Hashimoto (1982) reported that the oral LD_{50} of Ethyl Methacrylate for mice was 68.64 mmol/kg (7.8 g/kg).

In another study, groups of 10 rats were administered Ethyl Methacrylate via stomach tube at doses ranging from 12.70–18.14 g/kg. The LD_{50} was between 12.70 and 14.51 g/kg. Two to four minutes following administration, the rats had an increased rate of respiration with lacrimation. After 15–40 min, they had motor weakness and their respiration decreased and breathing was irregular and labored. There was increased defecation and urination, blood was present in the urine, and reflex activity disappeared. The animals died in coma 1–1.5 h following dosing. At necropsy, lesions were found primarily in the respiratory system. The lungs, trachea, and bronchi were markedly congested and edematous. The lungs were also spotted with areas of hemorrhage and emphysema. The thymus gland was swollen and congested. The ventricles were well contracted and the auricles were dilated and filled with dark, clotted blood. Fluid blood was found in the dilated abdominal vessels. The greatly distended urinary bladder often contained blood and areas of hemorrhage, necrosis, and detachment of the mucosa. Congestion of the intestine and acute inflammation of the mucosa were also evident (Deichmann, 1941).

The oral LD_{50} for rabbits was between 3.63 and 5.44 g/kg. Signs of toxicity were similar to those seen in the rats (Deichmann, 1941).

Subcutaneous

Six of 10 rats died 8–18 h following a single subcutaneous injection of 25 cc Ethyl Methacrylate. The animals had clinical signs of toxicity similar to those seen in the acute oral studies. A sudden increase in respiration was followed by reduced and labored respiration, the urine contained blood, and motor control and reflex activity were severely diminished. Lesions found at necropsy were the same as those found in the rats of the acute oral studies. The researchers noted that the LD_{50} dosage was greater for the subcutaneous study than for the oral study, suggesting that subcutaneous absorption was less rapid (Deichmann, 1941).

Intraperitoneal

The intraperitoneal LD_{50} for rats was 1.2228 ml/kg (Singh et al., 1972).

Inhalation

The $LC_{50/24}$ for 10 Sprague–Dawley rats exposed to Ethyl Methacrylate in their air for 4 h was 8,300 ppm. During exposure, the behavior of the rats reflected irritation of the eyes, nose, and respiratory tract. The rats squinted, huddled, and had labored respiration. The investigations noted that death was predictable by the blanching of the pinnae and paws. Animals that survived the first 24 h also survived the 14-day observation period. At necropsy, no gross abnormalities were found (Oberly and Tansy, 1985).

Groups of two rats, one guinea pig, and one rabbit were exposed to 12.4, 15.0, and 17.7 mg/L Ethyl Methacrylate for 8 h. Doses of 15.0 and 17.7 mg/L killed the rats within 3–4 h, but did not kill either the rabbits or guinea pigs. None of the animals exposed to 12.4 mg/L Ethyl Methacrylate died. At necropsy, the lungs, trachea, and bronchi of the rats were markedly congested and edematous, and the lungs had areas of hemorrhage and emphysema. Pathologic changes were also found in the thymus, heart, and abdomen. These changes were similar to those observed in the acute oral studies (Deichmann, 1941).

Subchronic Toxicity

Intravenous

Because hemoglobinuria was observed in acute studies, a study was conducted to determine whether or not Ethyl Methacrylate caused an increase in blood and urine porphyrin concentrations. Five rabbits were injected with 2 cc/kg of Ethyl Methacrylate once a week for 3 weeks, and the blood and urine were analyzed before the first dose and after the last dose. Porphyrins were detected in both fluids; however, the individual porphyrins were not identified (Deichmann, 1941).

Inhalation

A study conducted by Lawrence and Autian (1972) indicated that inhalation of Ethyl Methacrylate vapor affected drug metabolizing enzymes. Groups of ten male ICR mice were exposed to 84.79 mg/L of Ethyl Methacrylate in their breath-

ing air for 3.85, 7.70, and 19.25 min for 3 days. Sodium pentobarbital was administered 24 h following the last Ethyl Methacrylate exposure and sleeping time was compared with that of a control group which was not exposed to Ethyl Methacrylate. Sleeping time increased with the duration of exposure. The mean sleeping time for the control rats was 50.63 min, and for the rats in the low, mid, and high dosage groups the sleeping times was 51.06, 53.93, and 94.93 min, respectively. The researchers stated that this dose-related increase was an indication that Ethyl Methacrylate can have an effect on drug metabolizing enzymes.

Dermal Irritation

The clipped skin of rabbits (number not stated) was treated with 10 cc/kg Ethyl Methacrylate. The animals were restrained under a hood in such a way that they were unable to inhale the evaporating material. Signs of irritation were observed at the site of exposure and the animals were inactive. The animals recovered within 1 h (Deichmann, 1941).

Sensitization and Cross-Sensitivity

Ethyl Methacrylate was tested for sensitization potential in the guinea pig maximization test. Groups of ten Duncan Hartley guinea pigs were administered three pairs of intradermal injections of 0.1 ml Freund's complete adjuvant (FCA), Ethyl Methacrylate in peanut oil, and Ethyl Methacrylate in FCA in their backs. The concentrations of Ethyl Methacrylate tested were 0.17, 0.50, and 1.50 *M*. On day 7, an occlusive patch containing 1 *M* Ethyl Methacrylate was applied to the site of the injections for 48 h. After a 2-week non-treatment period, the right flank of each guinea pig was shaved and 3 *M* undiluted Ethyl Methacrylate was applied under occlusive patches for 24 h. The sites were scored at 24 and 48 h. On day 35, 3 *M* undiluted Ethyl Methacrylate was applied to the shaved left flank of each guinea pig and left uncovered. Readings were taken after 24 and 48 h. A control group of six guinea pigs received the same treatment, except that only the vehicle was used in the applications.

There was no evidence of sensitization in the guinea pigs induced with 0.17 *M* Ethyl Methacrylate. One guinea pig induced with 0.50 *M* Ethyl Methacrylate had evidence of sensitization after treatment on day 35 and one positive reaction was observed after both the 21- and 35-day treatments among the guinea pigs induced with 1.50 *M* Ethyl Methacrylate. When this experiment was repeated using a 0.5 *M* induction concentration on day 0, one of 10 guinea pigs reacted after both the 21- and 35-day applications (Van Der Walle et al., 1982).

Ethyl Methacrylate was also tested with Freund's complete adjuvant. Six guinea pigs were induced with intradermal injections of 5 × 0.5 *M* Ethyl Methacrylate in FCA and water on days 0, 2, 4, 7, and 9. On days 21 and 35, the shaved right and left flanks, respectively, were treated topically with 3 *M* undiluted Ethyl Methacrylate. The sites were left uncovered and readings were taken 24 and 48 h following each of these treatments. Two of the six guinea pigs had positive reactions following both the 21- and 35-day treatments (Van Der Walle et al., 1982).

Chung and Giles (1977) conducted a study that suggested the sensitization potential of Ethyl Methacrylate was dependent upon the vehicle of administration and that mutual cross-sensitivity exists between monomers of methacrylic acid. Guinea pigs were injected with 0.1 ml of Freund's complete adjuvant with heat-killed *Mycobacterium butyricum* into each foot pad (total volume 0.4 ml; total amount of *M. butyricum* 100 μg). One group of 25 animals was treated with topical applications of 0.03 ml of Ethyl Methacrylate in ethanol on days 0, 2, and 5. When the first challenge with 2 and 5% Ethyl Methacrylate in ethanol was administered on day 25, no sensitization was observed 72 h following the challenge application. The animals received a second challenge on day 60 with either a topical dose of 10% Ethyl Methacrylate in olive oil or an intradermal dose of Ethyl Methacrylate in saline (0.01 and 0.1 μl/site). The Ethyl Methacrylate in olive oil produced severe sensitization reactions. However, the intradermal dose of Ethyl Methacrylate in saline did not evoke any responses. A third challenge on day 122 with 0.4 and 2% Ethyl Methacrylate in olive oil caused sensitization within 72 h. The researchers suggested that Ethyl Methacrylate in ethanol evaporated before it could elicit a response.

Another group of nine guinea pigs was initially treated with 0.0077 ml of Ethyl Methacrylate in olive oil on day 60 (as controls) and was challenged with 2 and 5% Ethyl Methacrylate in olive oil on day 95. Positive reactions were observed in all of the animals after 72 h.

When the guinea pigs from both groups were challenged a second or fourth time with Ethyl Methacrylate and either 1% methyl methacrylate or 1% butyl methacrylate, strong cross-sensitivity was observed.

In another study, three guinea pigs sensitized to either 1 or 4 *M* Ethyl Methacrylate were tested for cross-reactivity with several acrylic monomers. The animals, sensitized in the Freund's Adjuvant Test or the Guinea Pig Maximization Test, were challenged on one flank with acrylates, methacrylates, diacrylates, and dimethacrylates (0.025 ml) 2 weeks after completing the tests. A second challenge with the monomers was conducted 2 weeks later on the other flank. Readings of the test sites were conducted 24 and 48 h following application. After the last challenge to test cross reactions, the guinea pigs were also challenged with Ethyl Methacrylate. Some of the animals had cross-reactions with acrylates, methacrylates, and dimethacrylates. However, these reactions were only to specific monomers and usually involved only one guinea pig. None of the guinea pigs reacted to the diacrylates (Van Der Walle and Bensink, 1982).

Photosensitivity

Deichmann (1941) speculated that edema and photosensitivity might occur in animals suffering from porphyrinuria or porphyrinemia when exposed to sunlight. In order to investigate this reaction, 0.5 cc Ethyl Methacrylate was applied to the skin of 10 rats six times a week for 20 weeks. Five rats were exposed daily to ultraviolet light from an Ashcraft ultraviolet generator (Model 476) for 1 h. Mild, transient irritation was the most severe reaction observed during the study.

Ocular Irritation

Two rabbits had 0.1 ml of undiluted Ethyl Methacrylate instilled into their right conjunctival sac. One rabbit's eye was rinsed after 20 s, and the other rabbit's eye was left unrinsed. The eyes were examined after 1 and 4 h, and after 1, 2, 3, and 7 days. A small area of opacity was observed in the cornea of the unrinsed eye, which diminished through days 2 and 3. Discharge from the eye was severe 1 h after treatment, moderate after 4 h, and mild at 24 h. The conjunctiva was slightly red and swollen through day 2. No effects were observed in the iris, and the cornea was transparent by day 7. Conjunctival irritation was milder in the rinsed eye. A small area of microscopic surface sheen was seen in the cornea at day 1, and mild transient conjunctivitis was observed. No effects on the iris were found and all signs of irritation disappeared by day 3 (Haskell Laboratory for Toxicology and Industrial Medicine, 1977).

REPRODUCTION AND DEVELOPMENTAL TOXICITY

Groups of five pregnant Sprague–Dawley rats were given 0.1223, 0.2446, and 0.4076 ml/kg Ethyl Methacrylate intraperitoneally on days 5, 10, and 15 of gestation. A control group of pregnant rats was left untreated. All of the rats were killed on day 20 of gestation and examined for evidence of embryonic–fetal toxicity and teratogenic effects. The number of corpora lutea in the treatment groups ranged from 53 to 58, and there were 60 corpora lutea in the control group. Resorptions occurred only in the test animals; five resorptions occurred in the 0.1223 ml/kg group, six in the 0.2446 ml/kg group, and seven in the 0.4076 ml/kg group. There were fewer fetuses in the test groups (42–51 fetuses) than in the control group (59 fetuses). All of the fetuses in the experimental groups were alive, but the mean weights of the fetuses in the mid- and high-dosage groups were significantly lower than that of the controls.

A significant number of gross abnormalities were found in the fetuses from the experimental groups. In the high-dosage group, eight gross abnormalities were found: one hemangioma each of the hind leg and foreleg, three cases of hemangiomas of the shoulders, one case of twisted hind legs, one case of no tail, and one fetus was very small with a compact head and neck. Three of the 27 fetuses examined had elongated and fused ribs. In the mid-dose group, five hemangiomas of the neck were found, and two of the 26 fetuses examined had elongated and fused posterior ribs. Similar abnormalities were observed in the low-dosage group. Two cases of hemangiomas on the shoulders were found, one fetus had twisted hind legs, and one fetus of the 25 examined had elongated posterior ribs. No gross or skeletal abnormalities were found in the fetuses from the untreated control group. The researchers concluded that Ethyl Methacrylate produced significant embryopathic and teratogenic effects (Singh et al., 1972).

MUTAGENICITY

Ethyl Methacrylate was evaluated at concentrations ranging from 33 to 10,000 μg/plate with the *Salmonella*/microsome test using *Salmonella typhimurium*

strains TA98, TA100, TA1535, and TA1537. Tests were conducted in triplicate both with and without activation with liver S9 from Aroclor-induced Sprague–Dawley rats and Syrian hamsters. Solvent and positive controls were also included with each trial. The positive controls used for tests without metabolic activation were sodium azide for strains TA100 and TA1535, 9-aminoacridine for TA1537, and 4-nitro-*o*-phenylenediamine for TA98. In tests with S9 activation, 2-aminoanthracene was used for all of the strains. Ethyl Methacrylate was negative in tests both with and without metabolic activation (Zeiger et al., 1987).

In another *Salmonella*/microsome test, Ethyl Methacrylate was tested at concentrations ranging from 40 to 2,500 μg/plate using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538. Metabolic activation was produced once with phenobarbital-induced S9 mix and once with Aroclor-1254–induced S9 mix. Two tests were conducted without metabolic activation. All of the tests were conducted in triplicate. In tests using phenobarbital-induced S9 mix, 2-aminoanthracene was the positive control for all of the strains. Benz[*a*]pyrene was the positive control used to test strains TA98, TA100, and TA1538 with activation with Aroclor-induced S9 mix; no positive controls were used to test strains TA1535 and TA37 in this system. The positive controls used for tests without activation were sodium azide for strains TA100 and TA1535, glycidyl methacrylate for TA1535, 9-aminoacridine for TA1537, and 4-nitro-*o*-phenylenediamine for TA98 and TA1538. Ethyl Methacrylate was negative both with and without phenobarbital or Aroclor-induced S9 mix (Waegemaekers and Bensink, 1984).

Ethyl Methacrylate was tested in the L5178Y mouse lymphoma cell assay. L5178Y/TK$^{+/-}$ cells were treated with 900–2,100 μg/ml of Ethyl Methacrylate without exogenous activation for 4 h. Control cells were treated with the solvent (dimethyl sulfoxide) alone. Cytogenic analyses were conducted on 200 cells per treatment group following cell treatment and washing. Other cells were maintained in log-phase growth for 2 days and then cloned with and without trifluorothymidine (TFT) selection. Following an incubation period of 9–11 days, the colonies were counted and sized. Cytotoxicity was only observed at concentrations >1,000 μg/ml. Toxicity plateaued at concentrations >1,500 μg/ml, where survival fluctuated from 2 to 37%. A weak positive response was observed in cultures with 10–20% survival (1,450, 1,500, 1,550, and 1,626 μg/ml). The greatest number of aberrations occurred at a concentration of 1,626 μg/ml (16% survival); Ethyl Methacrylate induced 83 mutants/10^6 survivors and 11 aberrations/200 cells. Some of the cultures with <10% survival had mutation frequencies three time greater than background. The colony size distribution was difficult to determine; however, the authors did note that cultures with mutation frequencies of 200 mutants/10^6 survivors (<10% survival) had an induction of primarily small colonies. The authors suggested that the genotoxicity of Ethyl Methacrylate was likely due to a clastogenic mechanism (Moore et al., 1988).

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation and Cross-Reactivity

Ethyl Methacrylate was tested on 542 dermatitis patients using either the A1-Test (Imeco Agency, Sweden) or the Finn Chamber method. Each subject was

TABLE 1. *Case studies of contact dermatitis caused by artificial fingernails*

Case study	Patch test	Results	Reference
A woman developed paronychial and eyelid dermatitis 2 days after new application of nails. The components of the nail preparation were a clear liquid monomer, clear powder polymer, and white powder polymer	An aluminum patch test using the components of the nail preparation and ethyl, methyl, and *N*-butyl methacrylate (5% in petrolatum and 1% in ethyl alcohol) were applied to the back	The liquid monomer and all of the methacrylate esters caused erythema, papules, and vesicles at 48 and 96 h	Marks et al. (1979)
A patient suffered from severe painful onychia and paronychia 3 weeks after applying nails containing Ethyl Methacrylate monomer and isobutyl methacrylate monomer	Patch tests with 1% Ethyl Methacrylate, 1% isobutyl methacrylate monomer, and methyl methacrylate monomer	Strong positive reaction developed for all three monomers	Fisher (1980)
A patient developed severe onychia and paronychia 4 weeks after applying nails containing Ethyl Methacrylate, tetrahydrofurfuryl methacrylate, and diethylene glycol dimethacrylate monomers	Patch tests with 1% of each monomer and methyl methacrylate monomer	Strong positive reactions were caused by all four monomers	Fisher (1980)
After 3 months of using nails containing Ethyl Methacrylate monomer and ethylene glycol dimethacrylate, a patient developed mild paronychia	Patch tests with 1 and 5% of each monomer and methyl methacrylate monomer	1% concentrations of all of the monomers caused faint positive reactions. Strong positive reactions occurred after testing with 5% concentrations	Fisher (1980)
A woman working in the manufacture and application of sculptured nails developed allergic contact dermatitis on her hands	Patch tests with a standard series and with plastics and acrylates, including 10% Ethyl Methacrylate, 10% methyl methacrylate, and 2% hydroxyethyl methacrylate	Positive reactions were present at 48 and 96 h for the methacrylates tested, as well as nickel sulfate (2.5%), Prains (10%), and cavity primer (1 & 10%)	Condé-Salazar et al. (1986)

TABLE 1. *Continued*

Case study	Patch test	Results	Reference
A 46-year-old woman developed onycholysis of the fingernails and dermatitis of the fingers, dorsa of the hands, arms, upper trunk, and face 6 months after beginning regular application of sculpture fingernails	Patch tests were performed using the components of the sculptured fingernails (Ethyl Methacrylate monomer liquid and polymethacrylate powder), the European standard series, and to a plastics and glue series	The subject had positive reactions to patch tests with 1% MEK Ethyl Methacrylate, 10% pet. polymer nail powder, and 1% pet. butyl methacrylate.	Fitzgerald and English (1994)

exposed for 48 h to 1% Ethyl Methacrylate in petrolatum, and scoring was conducted at 48 and 96 h. Only one subject developed signs of irritation. Four subjects who were sensitive to methyl methacrylate were also tested with Ethyl Methacrylate. No cross reactions were observed (Maibach et al., 1978).

Patients with acrylate allergies were patch tested with 35 acrylates, including 2% Ethyl Methacrylate in petrolatum. Fourteen of 22 patients had positive reactions to Ethyl Methacrylate. Eleven of these patients had occupational exposure to artificial fingernails and, among this subgroup, seven patients had positive reactions (Koppula et al., unpublished observations).

A number of case studies of allergic contact dermatitis caused by artificial fingernails containing Ethyl Methacrylate have been reported. The details of these studies are in Table 1. In all six patients reported sensitized to methacrylates in sculptured nails, cross-reactivity with other methacrylate monomers was seen.

Cases of contact dermatitis to anaerobic acrylic sealants have also been documented. Six workers who developed dermatitis after contact with various sealants in the work place were patch tested with the sealants (0.1–1%), a standard patch test series, a plastic series, and a variety of acrylates. Each worker was exposed to the chemicals for 48 h, and the sites were read at 48, 72, and 96 h. The workers were positive for the sealants tested and negative for the standard and plastic series. Five of the workers had positive reactions to 10% Ethyl Methacrylate after 96 h. These individuals also had sensitivity to 2% hydroxyethyl methacrylate, three were sensitive to 10% methyl methacrylate monomer and 1% ethylene glycol dimethacrylate, two were sensitive to 0.1% acrylic acid, and one had a reaction to 1% triethylene glycol dimethacrylate. A control group of 20 individuals was negative for all of the compounds tested (Condé-Salazar et al., 1988).

Occupational Exposure

Occupational contact dermatitis from acrylate- and methacrylate-based products was reported in workers exposed to anaerobic sealants (Kanerva et al., 1989; Guerra et al., 1993), dental composite resins (Kanerva et al., 1989), dental and medical prostheses (Kanerva et al., 1993), sculptured fingernails (Taylor, 1989;

Tosti et al., 1992), printing materials (Calnan, 1980), and plastic embedding media (Montgomery, 1989).

Savonius et al. (1993) report that acrylates also have the potential to cause respiratory symptoms, most commonly asthma.

Hiipakka and Samimi (1987) specifically studied nail sculptors for exposure to organic vapors and methacrylate dusts from acrylic fingernail extensions. Seventeen personal vapor samples were taken from nail salons and the mean time-weighted average concentration of Ethyl Methacrylate was 4.5 ppm. There is no threshold limit value (TLV) for Ethyl Methacrylate, but the authors speculated that this concentration was probably below the expected threshold, as the TLV for methyl methacrylate is 100 ppm. Twenty sculptors completed self-administered symptom questionnaires, in which they consistently reported nasal and cutaneous irritation, drowsiness, dizzy spells, and trembling hands. These signs were reported more often by nail sculptors but were not statistically greater than that reported by matched controls. Throat irritation was the only statistically significant symptom.

SUMMARY

Ethyl Methacrylate is the ester of ethyl alcohol and methacrylic acid and is used as the major structural monomer of artificial fingernail formulations which are cross-linked with one or more multifunctional methacrylates. Ethyl Methacrylate is used as a substitute for methyl methacrylate, which was banned from use in fingernail products in 1974 by the U.S. Food and Drug Administration due to numerous consumer complaints about onycholysis and nail dislocation and/or irritation.

In commercial fingernail formulations, Ethyl Methacrylate monomer is rapidly polymerized. Approximately 50% of the polymerization occurs within 5 min, and <1% monomer is available after 1 h. The monomer content detected in filings from these types of products was <2% after 45 min, and <1% after 90 min.

The oral LD_{50} for rats ranged between 12.70 and 18.14 g/kg Ethyl Methacrylate. Hemoglobinuria and lesions in the respiratory system were observed. In an acute inhalation study, the $LC_{50/24}$ for rats was 8,300 ppm Ethyl Methacrylate, and ocular, nasal, and respiratory tract irritation was observed. In another study, the lungs, trachea, and bronchi of the rats were markedly congested, edematous, and spotted. Hemorrhage and emphysema were also observed.

In subchronic studies, Ethyl Methacrylate increased the concentrations of blood and urinary porphyrins after intravenous administration in rabbits, and affected drug-metabolizing enzymes in mice after inhalation exposure.

Ethyl Methacrylate was irritating to the skin of rabbits and sensitization reactions were observed in both the guinea pig maximization test and the Freund's complete adjuvant test. One study indicated that the sensitization potential of Ethyl Methacrylate was dependent upon the vehicle of administration. Strong sensitization was observed in guinea pigs when olive oil was the vehicle, but no sensitization occurred when ethanol was used. Mutual cross-sensitivity exists between monomers of methacrylic acid and a small degree of cross-reactivity occurs with other acrylic monomers.

Mild, transient irritation was the most severe reaction observed when rats were given topical applications of Ethyl Methacrylate and were irradiated with UV light for 1 h. Ethyl Methacrylate also caused transient ocular irritation.

In a teratogenicity study, pregnant rats were injected intraperitoneally with 0.1223, 0.2446, and 0.4076 ml/kg of Ethyl Methacrylate. Evidence of embryotoxicity and teratogenic effects were observed in all three dosage groups.

Ethyl Methacrylate was negative in two *Salmonella*/microsome tests both with and without metabolic activation. However, it was positive in the L5178Y mouse lymphoma cell assay.

In a clinical irritation study, 542 patients were exposed to 1% Ethyl Methacrylate for 48 h. Only one subject developed signs of irritation. In several case studies, Ethyl Methacrylate and related methacrylates in artificial fingernails caused allergic contact dermatitis. Occupational contact dermatitis from acrylates and methacrylates has been observed in individuals exposed to sealants, dental resins, prostheses, and plastic embedding media, as well as those handling artificial nails. There appears to be some degree of cross-reactivity between the acrylates and methacrylates.

DISCUSSION

The sensitization and cross- or co-reactivity potential of Ethyl Methacrylate was of concern to the Expert Panel. Some animal studies indicate that Ethyl Methacrylate is a strong sensitizer. Although one study in humans indicated a lack of sensitizing potential, it was noted that the concentration tested (1%) was below the concentration typically used in patch tests (2%). Incidence data are not available because acrylates and methacrylates are not regularly used in clinical patch testing.

Ethyl Methacrylate is used as the major structural monomer of artificial fingernail formulations which are crosslinked with one or more multifunctional methacrylates. Due to the nature of these types of formulations, the monomer is entrapped quickly and very little free monomer is available even during filing of the fingernails. In order to minimize any exposure to the free monomer, the Expert Panel recommends that fingernail enhancement products containing Ethyl Methacrylate be applied only by trained individuals and that skin contact be avoided. Ethyl Methacrylate should not be used in products intended for retail sale.

Concern regarding the potential respiratory problems caused by the inhalation of Ethyl Methacrylate particles produced from filing of artificial fingernails was also discussed. Since this type of particulate matter is usually large enough to be seen and is not likely to be airborne for extended periods of time, Ethyl Methacrylate is not expected to cause respiratory problems.

The Expert Panel also discussed the teratogenic effects observed in a study with rats. They agreed that the study was a poor indicator of developmental toxicity because the route of exposure was intraperitoneal. Additional studies are not required because exposure to the monomer is expected to be low and because cutaneous absorption of this material is low. Negative mutagenicity results also alleviated the Expert Panel's concerns.

CONCLUSION

Based on the available data on the formulation of nail products containing Ethyl Methacrylate, the CIR Expert Panel concludes that this ingredient is safe as used. Skin contact should be avoided because of the sensitizing potential of Ethyl Methacrylate.

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