

Final Report on the Safety Assessment of Acrylates Copolymer and 33 Related Cosmetic Ingredients^{1,2}

Ingredients in the Acrylates Copolymer group all contain the monomers acrylic acid or methacrylic acid or one of their salts or esters. These ingredients are considered similar in that they are uniformly produced in chemical reactions that leave very little residual monomer. Although residual acrylic acid may be as high as 1500 ppm, typical levels are 10 to 1000 ppm. There is sufficient odor if residual monomers are present to cause producers to keep levels as low as possible. These ingredients function in cosmetics as binders, film formers, hair fixatives, suspending agents, viscosity-increasing agents, and emulsion stabilizers. Concentrations may be as high as 25% if used as a binder, film former, or fixative; or as low as 0.5% if used as a viscosity-increasing agent, suspending agent, or emulsion stabilizer. These very large polymers exhibit little toxicity. In rabbits and guinea pigs, Acrylates Copolymer did produce irritation, but no evidence of sensitization was found. The principle concern regarding the use of these polymer ingredients is the presence of toxic residual monomers. In particular, although 2-ethylhexyl acrylate was not genotoxic, it was carcinogenic when applied at a concentration of 21% to the skin of C3H mice. Lower concentrations (2.5%) and stop-dose studies at high concentrations (43%) were not carcinogenic. 2-Ethylhexyl acrylate was not car-

cinogenic in studies using NMRI mice. Whether an increase in carcinogenesis was seen or not, there was evidence of severe dermal irritation in these 2-ethylhexyl acrylate studies. Another concern regarding residual monomers was inhalation toxicity. Although the acrylic acid monomer is a nasal irritant, exposure to the monomer from use of these polymers in cosmetic formulations would always be less than the established occupational exposure limits for nasal irritation. Although there appears to be a huge variation in the mix of monomers used in the synthesis of these polymers, they are similar in that the polymers, except for dermal irritation, are not significantly toxic, and residual monomer levels are kept as low as possible. Although the monomers may be toxic, the levels that would be found in cosmetic formulations are not considered to present a safety risk. Accordingly, these Acrylate Copolymers are considered safe for use in cosmetic formulations when formulated to avoid irritation.

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²Related Cosmetic Ingredients: Ammonium Acrylates Copolymer, Ammonium VA/Acrylates Copolymer, Sodium Acrylates Copolymer, Ethylene/Acrylic Acid Copolymer, Ethylene/Calcium Acrylate Copolymer, Ethylene/Magnesium Acrylate Copolymer, Ethylene/Sodium Acrylate Copolymer, Ethylene/Zinc Acrylate Copolymer, Ethylene/Acrylic Acid/VA Copolymer, Acrylates/PVP Copolymer, Acrylates/VA Copolymer, Steareth-10 Allyl Ether/Acrylates Copolymer, Acrylates/Steareth-50 Acrylate Copolymer, Acrylates/Steareth-20 Methacrylate Copolymer, Acrylates/Ammonium Methacrylate Copolymer, Styrene/Acrylates Copolymer, Styrene/Acrylates/Ammonium Methacrylate Copolymer, Ammonium Styrene/Acrylates Copolymer, Sodium Styrene/Acrylates Copolymer, Acrylates/Hydroxyesters Acrylates Copolymer, Methacryloyl Ethyl Betaine/Acrylates Copolymer, Lauryl Acrylate/VA Copolymer, VA/Butyl Maleate/Isobornyl Acrylate Copolymer, Ethylene/Methacrylate Copolymer, Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer, Sodium Acrylates/Acrolein Copolymer, PVP/Dimethylaminoethylmethacrylate Copolymer, AMP-Acrylates Copolymer, Polyacrylic Acid, Ammonium Polyacrylate, Potassium Aluminum Polyacrylate, Potassium Polyacrylate, Sodium Polyacrylate.

INTRODUCTION

This report covers a large number of polymers that contain the monomers acrylic acid or methacrylic acid or one of their salts or esters. Table 1 lists each of the ingredients along with the monomers that are polymerized to create the copolymer.

Some of these monomers have previously been reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel, namely, PVP (polyvinyl pyrrolidone), steareth-10, steareth-20, and polymers containing VA (vinyl acetate), which are components of some of the copolymers included in this safety assessment. Significant toxicity issues regarding these ingredients were not found, and it was concluded that PVP (Andersen 1998), steareth-10 and steareth-20 (Elder 1988), PVP/VA copolymer (Elder 1983a), and VA/CA (vinyl acetate/crotonic acid) copolymer (Elder 1983b) were safe as used as cosmetic ingredients.

Ethyl methacrylate also has been reviewed by the CIR Expert Panel (Andersen 1995; CIR 1999). In an amended final safety assessment based on the available data on the formulation of nail products containing Ethyl Methacrylate, this ingredient was found safe as used when application is accompanied by directions to avoid skin contact because of the sensitizing potential of Ethyl Methacrylate.

Because acrylic acid is a major component of most, if not all, of the copolymers included in this review, relevant data on acrylic acid and some of its esters are summarized where applicable.

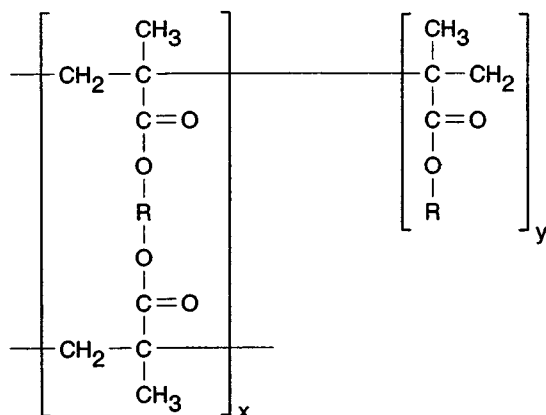
TABLE 1
 Ingredients descriptions (Wenninger, Canterbury, and McEwen 2000)

| Ingredient | Components |
|---|--|
| Acrylates Copolymer | Two or more of acrylic acid, methacrylic acid, or one of their simple esters |
| Ammonium Acrylates Copolymer | Two or more of acrylic acid, methacrylic acid, or one of their simple esters |
| Ammonium VA/Acrylates Copolymer | Vinyl acetate and two or more of acrylic acid, methacrylic acid, or one of their simple esters |
| Sodium Acrylates Copolymer | One or more of acrylic acid, methacrylic acid, or one of their simple esters |
| Ethylene/Acrylic Acid Copolymer | Ethylene and acrylic acid |
| Ethylene/Calcium Acrylate Copolymer | Ethylene and calcium acrylate |
| Ethylene/Magnesium Acrylate Copolymer | Ethylene and magnesium acrylate |
| Ethylene/Sodium Acrylate Copolymer | Ethylene and sodium acrylate |
| Ethylene/Zinc Acrylate Copolymer | Ethylene and zinc acrylate |
| Ethylene/Acrylic Acid/VA Copolymer | Ethylene, acrylic acid and vinyl acetate |
| Acrylates/PVP Copolymer | PVP and one or more of acrylic acid, methacrylic acid, or one of their simple esters |
| Acrylates/VA Copolymer | Vinyl acetate and one or more of acrylic acid, methacrylic acid, and one of their simple esters (contains 2-ethylhexyl acrylate) |
| Steareth-10 Allyl Ether/Acrylates Copolymer | Allyl ether of steareth-10 and one or more of acrylic acid, methacrylic acid, or one of their simple esters |
| Acrylates/Steareth-50 Acrylate Copolymer | Ester of acrylic acid and one or more of steareth-50 and acrylic acid, methacrylic acid, or one of their simple esters |
| Acrylates/Steareth-20 Methacrylate Copolymer | Ester of methacrylic acid and steareth-20 and one or more of acrylic acid, methacrylic acid, or one of their simple esters |
| Acrylates/Ammonium Methacrylate Copolymer | Ammonium methacrylate and one or more of acrylic acid, methacrylic acid, or one of their simple esters |
| Styrene/Acrylates Copolymer | Styrene, acrylic acid, methacrylic acid, or one of their simple esters |
| Styrene/Acrylates/Ammonium Methacrylate Copolymer | Styrene, ammonium methacrylate, and acrylic acid, methacrylic acid, or one of their simple esters |
| Ammonium Styrene/Acrylates Copolymer | Styrene and acrylic acid, methacrylic acid, or one of their simple esters |
| Sodium Styrene/Acrylates Copolymer | Styrene and acrylic acid, methacrylic acid, or one of their simple esters |
| Acrylates/Hydroxyesters Acrylates Copolymer | One or more of acrylic acid, methacrylic acid, or one of their simple esters and one or more of hydroxyacrylate esters |
| Methacryloyl Ethyl Betaine/Acrylates Copolymer | Methacryloyl ethyl betaine and two or more of methacrylic acid or its simple esters |
| Lauryl Acrylate/VA Copolymer | Lauryl acrylate and vinyl acetate |
| VA/Butyl Maleate/Isobornyl Acrylate Copolymer | Vinyl acetate, butyl maleate, and isobornyl acrylate |
| Ethylene/Methacrylate Copolymer | Ethylene and methyl methacrylate |
| Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer | Vinylcaprolactam, vinylpyrrolidone, and dimethylaminoethyl methacrylate |
| Sodium Acrylates/Acrolein Copolymer | Sodium acrylate and acrolein |
| PVP/Dimethylaminoethylmethacrylate Copolymer | Vinylpyrrolidone and dimethylaminoethylmethacrylate |
| AMP-Acrylates Copolymer | Aminomethyl propanol salt of Acrylates Copolymer |
| Polyacrylic Acid | Acrylic acid |
| Ammonium Polyacrylate | Acrylic acid |
| Potassium Aluminum Polyacrylate | Acrylic acid |
| Potassium Polyacrylate | Acrylic acid |
| Sodium Polyacrylate | Acrylic acid |

CHEMISTRY

Definition and Structure

Acrylates Copolymer. Acrylates Copolymer is a copolymer of two or more monomers consisting of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbury, and McEwen 2000) and has the basic chemical structure (Klein and DeSapio 1989) shown below.



Acrylates Copolymer

The smallest, or primary, units of Acrylates Copolymer are individual particles $<1 \mu$ in diameter which partially fuse to form agglomerates ranging in size from approximately $20\text{--}80 \mu$; agglomerates are held together by electrostatic forces and mechanical entanglement to form larger aggregates of $200\text{--}1200 \mu$ (Klein and DiSapio 1989).

Acrylates Copolymer is also known as Acrylic/Acrylate Copolymer and Acrylic/Acrylates Copolymer (Wenninger, Canterbury, and McEwen 2000).

Ammonium Acrylates Copolymer. Ammonium Acrylates Copolymer is the ammonium salt of a polymer of two or more monomers consisting of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbury, and McEwen 2000).

Ammonium VA/Acrylates Copolymer. Ammonium VA/Acrylates Copolymer is the ammonium salt of a polymer of vinyl acetate and two or more monomers consisting of acrylic acid, methacrylic acid, or their simple esters (Wenninger, Canterbury, and McEwen 2000). It is also known as Ammonium Vinyl Acetate/Acrylates Copolymer.

Sodium Acrylates Copolymer. Sodium Acrylates Copolymer is the sodium salt of a polymer consisting of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbury, and McEwen 2000).

Ethylene/Acrylic Acid Copolymer. Ethylene/Acrylic Acid Copolymer (CAS No. 9010-77-9) is a copolymer of ethylene and acrylic acid monomers (Wenninger, Canterbury, and McEwen 2000). It is also known as 2-Propenoic Acid with Ethene (Wenninger, Canterbury, and McEwen 2000); 2-Propenoic Acid,

Polymer with Ethene; Acrylic Acid, Polymer with Ethene; Ethylene Acrylic Acid (Chemline 1996); Acrylic Acid, Polymer with Ethylene; Acrylic Acid Copolymer with Ethylene; Acrylic Acid-Ethene Copolymer; Acrylic Acid-Ethylene Copolymer; Acrylic Acid-Ethylene Polymer; and Acrylic Acid-Polyethylene Polymer (Chemical Abstracts 1996).

Ethylene/Calcium Acrylate Copolymer. Ethylene/Calcium Acrylate Copolymer (CAS No. 26445-96-5) is a copolymer of ethylene and calcium acrylate monomers and has the empirical formula $(C_3H_4O_2 \cdot C_2H_4)_x \cdot xCa$ (Wenninger, Canterbury, and McEwen 2000). It is also known as 2-Propenoic Acid, Polymer with Ethene, Calcium Salt (Wenninger, Canterbury, and McEwen 2000); Acrylic Acid, Polymer with Ethylene, Calcium Salt (Chemline 1996); Ethene, Polymer with 2-Propenoic Acid, Calcium Salt; Ethylene, Polymer with Acrylic Acid, Calcium Salt; Acrylic Acid-Ethylene Copolymer Calcium Salt (Chemical Abstracts 1996).

Ethylene/Magnesium Acrylate Copolymer. Ethylene/Magnesium Acrylate Copolymer is a copolymer of ethylene and magnesium acrylate monomers and has the empirical formula $(C_3H_4O_2 \cdot C_2H_4)_x \cdot xMg$ (Wenninger, Canterbury, and McEwen 2000). It is also known as 2-Propenoic Acid, Polymer with Ethene, Magnesium Salt.

Ethylene/Sodium Acrylate Copolymer. Ethylene/Sodium Acrylate Copolymer (CAS No. 25750-82-7) is a copolymer of ethylene and sodium acrylate monomers and has the empirical formula $(C_3H_4O_2 \cdot C_2H_4)_x \cdot xNa$ (Wenninger, Canterbury, and McEwen 2000). It is also known as 2-Propenoic Acid, Polymer with Ethene, Sodium Salt (Wenninger, Canterbury, and McEwen 2000); Acrylic Acid, Polymer with Ethylene, Sodium Salt (Chemline 1996); Ethene, Polymer with 2-Propenoic Acid, Sodium Salt; Ethylene, Polymer with Acrylic Acid, Sodium Salt; Acrylic Acid-Ethylene Copolymer Sodium Salt; Acrylic Acid-Ethylene Polymer Sodium Salt; and Ethylene-Acrylic Acid Polymer Sodium Salt (Chemical Abstracts 1996).

Ethylene/Zinc Acrylate Copolymer. Ethylene/Zinc Acrylate Copolymer (CAS No. 59650-68-9; Chemical Abstracts 1996) is a copolymer of ethylene and zinc acrylate monomers and has the empirical formula $(C_3H_4O_2 \cdot C_2H_4)_x \cdot xZn$ (Wenninger, Canterbury, and McEwen 2000). It is also known as 2-Propenoic Acid, Polymer with Ethene, Zinc Salt (Wenninger, Canterbury, and McEwen 2000); 2-Propenoic Acid, Zinc Salt, Polymer with Ethene; and Ethene, Polymer with Zinc Di-2-Propenoate (Chemical Abstracts 1996).

Ethylene/Acrylic Acid/VA Copolymer. Ethylene/Acrylic Acid/VA Copolymer (CAS No. 26713-18-8) is a copolymer of ethylene, acrylic acid, and vinyl acetate monomers (Wenninger, Canterbury, and McEwen 2000). It is also known as 2-Propenoic Acid, Polymer with Ethene and Ethenyl Acetate (Wenninger, Canterbury, and McEwen 2000); Acrylic Acid, Polymer with Ethylene and Vinyl Acetate (Chemline 1996); Ethylene, Polymer with Acrylic Acid and Vinyl Acetate; Ethylene-Acrylic Acid-Vinyl Acetate Copolymer; Ethylene-Acrylic Acid-Vinyl

Acetate Polymer; Ethylene-Vinyl Acetate-Acrylic Acid Copolymer; Ethylene-Vinyl Acetate-Acrylic Acid Polymer; Acrylic Acid-Ethylene-Vinyl Acetate Copolymer; Acrylic Acid-Ethylene-Vinyl Acetate Polymer; Acrylic Acid-Ethylene-Vinyl Acetate Terpolymer; Ethene, Polymer with Ethenyl Acetate and 2-Propenoic Acid; Acetic Acid Ethenyl Ester, Polymer with Ethene and Ethenyl Acetate; and Acetic Acid Vinyl Ester, Polymer with Acrylic Acid and Ethylene (Chemical Abstracts 1996).

Acrylates/PVP Copolymer. Acrylates/PVP Copolymer (CAS No. 26589-26-4) is a copolymer of PVP and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbury, and McEwen 2000). It is also known as Methacrylic Acid, Polymer with Ethyl Methacrylate and 1-Vinyl-2-Pyrrolidinone; PVP/Ethyl Methacrylate/Methacrylic Acid Copolymer (Wenninger, Canterbury, and McEwen 2000); 2-Propenoic Acid, 2-Methyl, Polymer with 1-Ethenyl-2-Pyrrolidinone and Ethyl 2-Methyl-2-Propenoate; *N*-Vinyl-2-Pyrrolidone, Methacrylic Acid, Ethyl Methacrylate Polymer; 1-Ethylene-2-Pyrrolidinone, Methacrylic Acid, Ethyl Methacrylate Polymer (Chemline 1996); 2-Propenoic Acid, 2-Methyl-, Ethyl Ester, Polymer with 1-Ethenyl-2-Pyrrolidinone and 2-Methyl-2-Propenoic Acid; 2-Pyrrolidinone, 1-Ethenyl-, Polymer with Ethyl 2-Methyl-2-Propenoate and 2-Methyl-2-Propenoic Acid; 2-Pyrrolidinone, 1-Vinyl-, Polymer with Ethyl Methacrylate and Methacrylic Acid; and Methacrylic Acid, Ethyl Ester, Polymer with Methacrylic Acid and 1-Vinyl-2-Pyrrolidinone (Chemical Abstracts 1996).

Acrylates/VA Copolymer. Acrylates/VA Copolymer (CAS No. 25067-02-1) is a copolymer of vinyl acetate and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger et al. 2000). It is also known as 2-Propenoic Acid, 2-Ethylhexyl Ester, Polymer with Ethenyl Acetate; Vinyl Acetate/Acrylate Copolymer; Vinyl Acetate, 2-Ethylhexyl Acrylate Copolymer (Wenninger, Canterbury, and McEwen 2000); Acrylic Acid, 2-Ethylhexyl Ester, Polymer with Vinyl Acetate; Poly(Vinyl Acetate-2-Ethylhexyl Acrylate) (Chemline 1996); 2-Ethylhexyl Acrylate-Vinyl Acetate Copolymer; 2-Ethylhexyl Acrylate-Vinyl Acetate Polymer; Vinyl Acetate-2-Ethylhexyl Acrylate Copolymer; Acetic Acid Vinyl Ester, Polymer with 2-Ethylhexyl Acrylate; and Acetic Acid Ethenyl Ester, Polymer with 2-Ethylhexyl 2-Propenoate (Chemical Abstracts 1996).

Steareth-10 Allyl Ether/Acrylates Copolymer. Steareth-10 Allyl Ether/Acrylates Copolymer (CAS No. 109292-17-3) is a copolymer of the allyl ether of Steareth-10 (q.v.) and one or more monomers consisting of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbury, and McEwen 2000). *Quantum vis* (q.v.) translates to "as much as you please."

Acrylates/Steareth-50 Acrylate Copolymer. Acrylates/Steareth-50 Acrylate Copolymer is a copolymer of the ester of acrylic acid and Steareth-50 (q.v.) and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbury, and McEwen 2000).

Acrylates/Steareth-20 Methacrylate Copolymer. Acrylates/Steareth-20 Methacrylate Copolymer is a copolymer of the ester of methacrylic acid and Steareth-20 (q.v.) and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbury, and McEwen 2000).

Acrylates/Ammonium Methacrylate Copolymer. Acrylates/Ammonium Methacrylate Copolymer is a copolymer of ammonium methacrylate and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbury, and McEwen 2000). It is also known as Acrylate/Ammonium Methacrylate Copolymer.

Styrene/Acrylates Copolymer. Styrene/Acrylates Copolymer (CAS No. 9010-92-8) is a polymer of styrene and a monomer consisting of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbury, and McEwen 2000). It is also known as 2-Propenoic Acid, Butyl Ester, Polymer with Ethylbenzene and Styrene/Acrylate Copolymer.

Styrene/Acrylates/Ammonium Methacrylate Copolymer. Styrene/Acrylates/Ammonium Methacrylate Copolymer is a polymer of styrene, ammonium methacrylate, and a monomer consisting of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbury, and McEwen 2000). It is also known as Styrene/Acrylate/Ammonium Methacrylate Copolymer.

Ammonium Styrene/Acrylates Copolymer. Ammonium Styrene/Acrylates Copolymer is the ammonium salt of a polymer of styrene and a monomer consisting of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbury, and McEwen 2000).

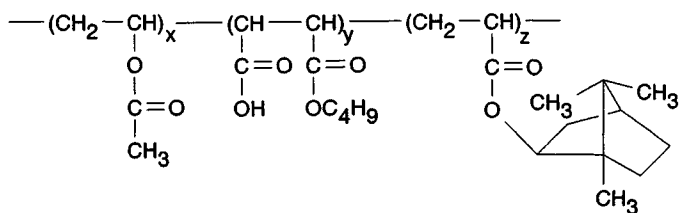
Sodium Styrene/Acrylates Copolymer. Sodium Styrene/Acrylates Copolymer (CAS No. 9010-92-8) is the sodium salt of a polymer of styrene and a monomer consisting of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbury, and McEwen 2000).

Acrylates/Hydroxyesters Acrylates Copolymer. Acrylates/Hydroxyesters Acrylates Copolymer is a copolymer of one or more monomers consisting of acrylic acid, methacrylic acid, or their simple esters, and one or more monomers of hydroxyacrylate esters (Wenninger, Canterbury, and McEwen 2000).

Methacryloyl Ethyl Betaine/Acrylates Copolymer. Methacryloyl Ethyl Betaine/Acrylates Copolymer is a polymer of methacryloyl ethyl betaine and two or more monomers of methacrylic acid or its simple esters (Wenninger, Canterbury, and McEwen 2000). It is also known as Methacryloyl Ethyl Betaine/Methacrylates Copolymer.

Lauryl Acrylate/VA Copolymer. Lauryl Acrylate/VA Copolymer is a copolymer of lauryl acrylate and vinyl acetate monomers (Wenninger, Canterbury, and McEwen 2000).

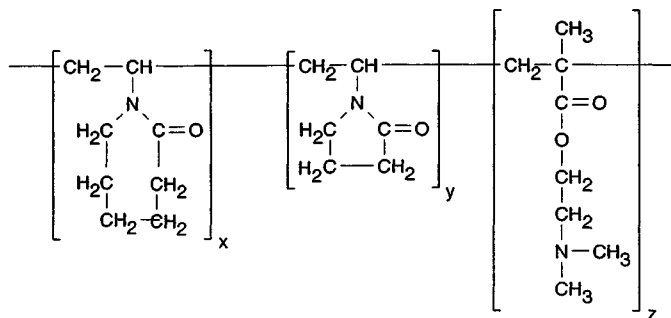
VA/Butyl Maleate/Isobornyl Acrylate Copolymer. VA/Butyl Maleate/Isobornyl Acrylate Copolymer is a copolymer of vinyl acetate, butyl maleate, and isobornyl acrylate monomers (Wenninger, Canterbury, and McEwen 2000) and has the following structure (Patel and Petter 1992):



VA/Butyl Maleate/Isobornyl Acrylate Copolymer

Ethylene/Methacrylate Copolymer. Ethylene/Methacrylate Copolymer is a copolymer of ethylene and methyl methacrylate monomers (Wenninger, Canterbury, and McEwen 2000).

Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer. Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer is a copolymer of vinylcaprolactam, vinylpyrrolidone, and dimethylaminoethyl methacrylate (q.v.) monomers (Wenninger, Canterbury, and McEwen 2000) and has the following chemical structure (Patel and Petter 1992):



Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer

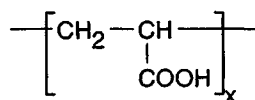
Sodium Acrylates/Acrolein Copolymer. Sodium Acrylates/Acrolein Copolymer is a polymer consisting of sodium acrylate and acrolein monomers (Wenninger, Canterbury, and McEwen 2000).

PVP/Dimethylaminoethylmethacrylate Copolymer. PVP/Dimethylaminoethylmethacrylate Copolymer (CAS No. 30581-59-0) is a polymer prepared from vinylpyrrolidone and dimethylaminoethylmethacrylate monomers (Wenninger, Canterbury, and McEwen 2000). It is also known as 2-Propenoic Acid, 2-Methyl-, 2-(Dimethylamino)Ethyl Ester, Polymer with 1-Ethenyl-2-Pyrrolidinone (Wenninger, Canterbury, and McEwen 2000); Methacrylic Acid, 2-(Dimethylamino)Ethyl Ester, Polymer with 1-Vinyl-2-Pyrrolidinone (Chemline 1996); 2-Pyrrolidinone, 1-Ethenyl-, Polymer with 2-(Dimethylamino)-Ethyl 2-Methyl-2-Propenoate; 2-Pyrrolidinone, 1-Vinyl-, Polymer with 2-(Dimethylamino)Ethylmethacrylate; Dimethylaminoethyl Methacrylate-*N*-Vinylpyrrolidinone Copolymer; Dimethylaminoethyl Methacrylate-*N*-Vinylpyrrolidone Copolymer; *N,N*-Dimethylaminoethyl Methacrylate-*N*-Vinylpyrrolidone Copolymer; *N,N*-Dimethylaminoethyl Methacrylate-Vinylpyrrolidone Copolymer; 2-(Dimethylamino)-Ethyl Methacrylate-*N*-Vinyl-2-Pyrrolidinone Copolymer;

2-(Dimethylamino)Ethyl Methacrylate-*N*-Vinyl-2-Pyrrolidinone Copolymer; 2-(Dimethylamino)Ethyl Methacrylate-*N*-Vinylpyrrolidinone Copolymer; *N*-Vinylpyrrolidinone-Dimethylaminoethyl Methacrylate Polymer; and *N*-Vinylpyrrolidone-Dimethylaminoethyl Methacrylate Copolymer (Chemical Abstracts 1996).

AMP-Acrylates Copolymer. AMP-Acrylates Copolymer is the aminomethyl propanol salt of Acrylates Copolymer (q.v.) (Wenninger, Canterbury, and McEwen 2000).

Polyacrylic Acid. Polyacrylic Acid (CAS No. 9003-01-4) is the polymer of acrylic acid that conforms generally to the formula (Wenninger, Canterbury, and McEwen 2000):



Polyacrylic Acid

Polyacrylic Acid is also known as 2-Propenoic Acid, Homopolymer (International Agency for Research on Cancer [IARC] 1979; Wenninger, Canterbury, and McEwen 2000; Registry of the Toxic Effects of Chemical Substances [RTECS] 1996); Acrylic Acid Homopolymer; Acrylic Acid Polymer; Acrylic Acid Resin; Acrylic Polymer; Acrylic Resin; Atactic Poly(Acrylic Acid); Polyacrylate; Poly(Acrylic Acid) (IARC 1979; RTECS 1996); Acrylic Acid, Polymers (RTECS 1996); Propenoic Acid Polymer (Chemline 1996); and Carboxypolyethylene (Chemical Abstracts 1996).

Ammonium Polyacrylate. Ammonium Polyacrylate (CAS No. 9003-03-6) is the ammonium salt of Polyacrylic Acid (q.v.) and has the empirical formula $(\text{C}_3\text{H}_4\text{O}_2)_x \cdot x\text{H}_3\text{N}$ (Wenninger, Canterbury, and McEwen 2000). It is also known as Poly(Acrylic Acid), Ammonium Salt; 2-Propenoic Acid, Homopolymer, Ammonium Salt (Wenninger, Canterbury, and McEwen 2000) Acrylic Acid, Polymers, Ammonium Salt; and Ammonium Homopolymer, 2-Propenoate (Chemline 1996).

Potassium Aluminum Polyacrylate. Potassium Aluminum Polyacrylate is a mixture of the potassium and aluminum salts of Polyacrylic Acid (q.v.) (Wenninger, Canterbury, and McEwen 2000).

Potassium Polyacrylate. Potassium Polyacrylate (CAS No. 25608-12-2) is the potassium salt of Polyacrylic Acid (q.v.) and has the empirical formula $(\text{C}_3\text{H}_4\text{O}_2)_x \cdot x\text{K}$ (Wenninger, Canterbury, and McEwen 2000). It is also known as Polyacrylic Acid, Potassium Salt (Wenninger, Canterbury, and McEwen 2000); 2-Propenoic Acid, Homopolymer, Potassium Salt; Acrylic Acid, Polymers, Potassium Salt; and Potassium Homopolymer, 2-Propenoate; (Chemline 1996).

Sodium Polyacrylate. Sodium Polyacrylate (CAS No. 9003-04-7) is the sodium salt of Polyacrylic Acid and has the empirical formula $(\text{C}_3\text{H}_4\text{O}_2)_x \cdot x\text{Na}$ (Wenninger, Canterbury, and McEwen 2000). It is also known as Polyacrylic Acid, Sodium Salt; 2-Propenoic Acid, Homopolymer, Sodium Salt (Wenninger,

Canterbery, and McEwen 2000); Acrylic Acid, Polymers, Sodium Salt; Sodium Homopolymer, and 2-Propenoate; Propenoic Acid (Chemline 1996).

Physical and Chemical Properties

Acrylates Copolymer. As manufactured by one company, Acrylates Copolymer is a white, mobile liquid with a slightly acrylic odor that is 30% solids and has a pH 3.0 (Allied Colloids 1997). It has a specific gravity of 1.05 g/cm³ (25°C), viscosity as supplied of 50 cPs (25°C), and a viscosity, 3.33% aqueous solution, of 10,000 cPs. Another company reported that different Acrylates Copolymers may appear as a hazy solution, clear solution, milky white dispersion, clear viscous liquid, or white granules (BFGoodrich Specialty Chemicals 1997). These Acrylates Copolymers, which exist as 29% to 100% solids, have molecular weights of 5000 to 210,000 Da, pH of 6.7 to 8.0, specific gravity of 1.04 to 1.2, acid number of 60 or 65, and viscosity of 10 to 2,000,000 cP. A third company reported it manufactures Acrylates Copolymer as a copolymer of ethyl acrylate, methyl methacrylate, methacrylic acid, and acrylic acid that is a solution consisting of 25% solids (Amerchol 1997). A sample of Acrylates Copolymer (approximately 24% solids) was miscible in water, had a freezing point of 0°C, a melting point of 99.9°C, and a vapor pressure of 18.4 mm Hg at 20°C (Bushy Run Research Center 1993a).

Ammonium Acrylates Copolymer. Ammonium Acrylates Copolymer, as manufactured by one company, is produced as a 30% solution in propylene glycol (5%) and water (65%) at a pH of 7.5 (Allied Colloids 1997). This product is a colorless, clear to slightly translucent liquid with a slight acrylic odor. It has an acid value of 19.0 and a density of 1.0 g/cm³ (20°C).

Acrylates/VA Copolymer. 2-Ethylhexyl acrylate, a component of Acrylates/VA Copolymer, has a reported octanol/water partition coefficient of 3.67 or 4.32 (IARC 1994).

VA/Butyl Maleate/Isobornyl Acrylate Copolymer. VA/Butyl Maleate/Isobornyl Acrylate Copolymer, supplied as a 50% solution in ethanol, is a clear, pale yellow solution at 25°C that consists of 48% to 52% solids (Patel and Petter 1992). It has a pH of 4.5 to 5.5, an acid number (mg KOH/g solid) of 170 to 190, a K-value (1% solids w/v in ethanol) of 33 to 39, and a Brookfield viscosity (25°C) of 2.500 to 3.000 cps.

Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer. Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer is a fine, white powder that has a moisture content of 2% maximum and a relative viscosity of 1.45 to 1.75 (25°C) (Patel and Petter 1992). It is soluble in water and alcohol and is compatible with hydrocarbon propellants.

Polyacrylic Acid. Polyacrylic Acid is a clear, brittle, hygroscopic solid that has a molecular weight of 10,000 to 800,000 and a melting point of 106°C (glass-transition temperature) (Miller 1964). Polyacrylic Acid is soluble in water (deliquescent), dioxane, dimethylformamide, ethanol, methanol, and isopropanol and it is insoluble in ether, benzene, and cyclohexane.

Manufacture and Production

Linear polymers of acrylic acid are produced by combining the monomer with a free-radical initiator, usually an azo compound or peroxide, which is largely consumed by the reaction (Thompson, Aardema, and LeBoeuf 1989); azo compounds as an initiator are no longer used in the personal care industry (Cottrell, personal communication). The size of the polymer is determined by controlling the environment in which the polymerization occurs. Polymers of acrylic acid are characterized by their average molecular weight, but many species of greater and lesser molecular weight are present and unreacted monomer and catalysts can also be present.

Hydroquinone and monomethyl ether of hydroquinone are incorporated into acrylic acid and its esters and used as inhibitors to prevent spontaneous polymerization during shipping or storage (Union Carbide Chemical Co. 1998a). The acrylate esters normally have the inhibitors removed prior to polymerization. Acrylic esters and acrylic acid can be polymerized and copolymerized in four ways, by emulsion, suspension, solvent, or bulk polymerization (Union Carbide Chemical Co. 1998a). Emulsion polymerization of acrylates, the most widely used method, produces high-molecular-weight products and solvent polymerization produces lower molecular weight polymers. Bulk polymerization is used mainly for the manufacture of casting and molding resins.

Acrylates Copolymer. One company manufactures Acrylates Copolymer by emulsion polymerization in an aqueous medium (Allied Colloids 1997). It is produced as 30% solids at a pH of 3.0.

Ammonium Acrylates Copolymer. One company manufactures Ammonium Acrylates Copolymer by solution polymerization (Allied Colloids 1997). It is produced as a 30% solution in propylene glycol (5%) and water (65%), at a pH of 7.5.

Acrylates/VA Copolymer. 2-Ethylhexyl acrylate is used almost exclusively as a chemical intermediate in the manufacture of polymeric chemicals (Tyler 1993). Commercially, the most important reaction of 2-ethylhexyl acrylate is polymerization through a free-radical mechanism, with resulting formation of a variety of polymer types. Biologically important is the Michael addition reaction, i.e., the nucleophilic addition of a compound with an active hydrogen across the double bond. Thus, 2-ethylhexyl acrylate has the potential to react under physiological conditions with biologically important chemicals, such as glutathione (GSH) and possibly nucleic acids.

Polyacrylic Acid. Polyacrylic Acid is produced commercially by polymerizing an aqueous solution of ≤25% acrylic acid at 90°C to 100°C in the presence of a peroxydisulfate initiator or at 60°C using redox initiators, that is, a combination of potassium peroxydisulfate and potassium metabisulfite (Miller 1964). Production of polyacrylates is >1 million tons per year (Thompson, Aardema, and LeBoeuf 1989).

Sodium Polyacrylate. Sodium Polyacrylate is produced by the polymerization of acrylic acid and subsequent hydrolysis of

the Polyacrylic Acid with an aqueous sodium hydroxide solution (Rothschild 1991).

Analytical Methods

Acrylates Copolymer. Acrylates Copolymer was analyzed using gas chromatography (GC) (Chemir/Polytech Laboratories, Inc. 1996).

Polyacrylic Acid. Polyacrylic Acid can be determined by pyrolysis-GC (Szocik, Szelejewska, and Linkiewicz 1970), differential thermal analysis (Concilio and Jahnke 1972), conductometric titration of aqueous solutions (Crisp, Lewis, and Wilson 1975), and by a turbidimetric method for concentrations in the range of 5 to 40 mg/kg (ppm) (Wimberley and Jordan 1971).

Ultraviolet Absorbance

Ethylene/Acrylic Acid Copolymer. The ultraviolet (UV) absorption spectra of a low-molecular-weight formula of an Ethylene/Acrylic Acid Copolymer in *n*-hexane was determined (Food and Drug Administration [FDA] 1998a). The spectrum had a "broad background absorption, increasing in intensity toward shorter wavelengths with weak superimposed maxima near 256 and 280 microns. The absorption near 280 [microns] could be attributable to Ionol [not defined], since the copolymer contains 150 ppm Ionol."

Published data on the UV absorbance of the other ingredients included in this review were not found.

Impurities

Linear polymers of acrylic acid may contain unreacted starting material and catalysts (Thompson, Aardema, and LeBoeuf 1989). The Emulsion Polymers Council, Inc. (EPC) submitted the response of 10 companies to a survey regarding the amount of residual acrylic acid in polymers sold for cosmetic use; residual concentrations are "typically between 10 to 1000 ppm with an upper limit of 1500 ppm" (EPC 1999). The EPC felt that the responding companies represented the majority of the production of acrylate polymers sold for cosmetic use.

Acrylates Copolymer. Using GC with two runs per sample, three samples of Acrylates Copolymer had the following amounts of residual monomer: <0.2 ppm (below the limit of detection) to 0.8 ppm acrylic acid; 0.8 to 2.6 ppm methyl methacrylate; 1.3 to 3.9 ppm ethylene glycol dimethacrylate (Chemir/Polytech Laboratories, Inc. 1996).

A company reported that in its production of Acrylates Copolymer it controls impurities in the form of residual, unreacted monomer, i.e., ethyl acrylate, methyl methacrylate, methacrylic acid, and acrylic acid, to ≤ 20 ppm (Amerchol 1997).

Additional information submitted to CIR gave residual monomer information for two polymers, both defined as Acrylates Copolymer. In the first, the residual monomer concentrations were 36, 20, and 45 ppm *n*-butyl acrylate, methyl methacrylate, and methacrylic acid, respectively (CTFA 1999a). In the second polymer, the residual monomer concentrations were

1500 ppm stearyl acrylate and 200 ppm methacrylic acid (CTFA 1999b).

Acrylates/VA Copolymer. Two polymer producers reported that Acrylates/VA Copolymer contains <100 to 1000 ppm residual 2-ethylhexyl acrylate (Basic Acrylic Monomer Manufacturers [BAMM] 1999). The residual concentrations are dependent on the end-use application of the product. However, the 10 respondents of the survey by the EPC reported that they did not produce acrylate polymers with 2-ethylhexyl acrylate for use in the cosmetic industry (EPC 1999).

"Very low residual quantities of free monomer [2-ethylhexyl acrylate]" remain in pressure-sensitive adhesives that are high-molecular-weight polymers (Tyler 1993). In latex coatings, residual 2-ethylhexyl acrylate concentrations are generally 800 ppm or less. In a resin system composed of 45 parts 2-ethylhexyl acrylate, 50 parts styrene, and 5 parts acrylic acid, the amounts of residual 2-ethylhexyl acrylate and residual styrene were 0.15% and 0.27%, respectively (Union Carbide Chemical Co. 1998a).

As a commercial product, 2-ethylhexyl acrylate can contain 40 to 160 ppm hydroquinone and 10 to 220 ppm monomethyl ether of hydroquinone, both of which are inhibitors (IARC 1994).

Polyacrylic Acid. Detailed information on the possible presence of unreacted monomer in the polymer Polyacrylic Acid was not available to the IARC Working Group (IARC 1979). However, acrylic acid was detected in Polyacrylic Acid by UV spectroscopy, at 195 nm, with a limit of detection of 300 mg/kg (ppm).

Sodium Polyacrylate. A 90,000-Da sodium hydroxide-neutralized Polyacrylic Acid contained 77.5% Sodium Polyacrylate, 3.3% free acrylic acid, and 18.1% water (Nolen et al. 1989). A 4500-Da sodium hydroxide-neutralized Polyacrylic Acid contained 43.3% solids and 0.09% residual monomer.

USE

Cosmetic

The ingredients reviewed in this report have the functions shown in Table 2 (Wenninger, Canterbury, and McEwen 2000).

Product formulation data submitted to the Food and Drug Administration (FDA) in 1998 reported that Acrylates Copolymer was used in 227 cosmetic formulations, Ammonium Acrylates Copolymer was used in 21 formulations, Sodium Acrylates Copolymer was used in 5 formulations, Ethylene/Acrylic Acid Copolymer was used in 6 formulations, Ethylene/Sodium Acrylate Copolymer was used in 1 formulation, Acrylates/PVP Copolymer was used in 4 formulations, Steareth-10 Allyl Ether/Acrylates Copolymer was used in 6 formulations, Acrylates/Steareth-20 Methacrylate Copolymer was used in 35 formulations, Acrylates/Ammonium Methacrylate Copolymer was used in 1 formulation, Styrene/Acrylates Copolymer was used in 102 formulations, Styrene/Acrylates/Ammonium Methacrylate Copolymer was used in 1 formulation, Sodium Styrene/Acrylates Copolymer was used in 2 formulations, VA/Butyl

TABLE 2
Ingredient functions (Weninger, Canterbury, and McEwen 2000)

| Ingredient | Function |
|---|--|
| Acrylates Copolymer | Binder, film former, hair fixative, suspending agent—nonsurfactant |
| Ammonium Acrylates Copolymer | Binder, film former, viscosity increasing agent—aqueous |
| Ammonium/VA Acrylates Copolymer | Binder, film former, hair fixative, suspending agent—nonsurfactant |
| Sodium Acrylates Copolymer | Binder, film former, viscosity-increasing agent—aqueous |
| Ethylene/Acrylic Acid Copolymer | Binder, film former, viscosity-increasing agent—nonaqueous |
| Ethylene/Calcium Acrylate Copolymer | Binder, film former |
| Ethylene/Magnesium Acrylate Copolymer | Binder, film former |
| Ethylene/Sodium Acrylate Copolymer | Binder, film former, viscosity increasing agent—aqueous |
| Ethylene/Zinc Acrylate Copolymer | Film former |
| Ethylene/Acrylic Acid/VA Copolymer | Film former, viscosity increasing agent—nonaqueous |
| Acrylates/PVP Copolymer | Binder, film former, hair fixative, suspending agent—nonsurfactant |
| Acrylates/VA Copolymer | Binder, film former, hair fixative |
| Stearth-10 Allyl Ether/Acrylates Copolymer | Film former, viscosity-increasing agent—nonaqueous |
| Acrylates/Stearth-50 Acrylate Copolymer | Viscosity-increasing agent—aqueous |
| Acrylates/Stearth-20 Methacrylate Copolymer | Viscosity-increasing agent—aqueous |
| Acrylates/Ammonium Methacrylate Copolymer | Binder, film former, hair fixative |
| Styrene/Acrylates Copolymer | Film former |
| Styrene/Acrylates/Ammonium Methacrylate Copolymer | Film former, suspending agent—nonsurfactant |
| Ammonium Styrene/Acrylates Copolymer | Film former, suspending agent—nonsurfactant |
| Sodium Styrene/Acrylates Copolymer | Film former, viscosity-increasing agent—aqueous |
| Acrylates/Hydroxyesters Acrylates Copolymer | Film former |
| Methacryloyl Ethyl Betaine/Acrylates Copolymer | Film former, hair fixative, suspending agent—nonsurfactant |
| Lauryl Acrylate/VA Copolymer | Film former |
| VA/Butyl Maleate/Isobornyl Acrylate Copolymer | Film former |
| Ethylene/Methacrylate Copolymer | Film former |
| Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer | Film former, hair fixative |
| Sodium Acrylates/Acrolein Copolymer | Binder, film former, viscosity-increasing agent—aqueous |
| PVP/Dimethylaminoethylmethacrylate Copolymer | Binder, film former, hair fixative, suspending agent—nonsurfactant |
| AMP-Acrylates Copolymer | Film former |
| Polyacrylic Acid | Binder, emulsion stabilizer, film former, viscosity-increasing agent—aqueous |
| Ammonium Polyacrylate | Emulsion stabilizer, film former |
| Potassium Aluminum Polyacrylate | Absorbent, binder, viscosity-increasing agent—aqueous |
| Potassium Polyacrylate | Absorbent, binder, viscosity-increasing agent—aqueous |
| Sodium Polyacrylate | Film former, hair fixative, viscosity-increasing agent—aqueous |

Maleate/Isobornyl Acrylate Copolymer was used in 5 formulations, Ethylene/Methacrylate Copolymer was used in 5 formulations, Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer was used in 6 formulations, PVP/Dimethylaminoethylmethacrylate Copolymer was used in 43 formulations, Polyacrylic Acid was used in 19 formulations, and Sodium Polyacrylate was used in 8 formulations (FDA 1998b) (Table 3). The other ingredients considered in this safety assessment were not reported as being used in 1998.

Acrylates Copolymer can be used for polymeric adsorbent entrapment, with entrapment defined as “the process of adsorption using a porous, convoluted matrix throughout which actives such

as emollients, sunscreens, skin protectants or similar ingredients are dispersed” (Klein and DiSapio 1989). Acrylates Copolymer adsorbs other ingredients without shrinking or swelling.

Acrylates Copolymer in a urethane/Acrylate Copolymer system can be used as a micromatrix entrapment system “in which the entrapped material is dissolved, dispersed, adsorbed, or absorbed throughout the particle” (Scholz et al. 1993). The micromatrix entrapment system is insoluble and pressure insensitive, can be used with hydrophobic and hydrophilic systems, and is only limited by the amount of free water.

Concentration of use values are no longer reported to the FDA by the cosmetic industry (FDA 1992). However, one company

TABLE 3
Product types in which ingredients are used (FDA 1998b)

| Product category | Total no. of formulations in category | Total no. containing ingredient |
|--|---------------------------------------|---------------------------------|
| <i>Acrylates Copolymer</i> | | |
| Eyebrow pencil | 91 | 1 |
| Eyeliners | 514 | 6 |
| Eye shadow | 506 | 8 |
| Mascara | 167 | 17 |
| Other eye makeup preparation | 120 | 1 |
| Powders (fragrance preparations) | 247 | 8 |
| Hair sprays (aerosol fixatives) | 261 | 3 |
| Hair dyes and colors | 1572 | 10 |
| Hair bleaches | 113 | 3 |
| Other hair-coloring preparations | 59 | 1 |
| Blushers (all types) | 238 | 18 |
| Face powders | 250 | 27 |
| Foundations | 287 | 4 |
| Lipstick | 790 | 36 |
| Makeup bases | 132 | 2 |
| Other makeup preparations | 135 | 7 |
| Basecoats and undercoats | 48 | 16 |
| Nail creams and lotions | 17 | 1 |
| Nail polish and enamel | 80 | 21 |
| Other manicuring preparations | 61 | 15 |
| Deodorants (underarm) | 250 | 3 |
| Cleansing preparations | 653 | 3 |
| Face and neck preparations (excluding shaving) | 263 | 1 |
| Body and hand preparations (excluding shaving) | 796 | 2 |
| Moisturizing preparations | 769 | 5 |
| Paste masks (mud packs) | 255 | 3 |
| Other skin care preparations | 692 | 5 |
| 1998 total Acrylates Copolymer | | 227 |
| <i>Ammonium Acrylates Copolymer</i> | | |
| Eyeliners | 514 | 3 |
| Mascara | 167 | 18 |
| 1998 total Ammonium Acrylates Copolymer | | 21 |
| <i>Sodium Acrylates Copolymer</i> | | |
| Hair dyes and color | 1572 | 5 |
| 1998 total Sodium Acrylates Copolymer | | 5 |
| <i>Ethylene/Acrylic Acid Copolymer</i> | | |
| Blushers (all types) | 238 | 1 |
| Foundations | 287 | 2 |
| Makeup fixatives | 11 | 1 |
| Other skin care preparations | 692 | 2 |
| 1998 total Ethylene/Acrylic Acid Copolymer | | 6 |
| <i>Ethylene/Sodium Acrylate Copolymer</i> | | |
| Eye shadow | 506 | 1 |
| 1998 total Ethylene/Sodium Acrylate Copolymer | | 1 |

(Continued on next page)

TABLE 3
Product types in which ingredients are used (FDA 1998b) (Continued)

| Product category | Total no. of formulations in category | Total no. containing ingredient |
|---|--|------------------------------------|
| <i>Acrylates/PVP Copolymer</i> | | |
| Tonics, dressings, and other hair-grooming aids | 549 | 2 |
| Wave sets | 5555 | 2 |
| 1998 total Acrylates/PVP Copolymer | | 4 |
| <i>Steareth-10 Allyl Ether/Acrylates Copolymer</i> | | |
| Hair dyes and color | 1572 | 6 |
| 1998 total Steareth-10 Allyl Ether/Acrylates Copolymer | | 6 |
| <i>Acrylates/Steareth-20 Methacrylate Copolymer</i> | | |
| Baby shampoos | 21 | 1 |
| Other baby products | 29 | 1 |
| Other bath preparations | 159 | 1 |
| Other fragrance preparations | 148 | 1 |
| Hair conditioners | 636 | 1 |
| Hair sprays (aerosol fixatives) | 261 | 1 |
| Shampoos (noncoloring) | 860 | 6 |
| Tonics, dressings, and other hair-grooming aids | 549 | 6 |
| Hair bleaches | 113 | 5 |
| Nail polish and enamel removers | 34 | 1 |
| Bath soaps and detergents | 385 | 1 |
| Shaving cream | 139 | 2 |
| Cleansing preparations | 653 | 7 |
| Moisturizing preparations | 769 | 1 |
| 1998 total Acrylates/Steareth-20 Methacrylate Copolymer | | 35 |
| <i>Acrylates/Ammonium Methacrylate Copolymer</i> | | |
| Mascara | 167 | 1 |
| 1998 total Acrylates/Ammonium Methacrylate Copolymer | | 1 |
| <i>Styrene/Acrylates Copolymer</i> | | |
| Eyeliners | 514 | 3 |
| Permanent waves | 192 | 8 |
| Tonics, dressings, and other hair-grooming aids | 549 | 1 |
| Hair dyes and colors | 1572 | 66 |
| Hair bleaches | 113 | 1 |
| Basecoats and undercoats | 48 | 1 |
| Nail polish and enamel | 80 | 7 |
| Bath soaps and detergents | 385 | 1 |
| Deodorants (underarm) | 250 | 1 |
| Other personal cleanliness products | 291 | 6 |
| Cleansing preparations | 653 | 2 |
| Face and neck preparations (excluding shaving) | 263 | 4 |
| Body and hand preparations (excluding shaving) | 796 | 1 |
| 1998 total Styrene/Acrylates Copolymer | | 102 |
| <i>Styrene/Acrylates/Ammonium Methacrylate Copolymer</i> | | |
| Eyeliners | 514 | 1 |
| 1998 total Styrene/Acrylates/Ammonium Methacrylate Copolymer | | 1 |
| <i>Sodium Styrene/Acrylates Copolymer</i> | | |
| Shampoos (noncoloring) | 860 | 2 |
| 1998 total Sodium Styrene/Acrylates Copolymer | | 2 |

(Continued)

TABLE 3
Product types in which ingredients are used (FDA 1998b) (Continued)

| Product category | Total no. of formulations in category | Total no. containing ingredient |
|---|---------------------------------------|---------------------------------|
| <i>VA/Butyl Maleate/Isobornyl Acrylate Copolymer</i> | | |
| Other hair preparations | 276 | 5 |
| 1998 total VA/Butyl Maleate/Isobornyl Acrylate Copolymer | | 5 |
| <i>Ethylene/Methacrylate Copolymer</i> | | |
| Blushers (all types) | 238 | 1 |
| Foundations | 287 | 1 |
| Makeup bases | 132 | 1 |
| Other makeup preparations | 135 | 2 |
| 1998 total Ethylene/Methacrylate Copolymer | | 5 |
| <i>Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer</i> | | |
| Hair sprays (aerosol fixatives) | 261 | 2 |
| Tonics, dressings, and other hair-grooming aids | 549 | 3 |
| Other hair preparations | 275 | 1 |
| 1998 total Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer | | 6 |
| <i>PVP/Dimethylaminoethylmethacrylate Copolymer</i> | | |
| Mascara | 167 | 3 |
| Hair conditioners | 636 | 4 |
| Tonics, dressings, and other hair-grooming aids | 549 | 21 |
| Wave sets | 55 | 2 |
| Other hair preparations | 276 | 13 |
| 1998 total PVP/Dimethylaminoethylmethacrylate Copolymer | | 43 |
| <i>Polyacrylic Acid</i> | | |
| Tonics, dressings, and other hair-grooming aids | 549 | 1 |
| Foundations | 287 | 1 |
| Leg and body paints | 4 | 1 |
| Nail polish and enamel | 80 | 2 |
| Bath soaps and detergents | 385 | 2 |
| Aftershave lotion | 216 | 1 |
| Cleansing preparations | 653 | 3 |
| Face and neck preparations (excluding shaving) | 263 | 1 |
| Body and hand preparations (excluding shaving) | 796 | 2 |
| Night preparations | 188 | 1 |
| Paste masks (mud packs) | 255 | 2 |
| Other skin care preparations | 692 | 2 |
| 1998 total Polyacrylic Acid | | 19 |
| <i>Sodium Polyacrylate</i> | | |
| Hair spray (aerosol fixative) | 261 | 1 |
| Shampoos (noncoloring) | 860 | 1 |
| Other hair preparations | 276 | 1 |
| Bath soaps and detergents | 385 | 2 |
| Other skin care preparations | 692 | 3 |
| 1998 total Sodium Polyacrylate | | 8 |

reported that Acrylates Copolymer and a mixture containing 30% Ammonium Acrylates Copolymer have "typical use" concentrations of 3% to 10% and 2% to 10%, respectively, as supplied, in cosmetic formulations; however, one "prototype formu-

lation" proposed a mixture containing 30% Ammonium Acrylates Copolymer be used at 15% (Allied Colloids 1997). Another company reported using Acrylates Copolymer at concentrations of 7.5% and 21.87% (BFGoodrich Specialty Chemicals 1997).

A third company reported that Acrylates Copolymer is "typically used" at concentrations of 5% to 10% on a solids basis (20% to 40%) (Amerchol 1997). A survey by the EPC (to which 10 companies responded) reported that the estimated concentrations of acrylate polymers used in final cosmetic products are typically 2.5% to 6.0%, with a maximum of 7.5% to 25%, in binders, film formers, and fixatives and typically 0.5%, with a maximum of 2.0%, in viscosity-increasing agents, suspending agents, and emulsion stabilizers (EPC 1999). Nolen et al. (1989) reported that Sodium Polyacrylate is used as a dispersing agent in detergent formulations at concentrations of 1% to 5%.

In 1984, it was reported to the FDA that Acrylates Copolymer was used in 317 cosmetic formulations, some of which contained concentrations of >50%, Ammonium Acrylates Copolymer was used in 22 formulations at concentrations ≤5%, Ammonium/VA Acrylates Copolymer was used in 5 formulations at concentrations ≤25%, Ethylene/Acrylic Acid Copolymer was used in 2 formulations at ≤25%, Styrene/Acrylates Copolymer was used in 46 formulations at concentrations ≤25%, Styrene/Acrylates/Ammonium Methacrylate Copolymer was used in 21 formulations at unknown concentrations and at concentrations of 5% to 10%, Ammonium Styrene/Acrylates Copolymer was used in 2 formulations at unknown concentrations and at concentration of ≤0.1%, PVP/Dimethylaminoethylmethacrylate Copolymer was used in 1 formulation at 5% to 10%, Polyacrylic Acid was used in 3 formulations at concentrations of 0.1% to 5%, Ammonium Polyacrylate was used in one formulation at 25% to 50%, and Potassium Aluminum Polyacrylate was used in one formulation at 1% to 5%. The other ingredients named in this review were not reported to be used in 1984 (FDA 1984).

International

The ingredients in this review are not listed in Annex II (list of substances that must not form part of the composition of cosmetic products) or Annex III (list of substances that cosmetic products must not contain except subject to the restrictions and conditions laid down) of the *Cosmetics Directive of the European Union* (European Economic Community 1995). With the exception of Acrylates Copolymer and Sodium Polyacrylate, the ingredients in this review are also not listed in the *Comprehensive Licensing Standards of Cosmetics by Category* (CLS) (Yakuji Nippo, Ltd. 1994).

Acrylates Copolymer. Acrylates Copolymer, as Hydroxyethyl Acrylate·Butyl Acrylate·Methoxyethyl Acrylate Copolymer Solution or Hydroxyethyl Acrylate·Methoxyethyl Acrylate Copolymer Solution, is listed in the CLS and must conform to the specifications of the *Japanese Cosmetic Ingredient Codex* (Yakuji Nippo, Ltd. 1994). It can be used without restriction in all CLS categories except lipsticks and lip creams and dentifrices.

Sodium Polyacrylate. Sodium Polyacrylate is listed in the CLS and must conform to the specifications of the *Japanese Standards of Cosmetic Ingredients* (Yakuji Nippo, Ltd. 1994). It can be used in all CLS categories without restriction.

Noncosmetic

Acrylates Copolymer. 'Acrylate Ester Copolymer Coating,' copolymers of acrylic acid, and copolymers of acrylic acid and its methyl, ethyl, butyl, propyl, or octyl esters are reportedly cleared for indirect food additive use according to certain specifications (Rothschild 1991).

Ethylene/Acrylic Acid Copolymer. Ethylene/Acrylic Acid Copolymers are reportedly cleared for indirect food additive use under certain conditions (Rothschild 1991).

Ethylene/Sodium Acrylate Copolymer. Ethylene/Sodium Acrylate Copolymer is reportedly cleared for food additive use (Rothschild 1991).

Acrylates/VA Copolymer. Vinyl Acetate Copolymers, produced by copolymerizing vinyl acetate with one or more monomers, including acrylic acid, are cleared for use under §176.170 (components of paper and paperboard in contact with aqueous and fatty foods) and §176.180 (components of paper and paperboard in contact with dry food) under certain conditions (Rothschild 1991). The finished copolymers must contain at least 50 weight percent of polymer units derived from vinyl acetate and contain no more than 5 weight percent of total polymer units derived from the other monomers.

2-Ethylhexyl acrylate is cleared in the production of acrylic copolymers and vinyl acetate copolymers under §176.170 (components of paper and paperboard in contact with aqueous and fatty foods) (Rothschild 1991). 2-Ethylhexyl acrylate is cleared in homo- and copolymer formation under §175.105 (adhesives), and polymers, homopolymers, and copolymers of 2-ethylhexyl acrylate are cleared as the basic polymer under §176.180 (components of paper and paperboard in contact with dry food). It is also cleared in polymer formation under §177.1010 (semirigid and rigid acrylic and modified acrylic plastics). 2-Ethylhexyl acrylate-ethyl acrylate copolymers, prepared by copolymerization of 2-ethylhexyl acrylate and ethyl acrylate in a 7:3 weight ratio and having a number of average molecular weight range of 5800 to 6500 Da and a refractive index of N_D^{25} of 1.4130 to 1.4190, are cleared under §177.1210 (closures with sealing gaskets for food containers). 2-Ethylhexyl acrylate-methyl methacrylate-acrylic acid copolymers are cleared as modifiers for epoxy resins in §175.300 (resinous and polymer coatings) under §177.1210. "There is a minute possibility of potential ingestion from migration of very small quantities of residual monomer [2-ethylhexyl acrylate] during incidental contact of food which comes in contact with polymeric materials used in packaging" (Tyler 1993).

Styrene/Acrylates Copolymer. Styrene Acrylate-based copolymers and styrene with ethyl acrylate and/or methacrylic acid are reportedly cleared for indirect food additive use under certain conditions (Rothschild 1991).

Ethylene/Methacrylate Copolymer. Ethylene/Methacrylic Acid Copolymer is reportedly cleared for indirect food additive use under certain conditions (Rothschild 1991).

Polyacrylic Acid. Acrylic acid polymer, and its methyl and ethyl esters, homopolymers of acrylic acid, and homopolymers

and polymers of acrylic acid and its methyl, ethyl, butyl, propyl, or octyl esters are reportedly cleared for indirect food additive use under certain conditions (Rothschild 1991).

Polyacrylic Acid and its salts are used as textile warp sizes for man-made fiber monofilaments (especially nylon) and as thickeners for use in latex paints, natural and synthetic rubber, textile printing pastes, and wallcovering binders (IARC 1979). Other applications include use as flocculants, fluid loss-control additives in oil-well drilling muds, scale-inhibitor additives in formulations for treating cooling-water systems, sequestrants, and as temporary binders for ceramics before firing.

Ammonium Polyacrylate. Ammonium Polyacrylate is reportedly cleared for indirect food additive use under certain conditions (Rothschild 1991).

Sodium Polyacrylate. Sodium Polyacrylate is reportedly cleared for indirect food additive use under certain conditions (Rothschild 1991). Sodium Polyacrylate has use as a dispersing and thickening agent and as a flocculating agent for water purification (Hicks et al. 1989).

Acrylic Acid. Acrylic acid is mostly used "captively" in the production of other acrylates (IARC 1979).

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, Excretion

Published absorption, distribution, metabolism, and excretion data on the ingredients included in this report were not found. Information on the absorption, distribution, metabolism, and excretion of acrylic acid and its esters is summarized. The monomers should have greater potential for absorption and penetration than the copolymers.

Dermal

Acrylic Acid and Methyl Acrylate. Groups of three fasted male Sprague-Dawley rats were dosed dermally with acrylic acid to determine the absorption and distribution (Winter and Sipes 1993). One hundred microliters of a 4% (v/v) solution of 1-¹⁴C-acrylic acid in acetone (approximately 30 μ Ci/kg, 501 μ g/cm²) was applied through a skin-mounted aluminum trap that covered an 8.4-cm² area of skin on the mid-thoracic region of the back. A total of 96% of the radioactivity was recovered, with the majority of it (73%) recovered in the skin trap. Sixteen percent of the radioactivity was recovered in expired carbon dioxide and 6% was recovered from the dosing site; 0.9%, 0.4%, and 0.2% were recovered in the urine, tissues, and feces, respectively.

Groups of 15 male Fischer 344 rats and C3H/HeNCrIBR mice were given a single dermal dose of acrylic acid to determine absorption and metabolism (Black et al. 1995). The rats were dosed with 10 or 40 mg/kg (5 or 10 μ Ci/animal, respectively) and the mice were dosed with 10 or 40 mg/kg (5 or 20 μ Ci/animal, respectively). The doses were prepared by diluting acrylic acid in acetone to a final concentration of 1 ml/100 ml and administering a volume of 0.95 or 3.8 ml/kg; the dose was applied to

TABLE 4
Metabolic fate of radioactive label in rats and mice with dermal application of [¹⁴C]-Acrylic Acid (Black et al. 1995)

| Location | Rats | | Mice | |
|-------------------------------|------------|------------|-------------|-------------|
| | 10 mg/kg | 40 mg/kg | 10 mg/kg | 40 mg/kg |
| ¹⁴ CO ₂ | 13.5 ± 1.0 | 19.7 ± 2.2 | 9.3 ± 1.2 | 9.6 ± 2.2 |
| Volatilized dose | 41.3 ± 5.8 | 26.5 ± 6.9 | 70.9 ± 9.6 | 49.9 ± 12.6 |
| Urine | 0.8 ± 0.1 | 2.0 ± 0.7 | 0.3 ± 0.1 | 0.4 ± 0.1 |
| Feces | 0.5 ± 0.2 | 0.8 ± 0.1 | 0.4 ± 0.1 | 0.2 ± 0.1 |
| Tissues | 0.2 ± 0.0 | 0.1 ± 0.0 | 0.2 ± 0.1 | 0.0 ± 0.0 |
| Carcass | 2.8 ± 0.9 | 1.7 ± 0.5 | 0.5 ± 0.1 | 0.8 ± 0.8 |
| Dose site | 1.4 ± 0.6 | 1.0 ± 0.3 | 1.5 ± 2.3 | 0.2 ± 0.1 |
| Total recovery | 61.1 ± 5.3 | 52.2 ± 7.6 | 84.0 ± 10.5 | 61.5 ± 14.0 |

a 1.0 × 2.5-cm (low-dose rats), 2.5 × 4.0-cm (high-dose rats), or 1.0 × 1.0-cm (both groups mice) clipped shoulder region on the back of each animal, and "nonocclusive dose-containment devices" were used. Immediately following dosing, five animals per group were placed in metabolism cages and urine, feces, and expired ¹⁴CO₂ were collected at various intervals. The animals were killed after 1, 8, or 72 hours.

Absorption and elimination of acrylic acid were rapid and nearly complete after 8 hours for both dose groups of rats and mice. Seventy-two hours after administration, the distribution shown in Table 4, given as percent of administered dose, was reported based on 5 animals/group.

For both rats and mice, the amount of radioactivity found in the fat was greater after 72 hours than it was after 1 and 8 hours.

In guinea pigs that were exposed dermally to methyl [2,3-¹⁴C]acrylate, radioactivity was seen in the subcutaneous (SC) tissues and throughout the body (IARC 1999).

Oral

Acrylates/VA Copolymer. 2-Ethylhexyl acrylate is a component of Acrylates/VA Copolymer.

A group of six male Wistar albino rats was given a single oral dose of 100 mg/kg 2-ethylhexyl [2,3-¹⁴C]-acrylate (specific activity 3.7 MBq/kg) in soybean oil (Sapota 1988). Within 24 hours, 50.6% of the radioactivity was excreted in expired air; most of it was exhaled within 3 hours. A total of 40.2% of the dose was excreted in the urine in 48 hours (38.0% of it was excreted in 24 hours), whereas only 1.2% of the dose was excreted in the feces in 72 hours. Total excretion in 72 hours was 93%.

Acrylic Acid and Methyl, Ethyl, and Butyl Acrylates. Twenty-six Sprague-Dawley rats were dosed orally with [¹¹C]-acrylic acid (Kutzman, Meyer, and Wolf 1982). Six were killed after 1.5 minutes and groups of five were killed after 10, 20, 40, or 65 minutes. The [¹¹C]-acrylic acid was rapidly absorbed from the stomach and the uptake appeared biphasic. Radioactivity

in most tissues increased gradually with time, and the relative retention values of the liver, adipose tissue, and small intestine increased markedly between 40 and 60 minutes. $^{14}\text{CO}_2$ was expired rapidly, and elimination appeared biphasic. After 65 minutes, the animals retained 37% of the dose. The relative radioactivity of the urine "increased rapidly" with time, and urine collected after 65 minutes contained 1.8% of the dose per gram.

Groups of three male Sprague-Dawley rats were given a single oral dose of 4, 40, or 400 mg/kg of [2,3- ^{14}C]-acrylic acid or 2, 20, or 200 mg/kg [2,3- ^{14}C]-ethyl acrylate in 0.5% aqueous methylcellulose (25 $\mu\text{Ci}/\text{kg}$) at a volume of 10 ml/kg (DeBethizy et al. 1987). Urine, feces, and expired carbon dioxide were collected at various intervals up to 72 hours after dosing, and the animals were then killed. Acrylic acid and ethyl acrylate were eliminated rapidly, primarily in expired carbon dioxide (44% to 65%). Thirty-five percent to 60% of the acrylic acid and approximately 60% of the ethyl acrylate was eliminated within 8 hours. Urinary excretion of radioactive metabolites was greater with ethyl acrylate. Within 72 hours, 90% to 76% of the radioactivity was recovered from the animals dosed with 4 and 400 mg/kg acrylic acid; 19% to 25% was recovered in the tissues, with most being found in adipose tissue, (9% to 15%). With ethyl acrylate, 108% to 73% of the dose was recovered with 2 to 200 mg/kg; 13% to 10% was found in the tissues, with the most generally being found in muscle tissue (5.6% to 5%), and 28% to 8% was excreted in the urine.

DeBethizy et al. (1987) also dosed male Sprague-Dawley rats orally in quadruplicate with 4, 40, 400, and 1000 mg/kg acrylic acid or 2, 20, 100, or 200 mg/kg ethyl acrylate in 0.5% methylcellulose at a volume of 5 ml/kg with and without pretreatment with the carboxylesterase inhibitor tri-*o*-cresyl phosphate [TOCP]. Control animals were given 2 ml/kg corn oil with and without pretreatment. The animals were killed 1 hour after dosing. A "pronounced increase" in glandular and nonglandular stomach weights, edema, and hemorrhage were observed with >40 mg/kg acrylic acid. Acrylic acid, >4 mg/kg, significantly depleted nonprotein sulfhydryl [NPSH] content in the glandular stomach, but no significant effect on NPSH in the blood or liver was observed. Pretreatment with TOCP did not have a significant effect on stomach weight or NPSH content. With ethyl acrylate, a significant increase in forestomach weight was observed with the 200-mg/kg dose; no significant change in glandular stomach weight was observed. Treatment with TOCP enhanced the increase in forestomach weight. A linear depletion of NPSH content of the forestomach and glandular stomach was observed 1 hour after dosing with 2 and 20 mg/kg; NPSH content did not change with doses of 100 or 200 mg/kg. No significant dose-dependent effect of ethyl acrylate on NPSH concentration in the blood and liver was seen. Pretreatment with TOCP did not affect the depletion of NPSH content in the glandular stomach or forestomach; however, 100 and 200 mg/kg ethyl acrylate did induce a significant depletion of hepatic NPSH concentration.

Three fasted male Sprague-Dawley rats were given 400 mg/kg [1,2,3- $^{13}\text{C}_3$]-acrylic acid coadministered with [2,3- ^{14}C]-acrylic

acid (40 to 46 $\mu\text{Ci}/\text{kg}$) in distilled water by gavage (Winter et al. 1992). Urine, feces, and expired air were collected for 72 hours, and the animals were then killed. Total recovery was 98%. The majority of the radioactivity, 78%, was recovered in expired carbon dioxide. Approximately 13% of the radioactivity was recovered in the tissues, with almost 5% of the dose found in the muscle, 3% found in the liver, 2% found in the skin, and 1% found in adipose tissue. The tissue-to-blood radioactivity concentration ratios were 11.1, 3.2, 2.6, 2.4, 2.1, and 2.0 for the liver, kidneys, adipose tissue, stomach, spleen, and large intestine, respectively. Approximately 6% of the dose was eliminated in the urine and 1% was eliminated in the feces. Nuclear magnetic resonance spectroscopy did not detect unchanged acrylic acid in the urine.

Groups of three fasted male Sprague-Dawley rats were dosed orally with acrylic acid to determine the absorption and distribution (Winter and Sipes 1993). The animals were given 400 mg/kg purified [1- ^{14}C]-acrylic acid (44 $\mu\text{Ci}/\text{kg}$) in distilled water. Urine, feces, and expired air were collected for 72 hours, and the animals were then killed. A total of 98% of the radioactivity was recovered after administration, with the majority of it (83%) recovered in expired carbon dioxide. Nine percent, 5%, and 1.3% of the radioactivity was recovered in the feces, urine, and tissues, respectively.

Groups of 15 male Fischer 344 rats and C3H/HeNCrIBR mice were given a single oral dose of acrylic acid to determine absorption and metabolism (Black et al. 1995). The rats were dosed with 40 or 150 mg/kg (20 $\mu\text{Ci}/\text{animal}$) and the mice were with 40 or 150 mg/kg (20 or 10 $\mu\text{Ci}/\text{animal}$, respectively). The doses were prepared by diluting acrylic acid to a concentration of 4 or 15 mg/ml in filtered water, and the dose was administered by gavage at a volume of 10 ml/kg. Immediately following dosing, five animals per group were placed in metabolism cages and urine, feces, and expired $^{14}\text{CO}_2$ were collected at various intervals. The animals were killed after 1, 8, or 72 hours.

Following administration, absorption and elimination of acrylic acid were rapid and nearly complete after 8 hours for rats of the low-dose group and after 24 hours for rats of the high-dose groups and for mice of both groups. Seventy-two hours after administration, the distribution shown in Table 5, given as percent of administered dose, was reported based on 5 animals/group.

For both rats and mice, elimination of radioactivity from fat was slower than it was from other tissues.

A group of six male Wistar albino rats was given a single oral dose of 100 mg/kg methyl [2,3- ^{14}C]-acrylate (specific activity 3.7 MBq/kg) in soybean oil (Sapota 1988). Within 24 hours, 38.6% of the radioactivity was excreted in expired air; most of it was exhaled within 2 hours. A total of 51.2% of the dose was excreted in the urine in 48 hours (38.0% of it was excreted in 24 hours), whereas only 1.5% of the dose was excreted in the feces in 72 hours. Total excretion in 72 hours was 91.3%.

Two hours after oral administration of methyl [2,3- ^{14}C]-acrylate to guinea pigs, the radioactivity was distributed in internal organs, especially the liver and bladder, and in the brain.

TABLE 5

Metabolic fate of radioactive label in rats and mice given a single oral dose of [¹⁴C]-Acrylic Acid (Black et al. 1995)

| Location | Rats | | Mice | |
|---------------------------------------|------------|------------|------------|------------|
| | 40 mg/kg | 150 mg/kg | 40 mg/kg | 150 mg/kg |
| Exhaled ¹⁴ CO ₂ | 90.3 ± 1.0 | 81.6 ± 1.8 | 76.8 ± 2.8 | 80.0 ± 4.1 |
| Exhaled volatiles | 0.1 ± 0.2 | 0.2 ± 0.4 | 0.1 ± 0.0 | 0.1 ± 0.0 |
| Urine | 2.9 ± 0.2 | 4.2 ± 1.0 | 3.0 ± 1.4 | 3.4 ± 1.3 |
| Feces | 0.7 ± 0.0 | 0.6 ± 0.1 | 1.2 ± 0.4 | 1.2 ± 1.2 |
| Tissues | 0.3 ± 0.2 | 0.3 ± 0.1 | 0.3 ± 0.0 | 0.1 ± 0.1 |
| Carcass | 0.8 ± 0.1 | 1.0 ± 0.2 | 0.8 ± 0.1 | 0.3 ± 0.1 |
| Total recovery | 95.2 ± 0.9 | 88.1 ± 2.0 | 82.5 ± 2.1 | 86.9 ± 6.1 |

After 16 hours, it was seen only in mucous linings of the stomach, intestines, and mouth epithelium.

Groups of three male Fisher 344 rats were dosed orally with 100, 200, or 400 mg/kg [2,3-¹⁴C]-ethyl acrylate (50 to 60 μCi/kg; approximately 90% to 92% of the radioactivity was [2,3-¹⁴C]-ethyl acrylate and the remainder was [¹⁴C]-acrylic acid) in corn oil at a volume of 5 ml/kg (Ghanayem, Burka, and Matthews 1987). (Ethyl acrylate was inhibited with 15 to 20 ppm hydroquinone monomethyl ether.) Expired air was the major route of excretion; approximately 70% of the 200 mg/kg dose was expired as ¹⁴CO₂ within 24 hours of dosing. Approximately 10% and 4% of this dose was recovered in the urine and feces, respectively, in 24 hours. At all doses, >90% of the dose was absorbed from the stomach within 4 hours of administration. Radioactivity was distributed in all major tissues; total recovery was 74% to 82% (excluding that found in the carcass). Four hours after dosing, the greatest concentration of radioactivity was found in the glandular stomach, forestomach, small intestine, adrenal glands, and liver of animals dosed with 100 mg/kg, in the forestomach, glandular stomach, small intestine, liver, and thymus gland of the animals dosed with 200 mg/kg, and in the glandular stomach, small intestine, liver, forestomach, and kidneys of the animals dosed with 400 mg/kg.

Male Fischer 344 rats were given an oral dose of 4, 40, or 400 mg/kg butyl [2,3-¹⁴C]-acrylate (specific activity 7, 20, or 20 μCi/kg, respectively) in corn oil (Sanders, Burka, and Matthews 1988). Subgroups of three animals per dose were killed at various intervals between 15 minutes and 3 days after dosing. The majority of the dose was excreted in CO₂; 74.2%, 65.5%, and 78.0% of the 4-, 40-, and 400-mg/kg doses, respectively, were excreted in expired air 24 hours after administration. In these dose groups, 12.6%, 7.7%, and 7.6%, respectively, of the dose was excreted in the urine at 24 hours. In animals of the 4-mg/kg group, the greatest concentrations in the tissues were found in the muscle, skin, blood, and liver (5.9%, 3.4%,

1.9%, and 1.9% of the dose, respectively). In animals of the 40- and 400-mg/kg groups, the greatest concentrations at 24 hours were in the adipose tissue, muscle, and skin (8.6%, 5.4%, and 2.9%, respectively, for the 40-mg/kg animals and 5.7%, 5.7%, and 3.2%, respectively, for the 400-mg/kg animals).

Inhalation

Acrylic Acid. Groups of female Sprague-Dawley rats were exposed to a maximum of 29 μg/kg [¹⁴C]-acrylic acid by inhalation using a dynamic nose-exposure apparatus with a 1-minute exposure time or orally (Kutzman, Meyer, and Wolf 1982). Thirteen rats were nose-exposed; 10 were killed 1.5 minutes after exposure and the remaining three were killed 65 minutes after exposure.

The animals accumulated 18.3% of the radioactivity delivered to the nose cone. For the animals killed after 1.5 minutes, 28.4% of the activity was associated with the snout and 42.9% of the activity was in the head minus the snout. The upper respiratory tract also had "relatively large amounts" of [¹⁴C]-acrylic acid. For the animals killed after 65 minutes, approximately 25% of the administered ¹⁴C was retained and 8.1% of the activity was associated with the snout. Approximately 65% of the radioactivity had been expired as ¹⁴CO₂, and elimination appeared biphasic. The relative radioactivity of the liver and adipose tissue increased "markedly" between 1.5 and 65 minutes.

Parenteral

Acrylates/VA Copolymer. 2-Ethylhexyl acrylate is a component of Acrylates/VA Copolymer.

A group of six male Wistar albino rats was given a single intraperitoneal (IP) dose of 100 mg/kg 2-ethylhexyl [2,3-¹⁴C]-acrylate (specific activity 3.7 MBq/kg) in soybean oil (Sapota 1988). Within 72 hours, a total of 77.9% of the radioactivity was excreted in expired air (75.1% of it was excreted in 24 hours); most of it was exhaled within 3 hours. A total of 9.6% of the dose was excreted in the urine in 72 hours (4.3% and 4.6% were excreted in 0 to 24 and 24 to 48 hours, respectively), while only 2.9% of the dose was excreted in the feces in 72 hours. Total excretion in 72 hours was 90.4%. The total amount of the dose found in the tissues was 6.51%, 3.95%, 3.10%, 2.37%, and 1.07% after 3, 10, 24, 48, and 72 hours, respectively. At 3 hours, the greatest specific activity was in the liver, kidneys, and plasma (3.76, 1.91, and 1.56 kBq/g, respectively); at 10 hours, it was in the spleen, liver, and kidneys (1.75, 1.73, and 1.38 kBq/g, respectively); and at 24 hours, it was in the liver, spleen, and kidneys (1.40, 1.26, and 1.24 kBq/g, respectively). In erythrocytes, the loss of ¹⁴C was biphasic, whereas in plasma, it was monophasic with a half-life of 22 hours.

Methyl and Butyl Acrylate. A group of six male Wistar albino rats was given a single IP dose of 100 mg/kg methyl [2,3-¹⁴C]-acrylate (specific activity 3.7 MBq/kg) in soybean oil (Sapota 1988). Within 48 hours, a total of 54.4% of the radioactivity was excreted in expired air (51.8% of it was expired in 24 hours); most of it was exhaled within 2 hours. A total of

40.0% of the dose was excreted in the urine in 24 hours (38.7% of it was excreted in 24 hours), whereas only 1.5% of the dose was excreted in the feces in 72 hours. Total excretion in 72 hours was 95.9%. The total amount of the dose found in the tissues was 6.72%, 2.43%, 1.89%, and 1.21% after 1, 8, 24, and 48 hours, respectively. At 1 and 8 hours, the greatest specific activity was in the liver, kidneys, and lungs (3.62, 3.55, and 2.70 kBq/g, respectively, at 1 hours and 1.75, 1.73, and 1.38 kBq/g, respectively, at 8 hours), and at 24 hours, it was in the liver, lungs, and spleen (0.85, 0.61, and 0.60 kBq/g, respectively). In erythrocytes, the loss of ^{14}C was biphasic. In plasma, elimination was also biphasic, with fast and slow compartment half-lives of 5 and 34 hours, respectively.

Following IP injection of methyl [2,3- ^{14}C]-acrylate to guinea pigs, radioactivity was concentrated in the peritoneum and the liver and seen in most other organs after 1 hours; radioactivity was generally not detected after 24 or 48 hours, except for some retention in mucous linings (IARC 1999). Following IP dosing of methyl [2,3- ^{14}C]-acrylate to male guinea pigs, 35% and 40% of the radioactivity was excreted in expired air as $^{14}\text{CO}_2$ after 8 and 72 hours, respectively.

Male Fischer 344 rats were given an IP dose of 40 mg/kg butyl [2,3- ^{14}C]-acrylate (specific activity 20 $\mu\text{Ci}/\text{kg}$) in a 1:1:8 v/v solution of ethanol, Emulphor EL-620, and water at 1 ml/kg (Sanders, Burka, and Matthews 1988). Subgroups of three animals per dose were killed at various intervals between 15 minutes and 3 days after dosing. Butyl acrylate was rapidly delivered to all major tissues; peak concentrations were seen at or before 15 minutes in all tissues except adipose tissue. There was a rapid initial decrease in radioactivity in all major tissues, except adipose tissue, during the first 2 hours after dosing; the elimination slowed to a negligible rate and remained relatively constant between 2 hours and 3 days after dosing. Fifteen minutes after dosing, 154.3, 98.6, and 51.4 $\mu\text{g}/\text{g}$ radioactivity was found in the kidneys, liver, and blood, respectively; the amounts found in the liver, kidneys, and blood were 86.0, 78.7, and 27.0 $\mu\text{g}/\text{g}$, respectively, after 45 minutes; 53.5, 33.7, and 18.5 $\mu\text{g}/\text{g}$, respectively, after 2 hours; and 45.0, 23.0, and 19.8 $\mu\text{g}/\text{g}$, respectively, after 6 hours. (The radioactivity concentration in adipose tissue at 15 minutes, 45 minutes, 2 hours, and 6 hours was 10.8, 10.6, 8.5, and 14.0 $\mu\text{g}/\text{g}$, respectively.) The majority of the dose was excreted in CO_2 . After 24 hours, 45.3% of the dose was excreted in expired air and 15.6% was excreted in the urine. The greatest amount of radioactivity was found in the adipose tissue, muscle, and skin at this time (12.2%, 5.2%, and 2.7% of the dose, respectively).

In Vitro

Acrylic Acid. The disposition of [^{14}C]-acrylic acid was determined in vitro using clipped dorsal skin from male rats according to the method of Frantz et al. (1990) (Black et al. 1995). One percent (v/v) [^{14}C]-Acrylic Acid, 95 μl , was applied to the exposed epidermal surface (1.77 cm^2), and an evaporation trap was fitted over the skin. Over a 6-hour period, 23.9% \pm 5.4% of

the dose was absorbed in the effluent or was found in the skin and at least 60% of the dose was evaporated. Total recovery of the applied dose was approximately 85%.

Immunologic Effects

Acrylates/PVP Copolymer. Copolymers were obtained by radical copolymerization of acrylic acid and *N*-vinyl pyrrolidone; these copolymers contained 25 to 91 mole percent acrylic acid links and had a molecular weight of 300,000 to 400,000 Da (Nadzhitmidinov et al. 1979). The immunostimulating action of these copolymers was studied using mice. The copolymers increased the migration of stem cells, the migration of B and T lymphocytes, and intensified the cooperative interaction between T and B lymphocytes.

Polyacrylic Acid. Groups of six female NMRI/HAN mice were injected intraperitoneally with 2×10^8 sheep erythrocytes (SRBCs) to determine whether administration of Polyacrylic Acid (molecular weight 20,000 to 30,000 Da), a B-cell mitogen, at a "nonoptimal time" would have a suppressive effect on primary immune response (Diamantstein et al. 1976). The mice were injected intraperitoneally with 1 mg Polyacrylic Acid in 0.5 ml phosphate-buffered saline (PBS) 30 minutes or 2, 3, or 4 days prior to immunization with SRBCs. The kinetics of the response to SRBCs were then examined by injecting a group of mice with 1 mg Polyacrylic Acid on the day that gave the optimal conditions for immunosuppression; the number of plaque-forming cells (PFCs) and of hemolysin titres were determined 2, 3, 4, and 5 days after immunization. The adjuvant effect of 1 mg Polyacrylic Acid was tested under known optimal conditions, i.e., IP injection 30 minutes before immunization with 2×10^6 SRBCs/0.5 ml, and the direct (19S) PFC response was determined in individual spleens after days 2, 3, 4, and 5.

Polyacrylic Acid had an immunosuppressive effect on the response to SRBCs. The maximum decrease in the PFC response was in the groups dosed with Polyacrylic Acid 3 and 4 days before immunization and the maximum reduction in hemolysin titres was observed in the group dosed with Polyacrylic Acid 3 days before immunization. Hence, to examine the kinetics of the response, Polyacrylic Acid was injected on day 3 prior to immunization; a reduction in the numbers of PFCs and hemolysin titres was observed 2, 3, 4, and 5 days after immunization. A second injection of Polyacrylic Acid 30 minutes prior to immunization with SRBCs abolished the immunosuppressive effect. Under optimal conditions (assessing the adjuvant effect), Polyacrylic Acid significantly increased the number of PFCs on all days.

A Polyacrylic Acid-IgG (PAIGP) complex was prepared and its influence on a number of immunological reactions were examined (Klauser et al. 1990). The complex had a Polyacrylic Acid:IgG weight ratio of 0.143 and a mean molecular weight 1.77×10^6 . Complement consumption was determined using a modified version of the hemolytic complement consumption of Kabat and Mayer (1971). Increasing concentrations of PAIGP consumed complement in a dose-dependent manner. The 50%

effective concentration was 2.3 $\mu\text{g/ml}$ PAIGP; the hemolytic activity of the complement was almost completely lost at concentrations of 50 $\mu\text{g/ml}$ PAIGP.

The activation of phagocytic cells by PAIGP was examined using luminol enhanced chemiluminescence. PAIGP stimulated chemiluminescence of isolated human polymorphonuclear (PMN) leukocytes in the presence and absence of autologous serum and in the presence of human citrated blood. The chemiluminescence of leukocytes increased in a dose-dependent manner. In the presence and absence of serum, monoclonal antibodies against leukocyte antigens (anti-Leu 11B) dose-dependently inhibited the chemiluminescence induction by PAIGP. Also, the formation of superoxide anion by PMN leukocytes activated by PAIGP was measured using ferricytochrome *c*; superoxide was released. Additionally, the release of elastase from stimulated human PMN leukocytes in whole blood was examined. PAIGP was a weak inducer of elastase release.

Mitochondrial Effects

Acrylic Acid. Hepatic mitochondria from adult male Sprague-Dawley rats were used to determine the effects of acrylic acid (Custodio et al. 1998). Addition of acrylic acid to succinate-energized mitochondria that were preloaded with 40 nmol calcium/mg protein caused a dose-dependent stimulation of mitochondrial swelling. Incubation of isolated mitochondria with 20 μM calcium and 1 mM acrylic acid caused a "rapid and profound decrease in light scattering." In examining the effect on membrane potential, acrylic acid caused a "slight (10–15 mV) but direct depolarization of membrane potential." The effect of acrylic acid on mitochondrial GSH concentrations were also determined. The distribution of mitochondrial GSH between the matrix and the extramitochondrial medium was not altered by 1 mM acrylic acid. Acrylic acid increased the sensitivity of isolated mitochondria in vitro to the calcium-dependent induction of the mitochondrial permeability transition.

ANIMAL TOXICOLOGY

Acute Toxicity

Dermal

Acrylates Copolymer. The acute dermal toxicity of Acrylates Copolymer (approximately 24% solids) was determined using five male and five female New Zealand white rabbits (Bushy Run Research Center 1993a). A dose of 16 g/kg was applied for 24 hours under an occlusive patch to a shaved area on the dorsal surface of each animal. The amount of test article/dose area ranged from approximately 96 (for females) to 97 mg/cm^2 (for males). The animals were killed 14 days after dosing. All animals survived until study termination. Erythema, edema, desquamation (one animal), and alopecia (one animal) were observed.

The acute dermal toxicity of Acrylates Copolymer (containing 1500 ppm stearyl acrylate, 200 ppm methacrylic acid; Cos-

metic, Toiletry, and Fragrance Association [CTFA] 1999b) was determined using five male and five female New Zealand white rabbits (MB Research Laboratories 1999a). A dose of 2 g/kg moistened with mineral oil was applied under an occlusive patch for 24 hours to clipped intact skin on the dorsal area of the trunk. The test site was scored 24, 48, and 72 hours and 7 and 14 days after dosing using the Draize scale. None of the animals died during the study. No reactions were observed; the modified primary irritation index (PII) was 0, and the dermal LD_{50} was >2 g/kg.

Ethylene/Acrylic Acid Copolymer. An Ethylene/Acrylic Acid polymer had a "low order of acute toxicity" when applied dermally (Union Carbide Chemical Co. 1998b). A dose of 16.0 ml/kg of an aqueous emulsion of the ammonium salt of an Ethylene/Acrylic Acid polymer, 21.8% solids at pH 9.8, was applied to the skin of four rabbits; none of the animals died (Union Carbide Chemical Co. 1998c). Study details were not provided.

Acrylates/VA Copolymer. The dermal LD_{50} of Vinyl Acetate/Maleate/Acrylate Copolymer solution was determined using 10 New Zealand White rabbits, five per sex (Bio/dynamics Inc. 1984a). The test material, 5 g/kg, was applied undiluted at a dose volume of 5.05 ml/kg under an occlusive patch to a clipped area of the back. The patches were removed after 24 hours and excess material was removed. The animals were observed for 14 days after dosing and then were killed. Severe dermal effects that generally persisted until study termination, i.e., necrosis followed by eschar formation, fissuring, and/or exfoliation of the eschar tissue, were observed at the test site for most animals. Generally, signs of toxicity were not observed, with the exception of nasal discharge. All animals survived until study termination except one male; it could not be determined whether the death was treatment-related because no lesions were observed at necropsy. The dermal LD_{50} of Vinyl Acetate/Maleate/Acrylate Copolymer solution using rabbits was >5 g/kg.

Acrylic Acid. The range of the dermal LD_{50} of acrylic acid reported for rabbits was 295 to 950 mg/kg (IARC 1979).

Oral

Acrylates Copolymer. The acute oral toxicity of Acrylates Copolymer (approximately 24% solids) was determined using Sprague-Dawley rats (Bushy Run Research Center 1993a). In preliminary testing, two female rats were dosed with 4 or 16 ml/kg Acrylates Copolymer; neither animal died. In the definitive test, a group of five male and five female rats were dosed with 16 ml/kg Acrylates Copolymer. The animals were killed 14 days after dosing. All animals survived until study termination. Signs of toxicity were not reported.

The oral LD_{50} of Acrylates Copolymer was determined using 10 Wistar rats, 5 males and 5 females (BASF 1994a). The animals were dosed with an aqueous solution of 2 g/kg Acrylates Copolymer (supplied as a white powder) and observed for 14 days. One male had an impaired general state and dyspnea, but appeared normal after 1 day. All animals survived until study

termination, and the oral LD₅₀ of Acrylates Copolymer using rats was >2 g/kg.

The oral LD₅₀ of Acrylates Copolymer (containing 36, 20, and 45 ppm *n*-butyl acrylate, methyl methacrylate, and methacrylic acid, respectively; CTFA 1999a) was determined using five male and five female Wistar albino rats (MB Research Laboratories 1996a). The animals were given a single oral dose of 5 g/kg and observed 1, 2, and 4 hours and daily for 14 days after dosing. The oral LD₅₀ was >5 g/kg.

The oral LD₅₀ of Acrylates Copolymer, 30% total solids and pH 7 to 7.4, was determined using fasted white rats (number of animals not specified) (BFGoodrich Specialty Chemicals 1997). The animals were dosed with ≤9 g/kg Acrylates Copolymer and observed for 7 days. All animals survived until study termination, and the LD₅₀ of Acrylates Copolymer using rats was >9 g/kg.

The oral LD₅₀ of a 15% solution of Acrylates Copolymer, 100% solids, in ammonia water was determined using fasted white rats (number of animals not specified) (BFGoodrich Specialty Chemicals 1997). The animals were dosed with ≤7.5 g/kg Acrylates Copolymer and observed for 7 days. All animals survived until study termination, and the LD₅₀ of Acrylates Copolymer using rats was >7.5 g/kg.

The oral LD₅₀ of Acrylates Copolymer (containing 1500 and 200 ppm stearyl acrylate and methacrylic acid, respectively; CTFA 1999b) was determined using five male and five female Wistar albino rats (MB Research Laboratories 1999b). The animals were given a single oral dose of 2 g/kg and observed 1, 2, and 4 hours and daily for 14 days after dosing. The oral LD₅₀ was >2 g/kg.

Ethylene/Acrylic Acid Copolymer. The acute oral toxicity of a heptane extract of an Ethylene/Acrylic Acid Copolymer mixed with mineral oil (containing 59.0% low-molecular-weight Ethylene/Acrylic Acid Copolymer and 41% mineral oil; residual acrylic acid was not detected in the copolymer using a method sensitive to 10 ppm) was determined using groups of six male and six female Sprague-Dawley rats (FDA 1998c). Doses of 0.5, 1, 2, and 4 g/kg were administered as a 25% suspension in corn oil. No test article-related lesions were observed, and all animals survived the 2-week observation period following dosing. The oral LD₅₀ for rats was >4 g/kg.

In a similar study, the oral LD₅₀ of a heptane extract of Ethylene/Acrylic Acid Copolymer (containing 56.5% low-molecular-weight Ethylene/Acrylic Acid Copolymer and <43.5% mineral oil) was determined using groups of six male and six female Sprague-Dawley rats (FDA 1998d). Doses of 0.625, 1.23, 2.5, and 5.0 g/kg were used were administered as a 34.9% suspension in corn oil. The rat oral LD₅₀ was >5.0 g/kg.

An Ethylene/Acrylic Acid polymer had a "low order of acute toxicity" via the peroral route (Union Carbide Chemical Co. 1998b). The oral LD₅₀ in rats of an aqueous emulsion of the ammonium salt of an Ethylene/Acrylic Acid polymer, 21.8% solids at pH 9.8, was 41.50 ml/kg (Union Carbide Chemical Co. 1998c).

The oral LD₅₀ of a low-molecular-weight formula of Ethylene/Acrylic Acid Copolymer (35% acrylic acid) was >5.0 g/kg (Dow Chemical Co. 1998).

Acrylates/VA Copolymer. The oral LD₅₀ of Vinyl Acetate/Maleate/Acrylate Copolymer solution was determined using 10 fasted Sprague-Dawley (CDR) albino rats, 5 males and 5 females (Bio/dynamics Inc. 1984b). The animals were given 5 g/kg of undiluted test material by gavage in a dose volume of 5.05 ml/kg. The animals were observed for 14 days after dosing and then killed. Nasal and oral discharge, wet rales, soft stools, and hypoactivity were observed within 24 hours after dosing; other signs of toxicity occurred sporadically in single animals. All animals appeared normal on days 11 to 14. All animals survived until study termination. The oral LD₅₀ of Vinyl Acetate/Maleate/Acrylate Copolymer solution using rats was >5 g/kg.

Polyacrylic Acid. The oral LD₅₀ of Polyacrylic Acid using rats was reported to be 2.5 g/kg (Berth et al. 1975).

Sodium Polyacrylate. Groups of one male and one female CSE rat were given a single oral dose of 0.005, 0.01, 0.025, 0.050, or 0.1 g/kg of 10% (w/v) Sodium Polyacrylate, molecular weight 3500 Da, and of 5% (w/v) Sodium Polyacrylate, molecular weight 13.1 × 10⁶ Da, and groups of four male and four female rats were dosed with 0.15 or 1 g/kg of both Sodium Polyacrylates (Hicks et al. 1989). The animals were observed continuously and all surviving animals were killed 10 h after dosing. Significant effects were not observed.

The oral LD₅₀ for 15% aqueous Sodium Polyacrylate using groups of 10 rats was >40 g/kg (Finnegan and Dienna 1953).

Acrylic Acid and Methyl, Ethyl, and Butyl Acrylate. The oral LD₅₀ of acrylic acid for rats was 2100 to 3200 mg/kg (IARC 1979). The oral LD₅₀ of glacial acrylic acid for rats was 193 to 350 mg/kg. Dow Chemical Co. (1998) reported the oral LD₅₀ of glacial acrylic acid for rats was 0.34 ml/kg.

The oral LD₅₀ of undiluted acrylic acid was 0.34 ml/kg for male rats (DePass et al. 1983). The oral LD₅₀ of a 10% aqueous dilution of acrylic acid was 2.59 ml/kg for male Carworth-Wistar rats.

The National Toxicology Program (NTP) conducted a series of studies on ethyl acrylate-induced gastric toxicity. Comparing single and repetitive dosing, Ghanayem, Maronpot, and Matthews (1985a) treated groups of eight male Fischer 344 rats by gavage with ethyl acetate in corn oil at 100, 200, and 400 mg/kg doses one time; and with ethyl acetate in corn oil at a 200-mg/kg dose once, twice, or four times. Control groups were given corn oil only. In the glandular stomach, the end points were mucosal congestion, submucosal edema, submucosal inflammation, and superficial mucosal necrosis. In the forestomach, the end points were mucosal edema (with or without vesicles), erosions or ulcers, mucosal hyperplasia, submucosal edema, submucosal inflammation, and vacuolization of tunica muscularis. The acute effect of ethyl acetate was dose-dependent. Repeated exposure caused similar damage to the glandular stomach and the forestomach, but the damage increased in severity. The time

course of stomach lesions increased in incidence and severity with time up to 8 hours after treatment. The authors also noted that a single 200-mg/kg dose of ethyl acrylate given subcutaneously produced no gastric toxicity and that the same dose via IP administration produced only mild gastric changes.

Ghanayem, Maronpot, and Matthews (1985b) extended this work by examining the effect of different acrylates. Male Fischer 344 rats were given a single oral dose of (a) 2 mmol acrylic acid, (b) methyl acrylate inhibited with 200 ppm hydroquinone monomethyl ether (HQMME), (c) ethyl acrylate inhibited with 15 to 20 ppm HQMME, or (d) butyl acrylate inhibited with 10 to 55 ppm HQMME, all in 5 ml/kg corn oil. Control animals were given corn oil only. The animals were killed 4 hours after dosing. Methyl acrylate and ethyl acrylate produced stomach lesions. Acrylic acid and butyl acrylate did not. If the volume of corn oil in which the ethyl acrylate was decreased (increasing the concentration of ethyl acrylate, but not the dose), gastric edema increased, up to a halving of the corn oil volume, and decreased when the corn oil volume was reduced to 1.25 ml. To further investigate the role of the vehicle, butyl acrylate (no stomach lesions in corn oil) was administered in a water-Emulphor vehicle (Emulphor is a polyethoxylated vegetable oil). Significant edema was observed in both the forestomach and the glandular stomach. Speculating that the water vehicle potentiated the partitioning of butyl acrylate in the stomach tissue compared to stomach contents, the authors concluded that the rate of delivery of acrylates influences gastric toxicity and that certain acrylate ester structures are needed to produce gastric toxicity.

In the third study in this series, Ghanayem, Maronpot, and Matthews (1986) gave 14 daily gavage doses of 100 or 200 mg/kg of ethyl acrylate to male Fischer 344 rats. Rats were killed at various times following the end of dosing. No glandular stomach lesions were observed after 14 daily doses, suggesting to the authors that the glandular stomach adapted to resist the effect of ethyl acrylate. Fewer gastric lesions were seen in the forestomach of animals receiving the repeated doses than had been seen previously with a single or double exposure. As a function of time after dosing, forestomach lesions decreased.

Inhalation

Acrylates Copolymer. The acute inhalation toxicity of Acrylates Copolymer (approximately 24% solids) was determined using a group of five male and five female Sprague-Dawley rats (Bushy Run Research Center 1993a). "A substantially saturated vapor was produced by enclosing 140 g [Acrylates Copolymer] in a sealed 120 liter animal chamber for approximately 17 hours under static conditions." The animals were placed in the chamber for 6 hours. The animals were killed 14 days after dosing. All animals survived until study termination. Signs of toxicity were not reported.

The LC₅₀ of Acrylates Copolymer as a liquid aerosol was determined using 10 Wistar rats, 5 males and 5 females (BASF 1994b). The animals were exposed to 5.2 mg/l Acrylates Copolymer in a single 4-hour dose, and the animals were observed for

14 days. The mass median aerodynamic diameter was 1.4 μm . The animals appeared normal throughout the study, and lesions were not found during gross examination. The LC₅₀ of Acrylates Copolymer for rats was >5.2 mg/l.

Ethylene/Acrylic Acid Copolymer. In an inhalation study in which six rats were exposed for 8 hours to a "substantially saturated vapor" of an aqueous emulsion of the ammonium salt of an Ethylene/Acrylic Acid polymer, 21.8% solids at pH 9.8, for 8 hours, none of the animals died (Union Carbide Chemical Co. 1998c).

Acrylic Acids. The LC₅₀ for rats exposed to acrylic acid vapors for 4 hours was 3600 mg/m³ (1200 ppm) (IARC 1979). In single inhalation studies using rats, 12 mg/l (4000 ppm) acrylic acid did not kill any of six rats exposed for 4 hours, whereas vapor concentrations approaching saturation in air killed half of a test group of rats (number of rats not stated) in 3.5 hours.

Parenteral

Ethylene/Acrylic Acid Copolymer. The IP LD₅₀ for rats of an aqueous emulsion of the ammonium salt of an Ethylene/Acrylic Acid polymer, 21.8% solids at pH 9.8, was 8.57 ml/kg (Union Carbide Chemical Co. 1998b).

Acrylates/PVP Copolymer. The intravenous toxicity of a copolymer of acrylic acid and *N*-vinyl pyrrolidone was determined using white mice (Nadzhitmidinov et al. 1979). Six copolymers, molecular weight 300,000 to 400,000 Da, were made containing 25 to 91 mole percent acrylic acid links. The copolymers containing 85% and 91% acrylic acid were toxic, with LD₅₀ values of 120 and 100 mg/kg, respectively. The copolymers containing 69% and 70% acrylic acid were slightly toxic, with LD₅₀ values of 350 and 225 mg/kg, respectively. The copolymers containing 25% and 45% acrylic acid were non-toxic, with LD₅₀ values of 800 and 625 mg/kg, respectively.

Sodium Polyacrylate. Groups of one male and one female CSE rat were given a single intravenous, (IV), IP, or SC dose of 5, 10, 25, 50, or 100 mg/kg of 10% (w/v) Sodium Polyacrylate, molecular weight 3500 Da, and of 5% (w/v) Sodium Polyacrylate, molecular weight 13.1×10^6 Da (Hicks et al. 1989). Additionally, groups of five male and five female rats were dosed intravenously or intraperitoneally with 25 or 50 mg/kg and groups of seven male and seven female rats were dosed intravenously or intraperitoneally with 100 mg/kg of the high-molecular-weight Sodium Polyacrylate. Five male and five female rats were pre-treated with a single IP dose of 110 mg/kg calcium chloride in aqueous solution, followed 15 minutes later by IP dosing with a single IP dose of 100 mg/kg the high-molecular-weight Sodium Polyacrylate. Groups of three male and three female rats were given a SC dose of 100 mg/kg of the low- or high-molecular weight Sodium Polyacrylate. The animals were observed continuously and all surviving animals were killed 10 hours after dosing.

Adverse effects were reported, including dyspnea, an immobile, crouched posture, and cyanosis, after IV and IP administration of 25 to 100 mg/kg of the high-molecular weight Sodium

Polyacrylate. IV dosing generally led to rapid death, usually within 30 minutes; however, some animals survived 9 hours after dosing and some of the animals dosed with 25 mg/kg survived 10 hours after dosing (study termination). Following IP dosing, adverse effects were observed after ≥ 3 hours and death occurred, preceded by tremors and convulsions, approximately 30 minutes after the onset of the adverse effects. Necropsy findings of animals that died due to test-article administration included arterial and venous vascular engorgement, ecchymoses in most organs, on muscle surfaces, and, in SC tissue, petechial hemorrhages on individual blood vessel, blood accumulation in the intestinal lumen, occasional gastric hemorrhages, coronary vessel hemorrhages, bloodstained pericardial fluid, and red discoloration of the lungs. Toxic effects were not observed upon dosing with the low-molecular-weight Sodium Polyacrylate. Likewise, toxic effects were not observed upon SC dosing with either the low- or high-molecular-weight Sodium Polyacrylate (Hicks et al. 1989).

In a continuation of this work, Hicks et al. (1989) dosed nine rats (sex not specified) intraperitoneally with 100 mg/kg of the high-molecular weight Sodium Polyacrylate. Three animals were killed after 1, 2, and 3 hours to determine the onset and progression of internal lesions. In animals killed after 1 hour, cardiovascular function was normal and hemorrhagic lesions and discoloration were not observed. Hemorrhage was not seen after 2 hours, and changes were minor. Three hours after dosing, hemorrhages were observed in the pericardium, lungs, intestines, stomach, and cranium.

Groups of four male rats were anesthetized, prepared for recording of respiration, systemic arterial blood pressure, heart rate, and electrocardiogram, and dosed intravenously with ≤ 40 mg/kg of both Sodium Polyacrylates (Hicks et al. 1989). Doses of 5 to 20 mg/kg of the high-molecular-weight Sodium Polyacrylate caused transient depressor effects on blood pressure, whereas doses of 24 to 40 mg/kg caused marked bradycardia and cardiac arrhythmias, decreased the frequency of respiration, and caused more prolonged depressor effects.

Six male rats were dosed intraperitoneally with 110 mg/kg of the high-molecular-weight Sodium Polyacrylate and were prepared for blood pressure, heart rate, and electrocardiogram after 2 to 2.5 hours (Hicks et al. 1989). These animals generally died after 4 to 5 hours, and changes, including the development of steep depressor effects, were mostly observed 30 minutes prior to death.

Acrylic Acid. The IP LD₅₀ of acrylic acid for rats was 24 mg/kg (IARC 1979).

Short-Term Toxicity

Oral

Acrylic Acid, Ethyl Acrylate, and Methyl Methacrylate. Groups of five male and five female Fischer 344 rats were used in a dose range-finding study (DePass et al. 1983). The animals were dosed daily with approximate concentrations of

0.15%, 0.30%, or 0.60% acrylic acid in water. The animals were weighed three times during the study, observed daily for signs of toxicity, and killed on day 7.

None of the animals died during the study. The dosages attained were 210, 420, and 680 mg/kg/day for the males and 220, 400, and 760 mg/kg/day for the females. In the high-dose group, body weight gain was statistically significantly reduced for males on days 4 and 7 and for females on day 1.

Male Fischer 344/N rats were dosed either by gavage with 2 to 200 mg/kg or in drinking water with 200 to 4000 ppm (23 to 369 mg/kg/day) ethyl acrylate (with 15 ppm 4-methoxyphenol) for 2 weeks (Frederick, Hazleton, and Frantz 1990). In the gavage study, in which the vehicle was corn oil and the animals were dosed once daily five times per week for 2 weeks, 10 and 4 animals per dose were used for histopathology and biochemistry, respectively. In the drinking water study, in which the animals were given dosing solutions at all times, 10 animals per dose were used for both histopathology and biochemistry.

“Primary compound-related histopathological changes were noted only in the forestomach” of the test animals. In the animals dosed by gavage, the following were observed in the forestomach: minimal diffuse epithelial hyperplasia in 2 animals of the 20-mg/kg group; mild diffuse epithelial hyperplasia in 1, 7, and 5 animals of the 20-, 50-, and 100-mg/kg groups, respectively; moderate diffuse epithelial hyperplasia in 5 and 3 animals of the 100- and 200-mg/kg groups, respectively; marked diffuse epithelial hyperplasia in 7 animals of the 200-mg/kg group; focal epithelial hyperplasia in 2 animals of the 200-mg/kg group; hyperkeratosis in 3, 8, 10, and 10 animals of the 20-, 50-, 100-, and 200-mg/kg groups, respectively; submucosal inflammation in 6 and 10 animals of the 100- and 200-mg/kg groups, respectively; submucosal edema in 2 and 9 animals of the 100- and 200-mg/kg groups, respectively; and ulcers and erosions of the epithelial layers in 6 animals of the 200-mg/kg group. In the glandular stomach, submucosal inflammation was observed in one and six animals of the 100- and 200-mg/kg groups, respectively, and submucosal edema seen in one animal of the 200-mg/kg group was viewed “as extensions of the main inflammatory process involving the forestomach.” Two hours after the last dose, the forestomach of animals of the high-dose group had an increase in weight of 281% compared to control values; this increase was not seen in the glandular stomach. The NPSH content of the forestomach was significantly elevated in test animals compared to controls. However, the total NPSH content was rapidly depleted with a 200-mg/kg dose, whereas only a marginal change was seen with a 20-mg/kg dose.

In the animals dosed via the drinking water, again compound-related findings occurred only in the forestomach, but were generally less severe. The following were observed in the forestomach: minimal diffuse epithelial hyperplasia in 10, 1, and 2 animals of the 1000-, 2000-, and 4000-ppm groups, respectively; mild diffuse epithelial hyperplasia in 8 and 6 animals of the 2000- and 4000-ppm groups respectively; moderate diffuse epithelial hyperplasia in 1 animal of each the 2000- and

4000-ppm groups, respectively; marked diffuse epithelial hyperplasia in 1 animal of the 4000-ppm group; hyperkeratosis in 9 and 10 animals of the 2000- and 4000-ppm groups, respectively; submucosal inflammation in 1 and 2 animals of the 2000- and 4000-ppm groups, respectively; and focal epithelial hemorrhage in 1 animal of each the 2000- and 4000-ppm groups. A slight increase in forestomach weight was observed in the high-dose group, whereas the weight of the glandular stomach was similar to that of controls.

Inhalation

CrI:CD(SD)BR Sprague-Dawley-derived rats were exposed 6 hours per day, 5 days per week, for 2 weeks to aerosol concentrations of 4.9 to 949.6 $\mu\text{g/l}$ of an acrylic polymer (not defined due to confidential business information status) that had a molecular weight of approximately 1,000,000 Da and that contained approximately 35% respirable ($\leq 5 \mu$) dust (Rohm and Haas Co. 1984a). Groups of 8 male and 8 female rats were exposed to 4.9, 47.8, or 258.6 $\mu\text{g/l}$ and a group of 16 male and 16 female rats was exposed to 949.6 $\mu\text{g/l}$ of the acrylic polymer. The aerosol particle size distribution ranged from a mean mass median diameter (MMD) of 3.1 to 6.6 μm and a geometric standard deviation (GSD) of 3.0 to 3.7. A control group of 16 males and 16 females was exposed to air only. Half of the male and female animals of the control and high-dose groups were used as a 3-week recovery group. Body weights were measured weekly, feed consumption was determined for the periods days 1 to 3, 5 to 7, 7 to 8, and 9 to 10, and signs of toxicity were assessed before, during, and after each exposure. At the end of the 2 weeks of dosing or the 3-week recovery period, necropsy was performed and some tissues were collected for microscopic examination.

One or two animals of the control, 258.6-, and 949.6- $\mu\text{g/l}$ groups had dry corneas, chromorhinorrhea, a "thrifless appearance," and alopecia, but persistent treatment-related signs of toxicity were not observed. Signs of toxicity were also not observed in animals of the 3-week recovery group. Dose-related differences in body weights and body weight gains were not observed between test and control animals. Overall feed consumption of the high-dose group was decreased compared to the controls. Treatment-related lesions were not observed at necropsy.

At microscopic examination of the lungs of all animals of the 258.6- and 949.6- $\mu\text{g/l}$ groups, lesions were characterized by a multifocal or diffuse pneumonitis that consisted of proliferation of alveolar septal cells and macrophages and the infiltration of a few PMN leukocytes in the terminal bronchioles, alveolar ducts, and adjacent alveoli. The alterations in the animals of the 949.6- $\mu\text{g/l}$ group were extensive, with mean severity scores of 2.4 for males and females and a diffuse distribution. The lesions in the 258.6- $\mu\text{g/l}$ group were of lesser severity, with mean severity scores of 1.0 and 1.1 for the males and females, respectively, and a multifocal distribution. A similar response was observed in the lungs of animals of the 949.6- $\mu\text{g/l}$ recovery group, with mean severity scores of 2.5 and 2.1 for males and females, respectively. Lesions were not observed in the lungs of

the animals dosed with 4.9 or 47.8 $\mu\text{g/l}$ of the acrylic polymer, and none of the control animals had pneumonitis. The minimum observed effect concentration was 258.6 $\mu\text{g/l}$ and the maximum no-observed-effect concentration was 47.8 $\mu\text{g/l}$.

Groups of 40 Fischer 344 rats, 20 per sex, were exposed to 0.1, 1.0, or 10 mg/m^3 polyacrylate micronized dust or untreated air for 6 hours per day, 5 days per week for 19 exposures (Lomax, Nitschke, and Pugh 1991). The mass median aerodynamic diameter and the geometric standard deviation were approximately 5.3 to 6.1 μm and 2.4 to 2.7, respectively. Ten rats per sex per group were killed the day after the last exposure and the remaining 10 rats per sex per group were killed 60 days after the last exposure. Treatment-related effects were confined to the lungs; animals that were exposed to 10 mg/m^3 and killed the day after exposure had increased lung weight and inflammation in the alveolar ducts and alveoli. After the 60-day recovery period, the changes in the lungs of the animals of this group were generally not observed. The animals exposed to 0.1 and 1.0 mg/m^3 had minimal macrophage aggregates in the alveoli.

Acrylic Acid and Ethyl and Butyl Acrylate. "Strong, local irritation, resulting in irreversible changes in skin and eyes of rats, was noted after exposure to vapours in air. Five weeks' exposure to acrylic acid vapours at a concentration of 700 mg/m^3 (240 ppm) of air for 4 hours daily led to reduced body weight gain and an increased number of blood reticulocytes. Single and repeated doses caused injury to the gastric mucosa and inflammation of the upper respiratory tract" (IARC 1979).

Groups of five male and five female Fischer 344 rats and B6C3F₁ mice were exposed to 25, 75, or 225 ppm (0.074, 0.221, 0.662 mg/l) acrylic acid in air 6 hours per day, 5 days per week, for 2 weeks; a control group breathed untreated air (Miller et al. 1981). Animals were observed twice daily and body weights were determined on days 4, 7, 10, and 14. None of the animals died while on study. Rats and mice of the 225-ppm dose group had signs of nasal irritation by scratching at their noses. Mice of the 25- and 75-ppm groups and rats and mice of the 225-ppm groups had significantly lower body weight gains. Inflammatory and degenerative lesions of the nasal mucosa were observed in most control rats and rats of the 25- and 75-ppm groups, but more severe lesions of the nasal mucosa, including slight focal squamous metaplasia, were observed in rats of the 225-ppm group. In mice, concentration-dependent lesions of the nasal mucosa were observed; mice of the 225-ppm group had slight focal squamous metaplasia.

In inhalation studies, 6-hour exposures to 300 or 1500 ppm acrylic acid for 20 or 4 days, respectively, resulted in nasal irritation or discharge, lethargy, reduced body weight gain or body weight loss, and renal congestion (1500 ppm only); 4-hour exposures to 238 ppm for 35 days resulted in respiratory tract inflammation, reduced body weight gain, and alterations of renal function; 6-hour exposures to 5 or 25 ppm for 90 days had no effect; 6-hour exposure to 75 ppm for 90 days caused nasal lesions (Klimisch and Hellwig 1991).

Groups of 10 male and 10 female Fischer 344 rats and B6C3F₁ mice were exposed to 75, 150, or 300 ppm ethyl acrylate in air 6 hours per day, 5 days per week, for 1 month (a total of 22 exposures), while a control group breathed untreated air (Dow Chemical Co. 1979). All animals were observed daily for signs of toxicity. Body weights were determined twice weekly. Tissues from four male and four female rats and mice of the control and high-dose groups were examined microscopically. A statistically significant decrease was observed in mean body weight gain of male and female rats of the 150- and 300-ppm groups after 26 days. For mice, mean body weight gain was statistically significantly decreased for males of the 300-ppm group after 27 days and significantly increased for females of the 150-ppm group after 27 days and for males and females of the 75-ppm group. Mean relative kidney weights were statistically significantly increased for male rats of the 300-ppm group, female rats of the 150- and 300-ppm groups, and male rats of the 75-ppm group; the increases observed in the mid- and high-dose groups were considered possibly compound related, whereas the significance for the males of the 75-ppm group was uncertain. Mean absolute and relative liver weights were decreased as compared to controls; this effect was possibly compound-related. Lesions were not observed at microscopic examination.

Groups of 10 male and female Chinese hamsters and Sprague-Dawley rats, which were housed one animal and two to three animals per cage, respectively, during dosing, were exposed to 817 and 820 ppm butyl acrylate, respectively, for three 6-hour and one 5-hour exposure(s) (Engelhardt and Klimisch 1983). Signs of toxicity, including dyspnea, disequilibrium, and bloody discharge from the eyes and noses, were observed. Four male Chinese hamsters died.

Subchronic Toxicity

Dermal

Acrylic Acid. Groups of 30 outbred female ICR mice, inbred male C3H mice, and hybrid female B6C3F₁ mice were treated dermally three times per week for up to 13 weeks with 100 μ l of 1% or 4% acrylic acid (containing 220 ppm maximum 4-methoxyphenol as an inhibitor) in acetone; corresponding controls were treated with vehicle only (McLaughlin et al. 1995). The test solutions were applied to a shaved site on the dorsal midline. Five animals per group were killed and necropsied 24 hours after dose 3, 6, 12, and 24, while the remainder were killed after dose 39.

Acrylic acid did not have a "consistent or remarkable effect on body weight" with any strain or dose. On microscopic examination, all animals treated with 1% acrylic acid, with the exception of 2 of 30 C3H mice and 1 of 30 B6C3F₁ mice, tolerated the dose. The majority of the animals (14 of 30 ICR mice, 21 of 30 C3H mice, and 21 of 30 B6C3F₁ mice) exceeded the maximum tolerated dose (MTD). The strain difference with respect to MTD was not significant. Upon gross examination at each week of the study, all animals exposed to 1% acrylic acid were classified as having tolerated the dose, whereas most animals exposed

to 4% acrylic acid reached or exceeded MTD at some point. The total number of high-dose ICR, C3H, and B6C3F₁ animals that exceeded MTD at least once, based on gross observations, was 1, 21, and 18, respectively, and the number that reached MTD at least once was 23, 7, and 7, respectively. Compared to controls, incidence values for reaching or exceeding MTD were significantly increased for all strains exposed to 4% by week 2 and generally persisted until week 8. A strain-dependent relationship, in which a greater number of C3H animals exceeded MTD compared to ICR animals, was seen at week 3 and continued until week 8. After week 8, the animals appeared to adjust to the repeated exposure. Only poor to fair agreement between microscopic and gross findings was observed when using the MTD classification given at the week of necropsy, whereas fair agreement was found when analyzing and comparing the most severe gross MTD classification to microscopic findings.

Oral

Acrylic Acid and Methyl, Ethyl, and Butyl Acrylates. Groups of 15 male and 15 female Fischer 344 rats were given a dose of 83, 250, or 750 mg/kg acrylic acid in drinking water daily for 90 to 94 days (DePass et al. 1983). A control group was given untreated water. Body weights, feed consumption, and water consumption were determined weekly. Urinalysis was performed and clinical chemistry and hematology parameters were examined 2 weeks prior to study termination. Necropsy was performed on all animals, and selected tissues of animals of the control and high-dose group were examined microscopically.

None of the animals died during the study. Mean body weight gain, feed consumption, and water consumption were significantly reduced for animals of the high-dose group compared to control values. Body weight gain was reduced for animals of the mid-dose group, but the decrease was significant only for females at the end of the study. Water consumption was significantly decreased for all animals of the mid-dose group and males of the low-dose group. Differences in absolute and relative organ weights for animals of the high-dose group as compared to controls were observed; most of these differences were considered a result of decreased water and feed consumption. However, the increase in relative kidney and testes weights in male animals and the increase in absolute and relative kidney weights in female animals of the high- and mid-dose groups were considered treatment-related. Changes in clinical chemistry, hematology, and urinalysis parameters were observed; for animals of the high-dose group, an increase in blood urea nitrogen (BUN) in males and an increase in BUN and alkaline phosphatase in females were considered treatment-related. Gross and microscopic lesions were not observed.

Groups of 10 male and 10 female Wistar rats were given 150 or 375 mg/kg aqueous acrylic acid by gavage 5 days per week for 3 months; a control group was given water by gavage (Hellwig, Deckardt, and Freisberg 1993). Feed and water consumption and body weights were determined weekly. Animals were examined daily and palpated weekly. After 3 months, the

animals were killed and necropsied, and selected tissues were examined microscopically.

Body weight gains were slightly to moderately decreased for male rats of the high-dose group; body weight gains were also decreased for females during the first 3 weeks of the study. Tympanites of the gastrointestinal tract, often associated with cyanosis and dyspnea, were found in most animals as of week 3. Six males and nine females of the high-dose group and five males and five females of the low-dose group died during the study. In the animals of the high-dose group, irritation of the nonglandular and glandular stomach, elevation of the diaphragm, pulmonary edema/emphysema and alveolar hyperemia, dysteleclases, catarrhal or catarrhal-purulent rhinitides, and necrotizing tubular nephrosis were observed. Similar but less severe lesions were observed in the low dose animals.

In a 90-day drinking water study using rats, the maximum no ill-effect dose of acrylic acid was at or slightly less than 0.083 g/kg/day (Dow Chemical Co. 1998). Study details were not provided. The authors estimated the minimal effect concentration to be 0.25 g/kg/day.

Methyl acrylate, ≤ 20 mg/kg, administered in the water was not toxic to rats (Rohm and Haas Co. 1983). Butyl acrylate, given in the drinking water or by gavage, also was not toxic.

Groups of 46 to 50 male F344 rats were dosed orally with 100 or 200 mg/kg ethyl acrylate (inhibited with 15 to 20 ppm HQMME) in 5 ml corn oil 5 days per week for 13 weeks; 55 control rats were given corn oil only (Ghanayem, Matthews, and Maronpot 1991). Twenty-four hours, 8 weeks, and 19 months after dosing, 10 to 11, 10, and the remaining 26 to 35 animals per group, respectively, were killed. Lesions were observed in the forestomach, but not in the glandular stomach or the liver. The forestomach of most animals of the low-dose group were thickened at the termination of dosing, and the incidence of mild to moderate hyperplasia was 100%. Animals of the high-dose group killed 24 hours after dosing had "randomly distributed focal and multifocal raised nodules that were the same color as unaffected mucosa"; two to five nodules were seen. The incidence of severe to extensive hyperplasia in the high dose animals killed 24 hours after dose termination was 100%. After an 8-week recovery period, no lesions were observed in animals of the low-dose group and occasionally "one or more punctate-white foci on the forestomach mucosa" were observed in the high-dose group. At this time, one low-dose and six high-dose animals had mild hyperplasia. After a 19-month recovery period, no lesions were observed except an occasional "more opaque stomach" in a high-dose animal. Two of 26 low-dose and 9 of 26 high-dose 19-month recovery animals had mild hyperplasia; 2 of 35 corresponding control animals had moderate to severe hyperplasia.

Inhalation

Acrylates Copolymer. The inhalation toxicity of Acrylates Copolymer was determined in a study using groups of 15 male and 15 female CrI:CD(SD)BR rats (WIL Research Laboratories, Inc. 1997). In this study, the polymer backbone was *n*-butyl

acrylate, methyl methacrylate, and methacrylic acid (McEwen 1999). The animals were exposed via whole body inhalation 6 hours per day, 7 days per week, for 13 weeks to 1, 10, or 30 mg/m³ of the Acrylates Copolymer formulation. (Particle size was 2.4, 2.4, and 2.5 μ m, respectively; Lovelace Respiratory Research Institute 1998a.) Exposure concentrations of Acrylates Copolymer were measured by standard gravimetric methods and of the vehicle were measured using a total hydrocarbon analyzer or an infrared spectrophotometer. The measured exposure concentrations to the formulation were 1.14, 10.3, and 30.5 mg/m³, respectively. The vehicle and polymer formulation contained 69% ethanol (16.2% solids by weight, viscosity 16 cPs, pH 8.4); residual monomer levels were 5 ppm *n*-butyl acrylate, 33 ppm methyl methacrylate, and 15.7 ppm methacrylic acid (McEwen 1999). The actual concentrations of polymer that the animals were exposed to were 0.185, 1.67, and 4.94 mg/m³ (Lovelace Respiratory Research Institute 1998a; McEwen 1999). A vehicle-control group was exposed to 30 ppm ethanol and an untreated control group was exposed to filtered air. Exposure caging consisted of two cage batteries per group. Clinical observations were made twice daily. Body weights and feed consumption were measured weekly. Blood samples were taken from all animals at 4 and 13 weeks. Ocular examinations were conducted prior to the initiation of dosing and at the termination of dosing. Five males and five females per group were used as recovery groups and killed 4 weeks after the termination of dosing. All other animals were killed at the end of the dosing period.

None of the animals died during the study, and no test article-related lesions were observed. Body weights and feed consumption were generally similar for all groups. The mean body weights were significantly decreased for females of the high-dose groups during weeks 7 to 8 and males of the high-dose group during weeks 10 to 11. Males of the vehicle control group had a slight but significant increase in mean body weight during weeks 5 to 6. No exposure-related changes were observed in hematology or clinical chemistry parameters. No test article-related ophthalmological lesions were observed. At necropsy, no gross lesions were observed. A significant increase in mean absolute lung weights was observed in recovery females of the high-dose group; this increase was not observed in any other groups either at the termination of dosing or after the recovery period. At the termination of dosing, microscopic examination reported alveolar histiocytosis, characterized by focal accumulation of macrophages within the alveolar spaces, in 2, 3, 0, 2, and 9 males and 0, 2, 0, 1, and 7 females of the untreated-control, vehicle-control, 1-, 10-, and 30-mg/m³ groups, respectively (10 animals per sex per group). In the high-dose animals, the foci of the alveolar macrophages were sometimes located in the subpleural areas of the lungs, but were more frequently located in the alveoli near the junction of the terminal bronchioles and alveolar ducts. In the other groups, the foci of histiocytosis were located near the pleural surface of the lungs and consisted of small aggregates (approximately 5 to 20) of macrophages

with a pale, basophilic to amphophilic staining cytoplasm. In selected recovery groups, histiocytosis was observed in 1, 1, and 4 males and 1, 0, and 5 females of the untreated-control, vehicle-control, and high-dose groups, respectively (5 animals per sex per group). The researchers stated that "the increase in alveolar histiocytosis (and increased lung weight) in the 30-mg/m³ group was consistent with a normal, adaptive pulmonary response to an inhaled particulate matter." Alveolar histiocytosis "was not accompanied by any morphologic indicators of injury (i.e., macrophage necrosis, degenerative changes, inflammation, and/or hyperplastic or fibrotic responses)." Therefore, according to the researchers, this was a physiological rather than a pathological response and the no-observable-adverse-effect level (NOAEL) for the formulation containing Acrylates Copolymer was 30 mg/m³ (corresponding to 4.94 mg/m³ of the polymer).

A third party reviewer felt that the increase of and difference in alveolar histiocytosis in the high-dose animals indicated an adverse effect (Lovelace Respiratory Research Institute 1998b). The reviewer indicated that the NOAEL for the formulation was 10 mg/m³ (corresponding to 1.67 mg/m³ polymer). It was indicated that the "minimal severity of the lesions" and "their waning severity with 4 weeks recovery" indicated that "the particles have a relatively low pulmonary toxicity." The reviewer

noted that there were pulmonary lymphoid and neutrophilic infiltrates suggesting "an occult respiratory infection"; such an infection could contribute to alveolar histiocytosis in control animals.

Groups of Crl:CD(SD)BR rats were exposed to an acrylic polymer 6 hours per day, 5 days per week, according to the schedule shown in Table 6 (Rohm and Haas Co. 1985).

The 4-week mean respirable concentrations (calculated from the total dust concentrations and the respirable fraction) were 7.2, 29.7, 51.7, and 94.1 mg/m³ for groups 2 to 5, respectively, with MMD ranging from 4.4 to 5.4 μm and GSD from 2.6 to 2.7. The 13-week mean dust concentrations were 6.1, 22.1, and 52.4 mg/m³ for groups 2 to 4, respectively, with MMD ranging from 4.8 to 5.2 μm and GSD from 2.7 to 2.9. A control group (group 1, subgroups A to D2), exposed to untreated air, followed the same schedule as groups 2 to 4, subgroups A to D2. The animals were examined and body weights were determined weekly for 19 weeks and then bimonthly; the animals were observed daily for signs of toxicity. Clinical chemistry, hematology, and microscopic evaluations were conducted on all animals necropsied after 4 and 13 weeks of exposure and after the 13- and 26-week recovery periods.

Signs of treatment-related toxicity were not observed for any of the animals exposed for 4 or 13 weeks. Differences in response

TABLE 6
Exposure regimen for inhalation toxicity study (Rohm and Haas Co. 1985)

| Group | Subgroup | No. of animals | Target analytical concentration | | Exposure duration (weeks) | Recovery period (weeks) | Necropsy interval (weeks) |
|-------|----------|----------------|---------------------------------|---------------------------------|---------------------------|-------------------------|---------------------------|
| | | | Total (mg/m ³) | Respirable (mg/m ³) | | | |
| 2 | A | 10M/10F | 17.0 | 5.0 | 4 | 0 | 4 |
| | B | 10M/10F | | | 13 | 0 | 13 |
| | C | 10M/10F | | | 13 | 13 | 26 |
| | D1 | 10M/10F | | | 13 | 26 | 39 |
| | D2 | 8M/8F* | | | 13 | ** | ** |
| 3 | A | 10M/10F | 67.0 | 20.0 | 4 | 0 | 4 |
| | B | 10M/10F | | | 13 | 0 | 13 |
| | C | 10M/10F | | | 13 | 13 | 26 |
| | D1 | 10M/10F | | | 13 | 26 | 39 |
| | D2 | 8M/8F* | | | 13 | ** | ** |
| 4 | A | 10M/10F | 167.0 | 50.0 | 4 | 0 | 4 |
| | B | 10M/10F | | | 13 | 0 | 13 |
| | C | 10M/10F | | | 13 | 13 | 26 |
| | D1 | 10M/10F | | | 13 | 26 | 39 |
| | D2 | 8M/8F* | | | 13 | ** | ** |
| 5 | A1 | 10M/10F | 250.0 | 87.5 | 4 | 0 | 4 |
| | A2 | 10M/10F | | | 4 | 13 | 17 |
| | A3 | 10M/10F | | | 4 | 26 | 30 |
| | A4 | 18M/18F | | | 4 | ** | ** |

*Extra animals included to compensate for unexpected mortality, for special or extra microscopic evaluation, or in the event more follow-up was desired.

**Killed without necropsy at week 49.

were not noted for any of the 13- or 26-week recovery animals. Deaths that occurred during the study were not considered dose-related. Statistically significant increases in body weight and body weight gain were observed for females of groups 4 and 5 and males of group 5 at different intervals, but these increases were not considered treatment-related. Treatment-related changes in clinical chemistry values were not observed. A statistically significant decrease in lymphocyte counts was observed for male and female group 4, subgroups B to D, animals, and the monocyte count for males and the segmented neutrophil count for females was significantly increased; these changes were consistent with an inflammatory response to the test substance. Other treatment-related changes in hematologic parameters were not observed. At ophthalmologic examination, treatment-related ocular lesions were not observed.

At necropsy, a statistically significant increase was reported in lung weights for males and females of groups 4A, 4B, 4C, and 5A1, males of groups 3B and 3D, and females of group 3C and in the lung-to-body weight ratio for males and females of groups 3D, 4B, 4C, 4D, and 5A1, males of groups 3B, 4A, and 5A3, and females of group 3C. At microscopic examination, dose-related bronchiolar-centric interstitial pneumonia was observed in two animals of group 2A, all animals of groups 3A, 4A, 5A1, in nearly all animals of groups 2B, 3B, and 4B, and in all but one animal of groups 2C, 2D, 3C, 3D, 4C, 4D, 5A2, and 5A3. Nodular histiocytosis, characterized by aggregates of large macrophages and an absence of necrosis or other inflammatory cells, and lymphoid hyperplasia, characterized by an increase in the number of lymphocytes and the size of the lymph nodes, was observed in the bronchial and thoracic lymph nodes; the incidence was greater in the animals exposed for 13 weeks than for those exposed for 4 weeks. Bronchiolarization of the alveoli, characterized by the presence of dark cuboidal, usually ciliated, epithelium in the alveoli near the terminal bronchioles, was reported for animals of groups 3B and 4B, with the incidence decreasing slightly in animals of groups 3C and 4C, and then increasing in animals of groups 3D, 4D, and 5A3 as compared to the incidence for groups 3C and 4C. Significant parenchymal cell necrosis and significant fibrosis were not observed.

In another inhalation toxicity study by Battelle (1987), groups of 70 male and 70 female Fischer 344 (CD) rats were exposed to 0.05, 0.2, 1, and 10 mg/m³ of an acrylic acid polymer in an inhalation chamber 6 hours per day, 5 days per week, for 26 weeks for a total of 132 exposures (Battelle 1987). The polymer was comprised of acrylic acid, alkene-poly (alkenoate) and sodium acrylate (Procter and Gamble Co. 1987). Control groups of rats were exposed to a positive control, a nuisance dust, or untreated filtered air. The particle size distributions, as defined by mass median aerodynamic diameter (MMAD) and GSD, were similar and highly respirable for the test article and the controls (MMAD of 1.95 to 2.07). The mean chamber concentrations (and GSD) were 0.05 (0.01), 0.21 (0.04), 1.09 (0.17), and 9.68 (1.15) mg/m³ as compared to the target concentrations of 0.05, 0.2, 1, and 10 mg/m³.

TABLE 7

Exposure regimen for inhalation toxicity study (Battelle 1987)

| Necropsy group | Exposure/recovery |
|----------------|--|
| 1 | 20 exposures; 0/1-day recovery period |
| 2 | 20 exposures; 60/61-day recovery period |
| 3 | 64 exposures; 0/1-day recovery period |
| 4 | 64 exposures; 89/90-day recovery period |
| 5 | 132 exposures; 2/3-day recovery period |
| 6 | 132 exposures; 89/90-day recovery period |
| 7 | 132 exposures; 191/192-day recovery period |

Animals were observed while in the exposure chambers and twice daily for signs of toxicity. Body weights and feed consumption were determined weekly. Ten animals per sex per group were killed according to the schedule shown in Table 7.

Ophthalmic examinations were performed on all animals 1 week prior to necropsy. One animal per sex per necropsy group was used for serology and all animals were used for hematology and clinical chemistry evaluation.

None of the animals died as a result of treatment during the study. Treatment-related physical changes were not observed in animals of any group, and no ophthalmic lesions were observed in any of the animals. Mean body weights of necropsy group 7 male rats exposed to 0.2, 1, or 10 mg/m³ and female rats exposed to 10 mg/m³ were statistically significantly less than control values during the last 90 days of recovery; the differences were not considered treatment-related. Absolute body weight gains of male rats of necropsy groups 2 and 7 that were exposed to 1 and 10 mg/m³, respectively, female rats of necropsy group 3 that were exposed to 10 mg/m³, and female rats of necropsy group 5 that were exposed to 0.05 and 1 mg/m³ were significantly decreased. Absolute body weight gains of male rats at necropsy of necropsy group 3 that were exposed to 0.05 and 1 mg/m³ were significantly increased compared to control values. The differences in absolute body weight gain were not considered treatment-related. Terminal body weights of males at necropsy of group 7 that were exposed to 0.2 and 10 mg/m³ were significantly decreased compared to negative-controls. Significant differences in feed consumption were frequently observed between test and negative-control animals, but the overall pattern of feed consumption of test animals was not "remarkably different" from the controls.

Treatment-related changes in clinical chemistry parameters were not observed. Exposure to acrylic acid polymer produced concentration-dependent mild increases in the number of circulating mature neutrophils. Males of necropsy group 1 that were exposed to 1 mg/m³, females of necropsy groups 1 and 5 that were exposed to 0.2 mg/m³, and males and females of all necropsy groups except 4 and 2, respectively, that were exposed to 10 mg/m³ had a significant increase in the number or segmented neutrophils. With the exception of the changes in the animals of the 0.2-mg/m³ group, the changes were considered

treatment-related. For the animals of the 10-mg/m³ group, the total number of leukocytes was also significantly increased when the neutrophil counts were increased.

A significant decrease in lung weight was observed for females of necropsy group 2 that were exposed to 0.05 mg/m³. Absolute lung weight, the lung-to-body weight ratio, and the lung-to-brain weight ratio was significantly increased for male rats of necropsy group 6 exposed to 0.2 mg/m³. Absolute lung weight was significantly increased in males and females of necropsy group 3 and in males of necropsy group 5 that were exposed to 1 mg/m³. In the 10-mg/m³ group, significant increases in absolute lung weight and lung-to-body weight ratio were observed for males and females of all necropsy groups. The changes observed for animals of the 1- and 10-mg/m³ groups were considered treatment-related.

Mottled lungs were observed in one male of necropsy group 1, in all males and nine females of necropsy group 3 that were exposed to 1 mg/m³, and in all animals exposed to 10 mg/m³. Enlarged peribronchial and thymic lymph nodes were observed sporadically in rats exposed to acrylic acid polymer. Pulmonary inflammation was reported in animals of the 1 and 10 mg/m³ groups. For the animals of the 1-mg/m³ group, pulmonary inflammation was mostly mild in animals of necropsy group 1, nonexistent in animals of necropsy group 2, mostly mild to moderate in animals of necropsy groups 3 and 5, and mostly minimal in animals of necropsy groups 6 and 7. One and four males of necropsy groups 6 and 7, respectively, that were dosed with 1 mg/m³ acrylic acid polymer had collagen associated with the few foci of inflammation; this collagen formation was minimal. For the animals of the 10 mg/m³ group, the severity of pulmonary inflammation increased from mostly moderate after 20 exposures to mostly marked after 64 or 132 exposures. A reduction in inflammation and a more multifocal pattern was seen in the recovery groups. Collagen deposition occurred primarily in multifocal areas of inflammation along the periphery of the lungs. Two females of necropsy group 7 that were exposed to 10 mg/m³ had alveolar/bronchiolar adenomas. Granulomatous inflammation in the thymic and/or peribronchial lymph nodes was seen in necropsy groups 4 to 6 animals exposed to 10 mg/m³; these lesions were mostly minimal and did not increase in severity. Gross and microscopic lesions were also observed in the lungs of the positive-control group, but these lesions generally had patterns different than those of the test group. The researchers concluded that exposure-related effects occurred at all doses, but "due to the minimal nature of the pulmonary inflammation observed in the two lower exposure group, 0.05 and 0.2 mg/m³ [acrylic acid copolymer] are considered to be no-adverse effect levels in this study" (Battelle 1987).

Acrylic Acid and Ethyl and Butyl Acrylates. Groups of 15 male and 15 female Fischer 344 rats and B6C3F₁ mice were exposed to 5, 25, or 75 ppm (0.015, 0.074, or 0.662 mg/l) acrylic acid in air for 6 hours per day, 5 days per week for 13 weeks; a control group breathed untreated air (Miller et al. 1981). All animals were observed twice daily. Body weights were mea-

sured weekly. The mean body weight gains of female mice of the 25- and 75-ppm dose groups were significantly decreased as compared to controls after 12 weeks. Focal degeneration of the olfactory epithelium of the nasal mucosa was observed in rats of the 75-ppm group and mice of all test groups.

Groups of 10 male and 10 female Sprague-Dawley rats were exposed to 23, 124, 242, or 626 ppm ethyl acrylate (measured dose) in air for 6 hours per exposure 58 times over a 12-week period; a control group breathed untreated air (BASF 1978a). The animals were checked daily for signs of toxicity. Body weights were measured weekly. Clinical chemistry and urinalysis were performed three times during the study. None of the animals of the 23-, 124-, or 242-ppm groups died, but all of the animals of the 626-ppm group died during the study. A decrease in body weight gains for animals of the 124-, 242-, and 626-ppm dose groups was considered treatment-related. Animals of the 242-ppm dose group had slight to severe irritation of the mucosa and slight dyspnea between exposures 3 and 9. Animals of the 626-ppm dose group had increasingly severe irritation of the mucosa and difficulty in breathing with gasping as of exposure 3. No compound-induced changes were observed during clinical chemistry or urinalysis. Increases in relative liver weights in females of the 124- and 242-ppm groups and in relative lung weights of females of the 124-ppm group and males and females of the 242-ppm groups were considered compound-related. At microscopic examination, dose-dependent lesions were observed in the area of the nasal mucosa and the olfactory areas in animals of the 242- and 626-ppm groups (BASF 1980).

Groups of 20 male and 20 female Sprague-Dawley rats were exposed to 21, 108, 211, or 546 ppm *n*-butyl acrylate (measured dose) in air for 6 hours per exposure 63 times over a 13-week period; a control group breathed untreated air (BASF 1978b). The animals were checked daily for signs of toxicity. Body weights were measured weekly. Clinical chemistry and urinalysis were performed three times during the study. None of the animals of the 21-, 108-, or 211-ppm groups died, but 16 males and 15 females of the 546-ppm group died during the study. A decrease in body weight gains for animals of the 211- and 546-ppm dose groups was significant and dose-dependent. All animals of the 211-ppm dose group had discharge from the eyes and nose during exposure; these animals recovered after each exposure. Animals of the 546-ppm dose group had pronounced discharge from the eyes and noses, which, until day 10, subsided after exposure; as of day 11, the animals did not recover and had dyspnea and bloody discharge from the eyes and nose. A number of clinical chemistry and hematology parameters were affected by the high dose. Increases were observed in the relative liver weights of females of all test groups, in the relative lung weights of males and females of the 546-ppm group, in the relative adrenal gland weights of males of the 211-ppm and males and females of the 546-ppm groups, and in the thyroid gland weights of females of the 546-ppm group. At microscopic examination, dose-dependent lesions were observed in the area

of the nasal mucosa and the olfactory area in animals of the 108-, 211-, and 546-ppm groups (BASF 1980).

Chronic Toxicity

Oral

Acrylic Acid and Ethyl Acrylate. Male and female Wistar rats were given 120, 800, 2000, or 5000 ppm acrylic acid in the drinking water; groups of 10 males and 10 females were dosed for 3 months and groups of 20 males and 20 females were dosed for 12 months (Hellwig, Deckardt, and Freisberg 1993). The control groups were given untreated water. Feed and water consumption and body weights were determined weekly for the first 3 months; feed and water consumption was then determined every 3 months and body weights were measured every 4 weeks. The animals were examined daily and palpated weekly. Blood samples were taken from 10 animals of each main group after 4, 12, 26, and 51 weeks. The animals were killed and necropsied at the end of the study. Gross lesions of all animals, the livers and kidneys of the animals given 2000 or 5000 ppm acrylic acid for 12 months, selected tissues of the animals given 2000 or 5000 ppm for 3 months, and selected tissues of all animals given acrylic acid for 12 months were examined microscopically.

Actual concentrations in the test solutions were 95% to 107%, 90% to 96%, 95% to 100%, and 94% to 100% of the target concentrations of 120, 800, 2000, and 5000 ppm, respectively, which corresponded to a daily mean intake of 9, 61, 140, and 331 mg/kg, respectively. A statistically significant decrease in water consumption was observed during most of the study for the animals given 5000 ppm for 12 months and until week 14 for animals given 2000 ppm for 12 months. None of the animals in the study died as a result of dosing. Treatment-related changes in clinical chemistry, hematology, or urinalysis parameters were not observed. Treatment-related lesions were also not observed. No significant differences in organ weights were observed between test animals dosed for 3 or 12 months and control animals.

In a 2-year study, groups of 25 male and 25 female Wistar rats were dosed with 6, 60, and 2000 ppm ethyl acrylate in drinking water; after 5 months, the 6- and 60-ppm doses were increased to 7 and 70 ppm, respectively (Borzelleca et al. 1964). Groups of two male and two female beagle dogs were dosed (also for 2 years) with 10, 100, and 1000 ppm ethyl acrylate dissolved in corn oil in gelatin capsules. The 1000-ppm ethyl acrylate capsules had an emetic effect. Reducing the dose to 500 ppm on day 2 resulted in vomiting in two dogs. Dosing for this group was discontinued for the week, the animals were given 300 ppm at week 2, and the dose was increased until it reached 1000 ppm at week 16. Feed and water consumption was determined at various intervals, and the animals were weighed regularly. Body weights were significantly decreased for male rats during year 1 and for female rats throughout the study. Decreased growth paralleled periods of decreased feed consumption. Water consumption was decreased for rats dosed with 2000 ppm. No compound-related lesions were observed for rats or dogs.

Inhalation

Groups of 60 male and 60 female F344 rats were exposed to 0.05, 0.2, or 0.8 mg/m³ of respirable polyacrylate particles (not defined) (MMAD of 2 to 3 μ) for 24 months and a control group of 60 males and 60 females breathed untreated air (Institute for Polyacrylate Absorbents 1991). A subgroup of animals at each dose was used in a toxicokinetic study and exposed to radioactive material at 6, 12, and 20 months to determine the clearance kinetics. Necropsy of interim killed animals were performed after 6 and 12 months. Visible effects were not seen in animals of the low-dose group, and microscopic changes were not found at 6 and 12 months. One male and 3 females of the mid-dose group had nodules in the lungs and 7 males and 23 females of the high-dose group had pulmonary nodules; 1 female of the control group had pulmonary nodules. Nodules were not observed in animals at the 6- and 12-month necropsies. At 6 months, clearance of the radioactive material was altered at the doses where nodules formed. The researchers did not report that the incidence of pulmonary nodules was significant and considered it to be probably based on an irritant response involving altered clearance from the lungs.

Dermal Irritation

Acrylates Copolymer. The dermal irritation potential of Acrylates Copolymer (approximately 24% solids) was determined using three male and three female New Zealand white rabbits (Bushy Run Research Center 1993a). Acrylates Copolymer, 0.5 ml, was applied for 4 hours under an occlusive patch to intact skin on a clipped dorsal area on the trunk of each animal. The sites were scored 1 hour and 1, 2, 3, and 7 days after patch removal. Minor transient erythema was observed for three animals for <1 day and for two animals for <2 days, and minor transient edema was observed for one animal for <1 day.

Three white Vienna rabbits, two males and one female, were used to determine the dermal irritation potential of Acrylates Copolymer (BASF 1994c). One-half gram of the test material (supplied as a white powder and moistened with distilled water) was applied under a semiocclusive patch to intact skin on the back for 4 hours. The test site was scored for erythema and edema 1, 24, 48, and 72 hours, and 8 and 15 days after patch removal. The average score (24 to 72 hours) was 1.6/4 for erythema and 0.1/4 for edema. All three animals had very slight erythema and scaling on day 15. The researchers concluded that Acrylates Copolymer had "indication of an irritant property to the skin." However, the researchers stated that Acrylates Copolymer had adhesive effects upon moistening with water, making the test article difficult to remove from the skin. They stated that "signs of slight irritation have to be interpreted as sequela mechanically induced lesions of the superficial layers of the skin. Accordingly, the test substance cannot be considered 'irritant.'"

The dermal irritation potential of Acrylates Copolymer, 30% solids and pH 7 to 7.4, was determined in a Draize test using rabbits (BFGoodrich Specialty Chemicals 1997). Acrylates Copolymer was not a primary irritant.

In another Draize test using rabbits, a 25% solution of Acrylates Copolymer, 100% solids, in acetone also was not a primary irritant (BFGoodrich Specialty Chemicals 1997).

The dermal irritation potential of four Acrylates Copolymers was determined using New Zealand white rabbits according to Organization for Economic Cooperation and Development (OECD) guidelines (BFGoodrich Specialty Chemicals 1997). The test materials were applied for 4 hours to intact skin under semioclusive patches. At most, the Acrylates Copolymers produced very slight erythema, with an "isolated incident" of very slight edema. Using the Draize scoring scale, three of the Acrylates Copolymers had PII of 0.0 and were nonirritating to rabbit skin. One Acrylates Copolymer had a PII of 0.5 and was a mild irritant.

Female New Zealand white rabbits were used to determine the dermal irritation potential of Acrylates Copolymer (containing 36, 20, and 45 ppm *n*-butyl acrylate, methyl methacrylate, and methacrylic acid, respectively; CTFA 1999a) (MB Research Laboratories 1997). The test area, a 10 × 15-cm site on the dorsal area of the trunk, was clipped free of hair. Initially, one animal was dosed dermally for 4 hours with 0.5 ml Acrylates Copolymer under a semioclusive patch; the test site was scored according to the methods of Draize 1, 24, 48, and 72 hours after patch removal. Subsequently, five animals were dosed dermally for 4 hours using semioclusive patches, and the test sites were observed 1, 24, 48, and 72 hours and 7 days following dosing. The patches adhered to the skin of the animals and were not removable without causing damage to the skin; therefore, the perimeter of the test area was scored. With the exception of one animal that had a severe score at 72 hours the test article produced very slight to well-defined irritation through 72 hours. Very slight irritation was observed for one animal at day 7. (This was not the animal that had severe irritation at 72 hours.) This Acrylates Copolymer had a modified PII of 2.08. The researchers stated that "the elevated erythema scores [were] probably more a result of the animals effort to remove the test article rather than any irritating effect of the test article."

Ammonium Acrylates Copolymer. The dermal irritation potential of a mixture containing 30% Ammonium Acrylates Copolymer was determined using three rabbits (Allied Colloids 1997). The test material was applied under semioclusive patches for 4 hours to a shaved dorsal area on the trunk of each animal. The test sites were scored 1, 24, 48, and 72 hours after patch removal. One animal had very slight erythema 1 and 48 hours after patch removal; the other two animals did not have an irritant response. Edema was not observed at any of the test sites. Ammonium Acrylates Copolymer was "practically nonirritant to rabbit skin."

Ethylene/Acrylic Acid Copolymer. An aqueous emulsion of the ammonium salt of an Ethylene/Acrylic Acid polymer, 21.8% solids at pH 9.8, was applied to rabbits in an open test (Union Carbide Chemical Co. 1998c). Study details were not provided. The authors stated that irritation was minor with a grade of 4.

Acrylates/VA Copolymer. New Zealand white rabbits, five males and one female, were used to determine the primary irritation potential of Acrylates/VA Copolymer solution (Bio/dynamics Inc. 1988a). One-half milliliter of undiluted solution was applied under occlusive patches to two intact shaved sites on the back of each animal for 4 hours. The sites were scored for erythema and edema according to the Draize scale 30 minutes and 24, 48, and 72 hours after patch removal; if signs of irritation were still apparent after 72 hours, the sites were observed 7, 10, and 14 days after dosing or until no evidence of irritation was present.

After 30 minutes, four animals had very slight to slight erythema with edema and two animals had moderate erythema with edema. The test sites of one animal had superficial necrosis after 24, 48, and 72 hours and 7 days and severe erythema with edema until day 7, the left test site of one animal had necrosis after 24, 48, and 72 hours, superficial necrosis after 7 and 10 days, severe erythema with edema until day 7, and severe erythema until day 10, and the left test site of a third animal had superficial dermatitis after 72 hours and 7 days and severe erythema on day 7. Desquamation was observed at the test sites of these animals on days 7 and 10. Signs of irritation were not seen on day 14. The researchers concluded that an Acrylates/VA Copolymer solution "produced moderate to severe but reversible dermal irritation."

Two male and four female New Zealand white rabbits were used to determine the dermal irritation potential of Vinyl Acetate/Maleate/Acrylate Copolymer solution (Bio/dynamics Inc. 1984c). One-half milliliter of the test material was applied undiluted to two clipped sites on the back under a semioclusive patch for 4 hours and to two clipped sites under an occlusive patch for 24 hours. The sites were scored for irritation according to the Draize scale 30 minutes and 24, 48, and 72 hours after removal of the 4-hour semioclusive patch and 30 minutes and 24 and 48 hours after removal of the 24-hour occlusive patch. If irritation was observed after 72 and 48 hours, respectively, the sites were observed on days 7, 10, and 14 or until no evidence of irritation was present.

Thirty minutes after removal of the 4-hour semioclusive patch and the 24-hour occlusive patch, all animals had well-defined to severe erythema with edema. Epidermal tissue damage was observed at one or both 4-hour patch sites in four animals and at one or both 24-hour patch sites in three animals. Subepidermal damage was observed at both 24-hour patch sites in two animals. Very slight erythema was observed at the 4- and 24-hour patch sites through day 14 for all animals. The primary irritation index for the 24-hour exposure was 4.4.

Sodium Polyacrylate. Six albino rabbits were used to determine the irritation potential of Sodium Polyacrylate (Finnegan and Dienna 1953). Two milliliters of undiluted Sodium Polyacrylate was applied to the clipped back and sides of the animals once daily, 5 days per week for 4 weeks. Signs of irritation were not observed.

Acrylic Acid. Acrylic acid, 1% or 4% in acetone, was applied to the skin of groups of 30 female ICR, 30 male C3H,

and 30 female B6C3F₁ mice three times per week for 13 weeks (Tegeris et al. 1988). Control mice were dosed with acetone. Five mice per group were killed and necropsied after 1, 2, 4, and 8 weeks. Significant skin irritation, including desquamation, fissuring, and eschar, was observed in all three strains of mice treated with 4% acrylic acid. Proliferative, degenerative, and inflammatory changes in the epidermis and dermis were observed at microscopic examination of the skin of animals dosed with 4% acrylic acid. A low incidence of proliferative changes was observed in the animals dosed with 1%. No changes were observed in control animals.

Sensitization

Acrylates Copolymer. A Magnusson-Kligman maximization study was performed using albino guinea pigs to determine the sensitization potential of Acrylates Copolymer (approximately 25% solids; Amerchol 1997) (Pharmaco LSR 1993). A range-finding study was performed in which groups of two animals were dosed intradermally with 0.5%, 1.0%, or 5.0% v/v Acrylates Copolymer in propylene glycol. Extensive necrosis was observed 24 and 48 hours, but not 72 hours, after injection of 5.0% Acrylates Copolymer; local necrosis was produced by 0.5% and 1.0%. Also in a range-finding study, three male and three female animals were dosed dermally for 24 hours with 10%, 25%, 50% v/v and undiluted Acrylates Copolymer under an occlusive patch. Undiluted Acrylates Copolymer was nonirritating.

In the induction phase of the maximization study, a test group of 10 male and 10 female animals were dosed intradermally with 0.1 ml of 5% v/v Acrylates Copolymer (25% solids) and topically with undiluted Acrylates Copolymer (25% solids). After a 14-day nontreatment period, the animals were challenged with undiluted Acrylates Copolymer. An irritation control group of five male and five female animals were induced without test article and were challenged with undiluted Acrylates Copolymer. Acrylates Copolymer did not produce a sensitization reaction in any of the animals.

Female guinea pigs were used in a Magnusson-Kligman maximization test to determine the sensitization potential of Acrylates Copolymer (containing 36, 20, and 45 ppm *n*-butyl acrylate, methyl methacrylate, and methacrylic acid, respectively; CTFA 1999a) (Unilever Research U.S. 1996). During induction, the intrascapular region of 20 animals was clipped free of hair, and intradermal injection of 25% Acrylates Copolymer (w/v) in distilled water with and without Freund's complete adjuvant (FCA) was given. (One test animal died prior to challenge; the reason was not test article related.) One week after intradermal injection, the test site was again clipped and an occlusive patch of undiluted Acrylates Copolymer was applied to the injection site for 48 hour. A control group of 10 animals was treated in a similar manner using distilled water. The challenge was conducted 14 days after the induction by applying an occlusive patch of 25% w/v Acrylates Copolymer in distilled water to the clipped left flank of test and control animals for 24 hours. The test sites

were evaluated 24 and 48 hours after patch removal. Acrylates Copolymer was not a sensitizer in guinea pigs.

The sensitization potential of four Acrylates Copolymers was determined using groups of albino guinea pigs in Magnusson-Kligman maximization studies performed according to OECD guidelines (BFGoodrich Specialty Chemicals 1997). For three of the Acrylates Copolymers, groups of 20 test animals were dosed intradermally with 25% w/v test material in distilled water and topically with undiluted test material in the induction phase of the study. For one Acrylates Copolymer, the animals were challenged with 10% and 25% v/v test material, whereas for the other two Acrylates Copolymers, the animals were challenged with undiluted and 75% v/v test material in distilled water. For the fourth Acrylates Copolymer, a group of 20 test animals were dosed intradermally with 10% w/v test material in distilled water and topically with undiluted test material in the induction phase and challenged with undiluted and 75% v/v test material in distilled water. Control groups consisted of 10 animals. The Acrylates Copolymers did not produce a sensitization reaction in any of the animals.

Acrylates Copolymer (containing 1500 and 200 ppm stearyl acrylate and methacrylic acid, respectively; CTFA 1999b) was evaluated for its sensitization potential in a Magnusson-Kligman maximization test (MB Research Laboratories 1999c). During induction, 10 male and 10 female Hartley albino guinea pigs were given three pairs of intradermal injections consisting of 50% Acrylates Copolymer in mineral oil, mineral oil, and/or FCA. One week after intradermal injection, an occlusive patch containing undiluted Acrylates Copolymer was applied for 48 hours to the test site, which was pretreated with sodium lauryl sulfate. A negative-control group of five males and five females was treated in a similar manner using vehicle only. The challenge was performed 2 weeks after induction by applying for 24 hours an occlusive patch containing undiluted test article to one flank and containing vehicle to the other flank of test and control animals. During induction, weak to moderate erythema was observed; none was observed at challenge. Two test animals had diarrhea and soiling of the anogenital area, whereas one had soiling only. The researchers concluded that Acrylates Copolymer had "a weak sensitizing potential" but "did not produce any sensitizing response."

The sensitization potential of Acrylates Copolymer was determined in a Buehler sensitization test using guinea pigs (Allied Colloids 1997). (Details were not given.) No positive reactions were observed during induction or challenge, and Acrylates Copolymer was not a sensitizer in guinea pigs.

Ocular Irritation

In Vivo

Acrylates Copolymer. Two male and two female New Zealand white rabbits were used to determine the ocular irritation potential of Acrylates Copolymer (approximately 24% solids) (Bushy Run Research Center 1993a). The test article, 0.1 ml, was instilled into the conjunctival sac of one eye of each

animal; the contralateral eye served as an untreated control. The eyes were examined 1 hour and 1, 2, 3, and 7 days after dosing. Minor to moderate conjunctival irritation was reported for all animals 1 hour after dosing. The maximum mean total score at 1 hour was 8.0/110. All eyes were normal within 2 to 3 days. Acrylates Copolymer was mildly irritating to rabbit eyes.

The ocular irritation potential of Acrylates Copolymer (supplied as a white powder) was determined using one male and two female white Vienna rabbits (BASF 1994d). Thirty-two milligrams of the test article was placed in the conjunctival sac of one eye of each animal and the eye was not washed; the contralateral eye served as an untreated control. The eyes were examined 1, 24, 48, and 72 hours after application. The average score (24 to 72 hours) was 0.0/4 for corneal opacity and chemosis, 0.0/2 for the iris, and 0.1/3 for conjunctivae redness. Acrylates Copolymer was not an ocular irritant.

Six New Zealand white rabbits were used to determine the ocular irritation potential of Acrylates Copolymer (containing 36, 20, and 45 ppm *n*-butyl acrylate, methyl methacrylate, and methacrylic acid, respectively; CTFA 1999a) (MB Research Laboratories 1996b). One-tenth milliliter of the test article was placed in the conjunctival sac of the left eye, and the eye was not rinsed. The right eye served as a control. The eyes were examined for irritation 1 hour and 1, 2, 3, and 7 days after dosing. Corneal opacity, seen in four animals, and iritis, seen in three animals, cleared by day 7. Conjunctival irritation, which was observed in all animals, cleared in all but one animal by day 7. The researchers stated that Acrylates Copolymer was "an eye irritant but not corrosive."

The ocular irritation potential of Acrylates Copolymer, 30% solids and pH 7 to 7.4, was determined using rabbits (BFGoodrich Specialty Chemicals 1997). Study details were not reported, but the authors concluded that Acrylates Copolymer was not an ocular irritant.

The ocular irritation potential of a 15% solution of Acrylates Copolymer, 100% solids, in ammonia water, was determined according to the method of Carpenter and Smythe (BFGoodrich Specialty Chemicals 1997). Acrylates Copolymer was not an ocular irritant.

Using groups of three New Zealand white rabbits, the ocular irritation potential of four Acrylates Copolymers was determined according to OECD guidelines (BFGoodrich Specialty Chemicals 1997). The test materials were instilled into the conjunctival sac of one eye of each rabbit, and the eyes were not rinsed. The test materials produced minimal or minimal to moderate conjunctival irritation; the eyes appeared normal after 24 or 48 hours. Using the scoring of Kay and Calandra, the Acrylates Copolymers produced maximum group mean score of 2.7 to 5.3 and were minimal irritants.

The ocular irritation potential of Acrylates Copolymer (containing 1500 and 200 ppm stearyl acrylate and methacrylic acid, respectively; CTFA 1999b) was determined using New Zealand white rabbits (MB Research Laboratories 1999d). Initially, 0.1 ml Acrylates Copolymer was instilled into the conjunctival

sac of one male animal, and the eye was graded 1, 24, 48, and 72 hours after dosing. Subsequently, 0.1 ml was instilled into the eyes of four males and one female. Again, the eyes were evaluated 1, 24, 48, and 72 hours after dosing. No corneal opacity or iritis was observed. Conjunctival irritation, which was observed in all animals, cleared by 48 hours. The researchers stated that according to OECD guidelines, "the test article is an ocular irritant but not corrosive." According to the methods of Kay and Calandra, "the test article is minimally irritating."

Ammonium Acrylates Copolymer. The ocular irritation potential of a mixture containing 30% Ammonium Acrylates Copolymer was determined using three New Zealand white rabbits (Allied Colloids 1997). The eyes were examined 1, 24, 48, and 72 hours after instillation of the test article. Slight conjunctival redness and slight ocular discharge were observed for one animal 1 hour after instillation. Ammonium Acrylates Copolymer was "practically nonirritant to rabbit eyes."

Ethylene/Acrylic Acid Copolymer. In an ocular irritation study, an aqueous emulsion of the ammonium salt of an Ethylene/Acrylic Acid polymer, 21.8% solids at pH 9.8, produced trace corneal injury (grade 2) in rabbit eyes (Union Carbide Chemical Co. 1998c). Study details were not provided.

Acrylates/VA Copolymer. Six male New Zealand white rabbits were used to determine the ocular irritation potential of Acrylates/VA Copolymer solution (Bio/dynamics Inc. 1988b). One-tenth milliliter of undiluted solution was placed in the lower conjunctival sac of the right eye of each animal. The eyes were not rinsed immediately after dosing but were rinsed after 24 hours to remove residual material. The contralateral eye served as a control. The eyes were scored for irritation according to the Draize method 1, 24, 48, and 72 hours and 7, 14, and 21 days after dosing. All animals had moderate to severe conjunctival irritation, corneal opacity and/or ulceration, and iridal damage or changes. Four animals had alopecia around the eye and one animal vocalized after application. Ocular irritation was observed for 7 days in five animals and for 14 days in one animal. The researchers stated that an Acrylates/VA Copolymer solution "produced severe but reversible ocular irritation."

Three male and three female New Zealand white rabbits were used to determine the ocular irritation potential of Vinyl Acetate/Maleate/Acrylate Copolymer solution (Bio/dynamics Inc. 1984d). One-tenth milliliter of undiluted solution was placed in the lower conjunctival sac of the right eye of each animal. The eyes were not rinsed immediately after dosing but were rinsed after 24 hours to remove residual material. The contralateral eye served as a negative control. The eyes were scored for irritation according to the Draize method after 1, 24, 48, and 72 hours and at 7, 14, and 21 days after dosing. All animals had moderate to severe conjunctival irritation and corneal opacity and/or ulceration. Two animals had iritic changes and four animals had desquamation on the outer eyelids and/or alopecia around the eye. Ocular irritation was observed for 7 days in all animals and for 14 days in four animals. The researchers stated that an

Vinyl Acetate/Maleate/Acrylate Copolymer solution "produced moderate to severe but reversible ocular irritation."

Sodium Polyacrylate. A Draize test was performed in which 0.1 cc of Sodium Polyacrylate was placed in the conjunctival sac of groups of rabbits; using groups of 10 animals, the eyes were not rinsed and using groups of three animals, the eyes were rinsed (Finnegan and Dienna 1953). Irritation was scored 1, 2, 3, 4, and 7 days after instillation. The greatest tolerated concentration was 13% to 20% for unrinsed eyes and 20% to 30% for rinsed eyes.

An irritant threshold test was performed in which Sodium Polyacrylate was placed in the conjunctival sac of groups of five rabbits, and the eyes were examined for edema, erythema, and increased secretions after 1 hour (Finnegan and Dienna 1953). The threshold concentration, i.e., the greatest concentration that did not produce irritation in three or more of the five animals, was 2%.

Acrylic Acid. A 1% acrylic acid solution caused significant injury to the rabbit eye (IARC 1979).

In Vitro

Acrylates Copolymer. Two chorioallantoic membrane vascular assays (CAMVAs) and two bovine corneal opacity and permeability (BCOP) tests were performed to determine the ocular irritation potential of Acrylates Copolymer (MB Research Laboratories 1996c, 1996d). In both CAMVAs, Acrylates Copolymer was a nonirritant and in both BCOPs it was a mild irritant.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Oral

Sodium Polyacrylate. The teratogenic potential of 4500- and 90,000-Da molecular weight Sodium Polyacrylate was evaluated using groups of Charles River CD rats that were dosed by gavage following a FDA Segment II protocol with some modifications (Nolen et al. 1989). Concentrations of 500, 1000, and 3000 mg/kg/day of the low-molecular-weight Sodium Polyacrylate (43.3% solids; 0.09% residual monomer) in demineralized, distilled water at a dose volume of 10 ml/kg/day and 125, 375, and 1125 mg/kg/day of the high-molecular-weight Sodium Polyacrylate (77.5% Sodium Polyacrylate; 3.3% free acrylic acid) in distilled water (*w/v*) were used. Vehicle-control groups were used with both Sodium Polyacrylates and an untreated-control group was used with the high-molecular-weight Sodium Polyacrylate. In the study using the low-molecular-weight Sodium Polyacrylate, 30 animals per group were dosed on days 6 to 15 of gestation and killed on day 19. In the study using the high-molecular-weight Sodium Polyacrylate, eight dams per group were dosed on days 6 to 13 of gestation and killed on day 13; the remaining 20 to 21 dams per group were dosed on days 6 to 15 of gestation and killed on day 19.

In the low-molecular-weight Sodium Polyacrylate study, two animals of the mid-dose group and one of the high-dose group died accidentally during the study. Significant differences in body weight gains and feed consumption were not observed.

Dams of the high-dose group had soft or liquid stools. Effects on embryo viability and fetal growth were not observed, and significant differences in soft-tissue or skeletal abnormalities and variations were not seen between the treated and control groups.

In the high-molecular-weight Sodium Polyacrylate study, one dam of the mid-dose group and six dams of the high-dose group died during the study; three of the high-dose deaths were considered treatment-related, the others were accidental. Statistically significant differences from control values in maternal body weights and body weight gains during gestation were not observed. Changes in overall feed consumption during gestation were not seen; however, a decrease in feed consumption was observed for the high-dose animals on days 7 to 9 of gestation. Significant differences in reproductive and embryonic characteristics were not observed for the dams killed on day 13 or 19. The fetuses of the treated group were significantly longer and also somewhat heavier than the controls; this was not considered biologically significant. Significant differences in soft-tissue or skeletal abnormalities were not reported. Fetuses of both the control and test groups had some delayed skeletal ossification, but this was not considered a treatment-related effect.

Acrylic Acid. Groups of 10 male and 20 female Fischer 344 rats were given 83, 250, or 750 mg/kg acrylic acid in the drinking water daily, and the animals were mated after 13 weeks of dosing (DePass et al. 1983). The neonates, culled to litter size of 10 on day 5 of lactation, were weighed as litters on day 7 and individually on day 21. After weaning, five males and five females randomly selected from each group of the F₀ and F₁ generations were killed and necropsied.

For the F₀ generation, statistically significant decreases were observed in feed and water consumption and body weight gains for males and females of the high-dose group. Water consumption of males and body weight gains of females of the mid-dose group were significantly decreased. For males of the high-dose group, absolute liver weights were statistically significantly decreased and relative kidney weights and spleen and testes weights were statistically significantly increased. For female animals, absolute liver and spleen weights were statistically significantly decreased and relative kidney and brain weights were statistically significantly increased in the high-dose group and absolute kidney, relative kidney, and relative liver weights were statistically significantly increased in the mid-dose group. The researchers felt that most of the changes in organ weights were secondary effects of reduced body weight, with the exception of the increase in absolute and relative kidney weights in females.

Numerical, although not statistically significant, reductions in gestation index (89% for test animals, 100% for controls), number of live pups per litter (four for test animals, six for controls), and percentage of pups weaned (42% for test animals, 100% for controls) were observed in the high-dose group. Females of the high-dose group had a fertility index of 45%; however, the females of the control group had a relatively low fertility rate of 50%. The researchers noted that the control group was relatively atypical and the results of the high-dose group should be

interpreted cautiously. The researchers felt that a conclusion of no adverse effect at the mid or low dosages was correct; a number of the values observed for these groups were greater than those observed for control animals.

For the F₁ generation, the average body weights were statistically significantly decreased for neonates of the high-dose group as compared to those of the control group at days 7 and 21. At day 21, the absolute and relative liver weights and absolute kidney and heart weights were statistically significantly decreased and the relative brain weights were statistically significantly increased for male neonates of the high dose group. For females at day 21, absolute liver weights and absolute and relative spleen and body weights were statistically significantly decreased and relative brain weights were statistically significantly increased for neonates of the high-dose group and absolute liver and spleen weights were statistically significantly increased for neonates of the low-dose group. The researchers again felt that most of the changes in organ weights were due to decreased body weights, with the exception of the changes in weights of the liver and spleen.

Inhalation

Acrylic Acid and 2-Ethylhexyl, Methyl, Ethyl, Butyl, 2-Hydroxyethyl, and Hydroxypropyl Acrylate. In an inhalation study, gravid Sprague-Dawley rats were exposed to acrylic acid 6 hours per day on days 6 to 15 of gestation (Klimisch and Hellwig 1991). Groups of five animals were exposed to 225 or 450 ppm acrylic acid (analytical means of 217.6 and 438.9 ppm, respectively) in a dose range-finding study and groups of 30 animals were exposed to 40, 120, or 360 ppm (analytical means of 39.4, 114.0, 356.2 ppm, respectively) in the main study. (Particle size was not specified.) Control groups were used. The animals were killed on day 20 of gestation.

In the dose range-finding study, animals of both dose groups had signs of sensory irritation during dosing. Body weight gains and feed consumption of animals of the 450-ppm group were decreased throughout exposure. Maternal toxicity occurred at both concentrations, and was more pronounced at the higher dose.

In the main study, abnormal behavior was not noted in the 40- and 120-ppm dose groups, but signs of sensory irritation were observed for animals of the 360-ppm dose group. Body weights, body weight gains, and feed consumption were statistically significantly reduced for dams of the high-dose group throughout dosing. A significant decrease was observed in body weight minus uterine weight for animals of the mid- and high-dose groups. Acrylic acid was maternally toxic at doses of 120 and 360 ppm, and was possibly maternally toxic at a dose of 40 ppm acrylic acid. Acrylic acid was not teratogenic or embryotoxic.

Groups of 17 to 25 gravid Sprague-Dawley rats were exposed 6 hours per day on days 6 to 20 of gestation to acrylic acid or its esters via inhalation (Saillenfait et al. 1999). Exposure concentrations were 50 to 300 ppm acrylic acid (48.0 to 313.1 ppm actual), 25 to 200 ppm methyl acrylate (25.1 to 199.4 ppm

actual), 25 to 200 ppm ethyl acrylate (25.0 to 202.9 ppm actual), 100 to 300 ppm *n*-butyl acrylate (103.3 to 302.5 ppm actual), 50 to 100 2-ethylhexyl acrylate (51.0 to 102.5 ppm actual), 1 to 10 ppm 2-hydroxyethyl acrylate (1.1 to 10.6 ppm actual); and 1 to 10 ppm hydroxypropyl acrylate (1.0 to 10.3 ppm actual). Controls were exposed to filtered room air. Airborne particles were measured with an Aerodynamic Particle Sizer, with a minimum detection limit of 0.5 μ m; there was no difference in particle counts between clean filtered air (control) and vapor-laden air in the test chambers. (The particle sizes were not stated.) The animals were killed on day 21 of gestation.

No maternal deaths were observed in any test group. Reductions in maternal weight gain and feed consumption were observed at some doses with all test compounds. Decreased fetal body weights were observed with 300 ppm acrylic acid, 100 ppm methyl acrylate, 200 ppm ethyl acrylate, and 200 and 300 ppm butyl acrylate. No teratogenic or reproductive effects were seen with any of the test compounds.

Groups of 33 gravid Sprague Dawley rats were exposed to air with 50 or 150 ppm ethyl acrylate for 6 hours per day on days 6 to 15 of gestation; a control group was exposed to filtered air (Murray et al. 1981). All animals were observed daily for signs of toxicity. Maternal body weights were measured during gestation, and feed and water consumption was determined at 3-day intervals starting on day 6 of gestation. Maternal toxicity, as evidenced by decreased body weights and body weight gains, was observed in the 150-ppm dose group. Major malformations were observed in three neonates of the high-dose group; this was not statistically significant compared to controls and was not considered to be of toxicological significance. Ethyl acrylate was not embryotoxic or fetotoxic.

Gravid rats were exposed to \leq 250 ppm *n*-butyl acrylate in an inhalation study (Rohm and Haas Co. 1983). High concentrations (135 and 250 ppm) had toxic effects on the dams and the fetuses, and the dams had signs of irritation. No toxic effects were seen with 25 ppm *n*-butyl acrylate.

Parenteral

Acrylic Acid and Methyl, Ethyl, Butyl, Isobutyl, and Isodecyl Methacrylate. Twenty-two groups of five gravid female Sprague-Dawley rats were dosed by IP injection on days 5, 10, and 15 of gestation with 0.13 to 0.44 ml/kg methyl, 0.12 to 0.41 ml/kg ethyl, 0.23 to 0.77 ml/kg *n*-butyl, 0.14 to 0.47 ml/kg isobutyl, and 0.25 to 0.82 isodecyl methacrylate monomers plus 0.0023 to 0.0075 ml/kg acrylic acid; the dose values were one-tenth, one-fifth, and one-third the LD₅₀ (Singh, Lawrence, and Autian 1972). Groups of rats were given 0.82 ml/kg cottonseed oil, distilled water, or normal saline or were untreated and served as control groups. The dams were killed on day 20 of gestation.

Using a "pooled volume control," all three doses of ethyl methacrylate, the high doses of *n*-butyl methacrylate and isobutyl methacrylate, and the mid and high doses of isodecyl methacrylate significantly increased resorption. The incidence

of gross abnormalities was significantly increased in all dose groups, except the low-dose groups given methyl methacrylate and acrylic acid and the low- and mid-dose group given *n*-butyl methacrylate. The incidence of skeletal malformations was significantly increased in the acrylic acid high dose group.

Three groups of five gravid female rats were dosed by IP injection with 2.5, 4.7, or 8 mg/kg acrylic acid on days 5, 10, and 15 of gestation, while a control group was given vehicle (IARC 1979). Significant increases were observed in the number of "gross abnormalities" in the neonates of the mid- and high-dose groups and in skeletal abnormalities in the high-dose group as compared to controls. Embryotoxicity occurred in animals of the high-dose group.

On day 13 of gestation, the uterus of laparotomized gravid Sprague-Dawley rats was exposed, and each embryo in one uterine horn was given an intraamniotic injection of 10, 100, or 1000 $\mu\text{g}/\text{fetus}$ acrylic acid in 0.9% saline (Slott and Hales 1985). The contralateral embryos were given an equivalent dose of saline. The uterus was repositioned. The dams were killed on day 20 of gestation, and the fetuses were examined. Acrylic acid was not significantly embryotoxic at doses of 10 or 100 $\mu\text{g}/\text{fetus}$, but 78% of the fetuses were resorbed with a dose of 1000 $\mu\text{g}/\text{fetus}$.

GENOTOXICITY

Acrylates Copolymer. An Ames test was performed to determine the mutagenic potential of Acrylates Copolymer (25% solids; Amerchol 1997) (Bushy Run Research Center 1993b). Acrylates Copolymer was assayed in duplicate at concentrations of 0.10 to 10 mg/plate using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 without and with metabolic activation. Negative and positive controls were used. Acrylates Copolymer was not mutagenic.

The mutagenic potential of Acrylates Copolymer was determined in an Ames test (BASF 1994e). Acrylates Copolymer was assayed in a standard plate test and a preincubation test at concentrations of 20 to 5000 $\mu\text{g}/\text{plate}$ using *S. typhimurium* strains TA1535, TA100, TA1537, and TA98 with and without metabolic activation. Vehicle was used as a negative control. Acrylates Copolymer was not mutagenic.

Ammonium Acrylates Copolymer. The mutagenic potential of a mixture containing 30% Ammonium Acrylates Copolymer was determined in a modified Ames test using *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 and *Escherichia coli* WP2uvrA (Allied Colloids 1997). Ammonium Acrylates Copolymer was not mutagenic.

Acrylates/VA Copolymer. 2-Ethylhexyl acrylate is a component of Acrylates/VA Copolymer. A microbial mutagen test was performed using *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 to determine the mutagenic potential of 2-ethylhexyl acetate (Rohm and Haas Co. 1979). 2-Ethylhexyl acrylate in dimethylsulfoxide (DMSO) was tested at concentrations of 0.01 to 5.0 $\mu\text{l}/\text{plate}$ with and without metabolic activation. DMSO alone was used as a negative control and

2-anthramine, 2-aminofluorene, and 2-acetaminofluorene were used as positive controls. A statistically significant increase in revertants per plate was observed with TA1535 with metabolic activation at the lowest concentration of 2-ethylhexyl acrylate tested. Negative results were obtained when the test was repeated with 0.0001 to 0.01 $\mu\text{l}/\text{plate}$. 2-Ethylhexyl acrylate was considered not mutagenic in this microbial mutagen test.

The mutagenic potential of 2-ethylhexyl acrylate was examined in an Ames test (Zeiger et al. 1985). Concentrations of 100 to 10,000 $\mu\text{g}/\text{plate}$ were tested with and without metabolic activation using *S. typhimurium* strains TA100, TA1535, and TA98, and in strain TA1537, concentrations of 3.33 to 100 and 100 to 10,000 $\mu\text{g}/\text{plate}$ were tested without and with metabolic activation, respectively. Negative and positive controls were used. 2-Ethylhexyl acrylate was not mutagenic.

2-Ethylhexyl acrylate was assayed in a mammalian cell transformation test using the fibroblastic cell line C3H 10T1/2, clone 8 cells. The results of the test were based on type III foci; i.e., piling of cells that are highly polar (elongated) and criss-crossing at the interfaces of the focus and the monolayer (Rohm and Haas Co. 1982). 2-Ethylhexyl acrylate was tested at concentrations of 1.0 to 30.0 nl/ml; concentrations were determined based on the results of a range-finding toxicity test. The vehicle, DMSO, was used as a negative control and DMBA was the positive control. 2-Ethylhexyl acrylate did not induce any type III foci and was considered negative in this mammalian cell transformation test.

The mutagenic potential of 2-ethylhexyl acrylate in acetone was evaluated in a mouse lymphoma forward mutation assay using L5178Y TK⁺ cells with and without metabolic activation (Litton Bionetics, Inc. 1984). Vehicle was used as the negative control and ethylmethane sulfonate (EMS) and dimethylnitrosamine were used as the positive controls without and with metabolic activation, respectively. Multiple trials were performed without metabolic activation due to excessive toxicity and inconsistent results; doses of 1.95 to 1000 nl/ml were investigated, with concentrations up to 60 nl/ml giving usable results. Two trials were performed with metabolic activation, and concentrations of 7.810 to 150 nl/ml were tested. 2-Ethylhexyl acrylate was mutagenic in the presence of metabolic activation, inducing repeatable increases in the mutant frequency at the TK locus. Without metabolic activation, small but nonrepeatable increases in mutant frequency were observed with high toxicity.

The ability of 20 to 34 $\mu\text{g}/\text{ml}$ 2-ethylhexyl acrylate to induce mutations, aberrations, and micronuclei was examined using L5178Y mouse lymphoma cells without metabolic activation (Dearfield et al. 1989). Testing was done in duplicate. 2-Ethylhexyl acrylate produced equivocal mutagenic responses for increased mutant frequency and induced aberrations; increases were not consistent, nor were they dose-dependent. The number of micronuclei was not increased by 2-ethylhexyl acrylate.

The mutagenic potential of 2-ethylhexyl acrylate in DMSO was evaluated in monolayer and suspension assays using

Chinese hamster ovary (CHO) cells (Moore et al. 1991). Two tests were performed for each assay type. 2-Ethylhexyl acrylate was tested at concentrations of 5 to 80 $\mu\text{g/ml}$ in the monolayer assay and of 14 to 26 $\mu\text{g/ml}$ in the suspension assay without metabolic activation. 2-Ethylhexyl acrylate did not induce a dose-related increase in hypoxanthine-guanine phosphoribosyltransferase (HGPRT) frequency in either type of assay.

A battery of three in vitro assays was performed using 2-ethylhexyl acrylate in DMSO (Bushy Run Research Center 1980). In a CHO assay, 2-ethylhexyl acrylate was tested at concentrations of 0.001% to 0.0000625% without metabolic activation and 0.0005% to 0.00003125% with metabolic activation. In a sister-chromatid exchange (SCE), concentrations of 0.001% to 0.00003125% and 0.001% to 0.0000625% were tested without and with metabolic activation, respectively. In an unscheduled DNA synthesis (UDS) assay, concentrations of 0.001% to 0.00001% were tested. Appropriate positive, negative, and solvent controls were used for each test. 2-Ethylhexyl acrylate was not mutagenic in the CHO assay. In the SCE assay, a weak response was observed with metabolic activation at doses of 0.0005% and 0.00025%. A weak non-dose-related effect was found in the UDS assay. 2-Ethylhexyl acrylate was a probable, but weak, mutagen in this battery of tests. The researchers stated "a pattern of mutagenic action in the SCE and UDS tests indicated the probable mutagenic potential of 2-ethylhexyl acrylate. The relatively low levels of genetic activity obtained with this sample also could be an indication of a mutagenically active contaminant contained in the test agent. This speculative possibility is appropriate to the low levels of activity observed and is consistent with the finding (in the literature) that hydroquinone (listed as one of the polymerization inhibitors used in this product) is mutagenic in the Ames test, in mouse bone marrow cells . . . , in *E. coli* and several plant systems." The researchers also stated that the lack of response in the CHO test "is probably an indication that 2-ethylhexyl acrylate was more adequately activated by the metabolic systems used in the other two tests than in the CHO test. A different lot of liver homogenate was used in the CHO Mutation test and the SCE test which may explain the difference in the results for these two tests both performed with CHO cells."

In an in vivo cytogenetic study, groups of 24 male CD-1 mice were given a single oral dose of and groups of eight animals were dosed daily for 5 days with 0.25, 1.0, or 2.5 g/kg 2-ethylhexyl acrylate in corn oil at a volume of 12 ml/kg/day (Rohm and Haas Co. 1984b). In the groups given the single dose, eight animals per group were killed 6, 24, and 48 hours after dosing and in the groups dosed for 5 days, the animals were killed 6 hours after the last dose; bone marrow slides were prepared. The animals were given 1 mg/kg colchicine 3 hours prior to being killed. Negative control (24 animals) were given vehicle only and a positive-control group (eight animals) was given a single IP dose of triethylene melamine. When compared to the negative controls, 2-ethylhexyl acrylate did not induce chromosomal aberrations in mouse bone marrow cells.

Sodium Polyacrylate. The mutagenic potential of Sodium Polyacrylate, 97.3% pure, was evaluated in an Ames test using *S. typhimurium* strains TA92, TA1535, TA100, TA1537, TA94, and TA98 with metabolic activation (Ishidate et al. 1984). Duplicate plates of six concentrations ≤ 8.0 mg/plate were examined. The results were negative.

A *Salmonella*/mammalian microsome plate incorporation assay was performed according to the methods of Maron and Ames (1983) using 0.05 to 20 $\mu\text{l/plate}$ of 2000-Da molecular weight Sodium Polyacrylate (54% polymer prior to neutralization; 10% [w/v] sodium following neutralization) and 0.2 to 20 $\mu\text{l/plate}$ 4500-Da molecular weight Sodium Polyacrylate (48% polymer; $<0.02\%$ residual starting material) with and without metabolic activation (Thompson, Aardema, and LeBoeuf 1989). Plating was done in triplicate. Vehicle alone was used as the negative control. Positive controls were sodium azide (TA1535; TA100), 9-aminocaridine (TA1537), and 2-nitrofluorene (TA1538; TA98) without metabolic activation and 2-aminoanthracene with metabolic activation. Neither of the Sodium Polyacrylates was mutagenic.

A L5178Y TK[±] mouse lymphoma assay was performed according to the methods of Clive and Spector (1975) and Clive et al. (1979) using 2.8 to 37 and 2.1 to 28 $\mu\text{l/ml}$ of the 2000-Da molecular weight Sodium Polyacrylate without and with metabolic activation, respectively, and 7.5 to 75 and 3.2 to 32 $\mu\text{l/ml}$ of the 4500-Da molecular weight Sodium Polyacrylate without and with metabolic activation, respectively (Thompson, Aardema, and LeBoeuf 1989). Plating was done in triplicate. Two solvents (not specified) were used as negative controls. Positive controls were EMS without metabolic activation and 7,12-dimethylbenz(a)anthracene (DMBA) with metabolic activation. Evidence of a mutagenic response was not observed with either of the Sodium Polyacrylates.

A chromosomal aberration test was performed using a Chinese hamster fibroblast cell line in which the cells were exposed to three doses ≤ 2.0 mg/ml of Sodium Polyacrylate, 97.3% pure, in physiological saline for 48 hours without metabolic activation (Ishidate et al. 1984). The results were negative.

An in vitro CHO cell cytogenetic assay was performed according to the methods of Natarajan et al. (1976) as modified by Thompson et al. (1984) using 43 to 77 $\mu\text{l/ml}$ of 4500-Da molecular weight Sodium Polyacrylate without and with metabolic activation (Thompson, Aardema, and LeBoeuf 1989). Water and another negative control (not specified) were used. Positive controls were triethylene melamine without metabolic activation and cyclophosphamide with metabolic activation. Toxicity was not observed. Chromosome aberrations were not increased.

An UDS assay using primary cultures of rat hepatocytes was performed according to the methods of Williams (1977) and Williams, Bermudez, and Scaramuzzino (1977) as modified by Skare et al. (1986) using 0.005 to 5.0 $\mu\text{l/ml}$ of 2000-Da molecular weight Sodium Polyacrylate and 0.2 to 20.0 $\mu\text{l/ml}$ of the 4500-Da molecular weight Sodium Polyacrylate (Thompson, Aardema, and LeBoeuf 1989). DMSO was used as a negative

control and DMBA was used as a positive control. "Appreciable toxicity" was obtained with both Sodium Polyacrylates. Neither of the Sodium Polyacrylates induced UDS.

An in vivo mouse micronucleus assay was performed with 15 male and 15 female mice according to the methods of Matter and Schmid (1971) and Heddle (1973) as modified by Thompson, Aardema, and LeBoeuf (1989) using 13,850 mg/kg of 2000-Da molecular weight Sodium Polyacrylate (Thompson, Aardema, and LeBoeuf 1989). (The dose was expected to kill 10% of the animals within 72 hours.) Water was used as a negative control and mitomycin C was used as a positive control. Three females died. The number of micronuclei in polychromatic erythrocytes was not increased.

Acrylic Acid, Methyl, Ethyl, and Butyl Acrylate, and Methyl Methacrylate. A plate incorporation assay and a liquid preincubation assay were performed using *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 without and with metabolic activation to determine the mutagenic potential of acrylic acid (Lijinsky and Andrews 1980). The maximum non-toxic dose tested was 1000 μg in the plate incorporation assay and 250 μg in the liquid preincubation assay. Appropriate positive controls were used. Acrylic acid was not mutagenic in either assay.

The mutagenic potential of 3.3 to 1000 $\mu\text{g}/\text{plate}$ acrylic acid was determined using *S. typhimurium* strains TA100, TA1535, TA1537, and TA98 without and with metabolic activation (Zeiger et al. 1987). Acrylic acid was not mutagenic.

The mutagenic potential of acrylic acid was determined without and with metabolic activation in a plate incorporation assay using *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 (Cameron et al. 1991). Solvent (DMSO) and appropriate positive controls were used. Acrylic acid, ≤ 5000 $\mu\text{g}/\text{plate}$, was not mutagenic.

Methyl and ethyl acrylate were not mutagenic in an Ames test using *S. typhimurium* strains TA98, TA100, and TA1537 without metabolic activation (Ishidate, Sofuni, and Yoshikawa 1981).

Haworth et al. (1983) examined the mutagenic potential of ethyl acrylate and methacrylic acid in a *Salmonella*/mammalian microsome test. *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 were used without and with metabolic activation. Ethyl acrylate, tested at concentrations of 33 to 10,000 and 100 to 10,000 $\mu\text{g}/\text{plate}$ in water and DMSO, respectively, and methacrylic acid, tested at concentrations of 33 to 4000 $\mu\text{g}/\text{plate}$ in water, were not mutagenic.

A *Salmonella* microsome test was performed to determine the mutagenic potential of methyl, ethyl, and butyl acrylate and methyl, ethyl, and butyl methacrylate using *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 (Waegemaekers and Benskin 1984). The ingredients were tested at concentration ranges of 40 to 2500, 30 to 2000, 30 to 2000, 40 to 10,000, 40 to 2500, and 40 to 2500 $\mu\text{g}/\text{plate}$, respectively, without and with metabolic activation, and none were mutagenic.

Methyl and butyl acrylate and methyl methacrylate were also tested without and with metabolic activation in a liquid incubation assay using *S. typhimurium* strain TA100 at concentrations of 60 to 6000, 15 to 1500, and 100 to 10,000 $\mu\text{g}/2$ ml, respectively (Waegemaekers and Bensink 1984). Again, these ingredients were not mutagenic.

In a reverse mutation assay spot test using *S. typhimurium* strains TA100, TA1535, TA1537, and TA98, 3 $\mu\text{mol}/\text{plate}$ methyl acrylate was not mutagenic without or with metabolic activation (Florin et al. 1980). In another reverse mutation assay using these strains and strain TA1538, 590 $\mu\text{g}/\text{ml}$ methyl acrylate (highest ineffective dose [HID]) was not mutagenic without or with metabolic activation.

Ethyl acrylate, 0.001 to 5.0 $\mu\text{l}/\text{plate}$, was tested for mutagenic potential using *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 and *Saccharomyces cerevisiae* strain D4 without and with metabolic activation (Industry Acrylate Testing Group (IATG) 1982). Ethyl acrylate was not mutagenic. Ethyl acrylate was also evaluated using a liquid suspension modification of the Ames test without and with metabolic activation. A concentration-dependent increase in revertants per survivors was observed using *S. typhimurium* TA100 in the presence of metabolic activation.

An enhancement assay was performed using *S. cerevisiae* strain D61.M to determine the ability of ethyl acrylate to induce chromosome loss (Zimmermann and Mohr 1992). Ethyl acrylate was tested by itself, in a cold shock regimen, and in combination with propionitrile (a positive control) at concentrations of 368 to 914, 230 to 1095, and 27.2 to 271.8 $\mu\text{g}/\text{ml}$, respectively. Ethyl acrylate alone induced numerous white resistant colonies, most of which were respiratory deficient. Using the cold shock regimen, "a strong increase in the frequencies of red and white resistant colonies was induced." With the addition of propionitrile, an induction of chromosome loss was seen. Ethyl acrylate induced chromosomal malsegregation and mitotic recombination.

The mutagenic potential of acrylic acid was determined in a mouse lymphoma assay using L5178Y TK^{+/−} 3.7.C mouse lymphoma cells (Cameron et al. 1991). Solvent (DMSO) and appropriate positive controls were used. Acrylic acid, tested at concentrations of $\leq 5.44 \times 10^{-3}$ M without metabolic activation and $\leq 2.65 \times 10^{-2}$ M with metabolic activation, was mutagenic both without and with metabolic activation.

The genotoxicity of acrylic acid, methyl acrylate, and ethyl acrylate was studied using L5178Y mouse lymphoma cells with metabolic activation (Moore et al. 1988). Acrylic acid was tested at concentrations of 300 to 500 $\mu\text{g}/\text{ml}$, methyl acrylate was tested at concentrations of 16 to 24 $\mu\text{g}/\text{ml}$, and ethyl acrylate was tested at concentrations of 20 to 37.5 $\mu\text{g}/\text{ml}$. Acrylic acid, methyl acrylate, and ethyl acrylate were all mutagenic and clastogenic without metabolic activation.

A mouse lymphoma assay was performed to determine the mutagenic potential of ethyl acrylate (Litton Bionetics, Inc. 1980). Five trials were performed both without and with

metabolic activation. (Much toxicity was seen.) Without activation, concentrations of 1.56 to 60 nl/ml were tested; with activation, the test concentrations were 6.25 to 400 nl/ml. DMSO was used as the solvent. Ethyl acrylate was mutagenic at the TK locus without and with metabolic activation. "Without activation, the mutant frequency was elevated at 30 nl/ml and increased to about 7-fold over background for highly toxic treatments at 40 nl/ml. With activation, higher concentrations were required to achieve mutagenicity and high toxicity. The mutant frequency was first elevated at concentrations of 100–150 nl/ml and maximum increases of about 5 to 10 times the background were observed with highly toxic treatments at 200–300 nl/ml." Negative and positive controls generally gave expected results.

Ethyl acrylate in DMSO was tested in a L5178Y TK[±] mouse lymphoma cell forward mutation assay without metabolic activation (McGregor et al. 1988). Doses of 2.5 to 40 $\mu\text{g/ml}$ were tested, and positive and negative controls were used. Ethyl acrylate induced significant increases in mutant fraction at doses of 20 $\mu\text{g/ml}$ in one experiment and 40 $\mu\text{g/ml}$ in another; relative total growth was 62% and 35%, respectively.

The mutagenic potential of methyl and ethyl acrylate was determined in a mouse lymphoma assay using L5178Y TK[±] 3.7.2 cells without metabolic activation (Moore et al. 1989). Methyl and ethyl acrylate were tested at concentrations of 16.0 to 24.0 and 20 to 37.5 $\mu\text{g/ml}$. For methyl acrylate, survival was 100%, 34%, 23%, and 16% with 0.0, 16.0, 22.0, and 24.0 $\mu\text{g/ml}$, respectively. For ethyl acrylate, survival was 100%, 60%, 40%, 32%, and 15% with 0.0, 20.0, 25.0, 30.0, and 37.5 $\mu\text{g/ml}$, respectively. For 0.0, 16.0, 22.0, and 24.0 $\mu\text{g/ml}$ methyl acrylate, the total number of aberrations (100 cells scored) was 2, 30, 47, and 48, respectively, and the number of cells with aberrations was 2, 19, 26, and 28, respectively. For 20.0, 25.0, 30.0, and 37.5 $\mu\text{g/ml}$ ethyl acrylate, the total number of aberrations was 3, 15, 41, 57, and 98 (50 cells analyzed), respectively, and the number of cells with aberrations was 3, 15, 24, 32, and 36, respectively. The TK mutant frequency, presented as small/large colony frequency, was 29/16, 147/37, 263/86, and 297/88 $\times 10^{-6}$ for 0.0, 16.0, 22.0, and 24.0 $\mu\text{g/ml}$ methyl acrylate, respectively, and 148/37, 430/45, and 680/58 $\times 10^{-6}$ for 20.0, 30.0, and 37.5 $\mu\text{g/ml}$ ethyl acrylate, respectively. With 0.0 and 25.0 $\mu\text{g/ml}$ ethyl acrylate, colony sizing was not performed; the total mutant frequency was 61 and 331 $\times 10^{-6}$, respectively.

Dearfield et al. (1991) examined the mutagenic potential of ethyl acrylate and methyl methacrylate in DMSO without and with metabolic activation in a mouse lymphoma assay using L5178Y TK[±] 3.7.2C cells. Ethyl acrylate was mutagenic without metabolic activation, whereas methyl methacrylate was mutagenic with metabolic activation.

A mouse lymphoma assay to determine the mutagenic potential of ethyl acrylate was also performed by Ciaccio et al. (1998). Heterozygous L5178Y TK[±] mouse lymphoma cells were exposed to 10 to 40 $\mu\text{g/ml}$ (0.1 to 0.4 mM) ethyl acrylate for 4 hours. Ethyl acrylate was positive without metabolic activation, with a concentration dependent increase in mutant

frequency. The percentage of relative total growth (in both culture media and subsequent cloning efficiency in soft agar) was reduced approximately 50% and 80% with 20 and 30 $\mu\text{g/ml}$ ethyl acrylate.

Ciaccio et al. (1998) also performed a NPSH (consisting largely of reduced GSH) assay, rhodamine 123 (Rh 123) assay, alkaline elution assay and apoptosis assessment, and pulsed-field gel electrophoresis (PFGE) detection of DNA double-strand breaks in mouse lymphoma cells. In the NPSH assay, cellular concentrations of NPSH were reduced by $\geq 50\%$ with ≥ 20 $\mu\text{g/ml}$ ethyl acrylate within 30 minutes, and at 4 hours, the cellular concentrations were reduced 70% to 90% with 10 to 40 $\mu\text{g/ml}$ ethyl acrylate. In the Rh 123 assay, a 2-hour exposure did not reduce the mitochondrial Rh 123 uptake. Ethyl acrylate did induce a time- and concentration-dependent decrease in Rh 123 uptake after 4 + 0-hour or 4 + 2-hour exposure protocols. In the alkaline elution assay, 10 to 30 $\mu\text{g/ml}$ ethyl acrylate caused low to moderate reductions in relative cell growth (RCG), but no change in the alkaline elution slope was seen. Marked cytotoxicity (80% to 87% reduction in RCG) was induced with 40 and 50 $\mu\text{g/ml}$ ethyl acrylate, and the elution slope was three- to five-fold that of the vehicle control. In evaluating potential apoptotic oligonucleosomal DNA laddering effects and/or random smearing of DNA, "characteristic 180-bp DNA laddering effect below the random smearing of DNA, indicative of DNA double-strand breakage" was seen with 50 $\mu\text{g/ml}$ ethyl acrylate, but not 10 or 20 $\mu\text{g/ml}$. With PFGE detection of DNA double-strand breaks, 50 $\mu\text{g/ml}$ ethyl acrylate, which was cytotoxic, caused DNA double strand breaks in a range of sizes.

Acrylic acid was assayed in a CHO/HGPRT test using CHO K₁-BH₄ cells at concentrations of ≤ 1.9 and ≤ 2.8 $\mu\text{l/ml}$ without and with metabolic activation, respectively (McCarthy et al. 1992). Acrylic acid was not mutagenic.

Methyl and ethyl acrylate were tested in a CHO assay examining the *hgp* locus without metabolic activation (Moore et al. 1989). Doses of 14.0 to 18.0 and 21 to 24 $\mu\text{g/ml}$ methyl and ethyl acrylate, respectively, were used. Total mutant frequencies were 17, 6, and 20 $\times 10^{-6}$ with 14, 16, and 18 $\mu\text{g/ml}$ methyl acrylate, respectively, with survival of 53%, 22%, and 17%, respectively, and 9, 2, 21, and 1 $\times 10^{-6}$ for 21, 22, 23, and 24 $\mu\text{g/ml}$ ethyl acrylate, respectively, with survival of 25%, 20%, 13%, and 8%, respectively.

The mutagenic potential of methyl and ethyl acrylate in DMSO was evaluated in a monolayer assay and of methyl acrylate in DMSO in a suspension assay using CHO cells (Moore et al. 1991). Two tests were performed for each assay type. Methyl and ethyl acrylate were tested at concentrations of 5 to 80 and 14 to 25 $\mu\text{g/ml}$, respectively, in the monolayer assay and methyl acrylate was tested at concentrations of 10 to 20.5 $\mu\text{g/ml}$ in the suspension assay without metabolic activation. Methyl and ethyl acrylate did not induce a clear dose-related increase in HGPRT frequency.

A chromosomal aberration assay using Chinese hamster lung cells was also performed to determine the mutagenic potential

of methyl and ethyl acrylate (Ishidate, Sofuni, and Yoshikawa 1981). Both were mutagenic without metabolic activation. Methyl and ethyl acrylate had D_{20} values (the dose at which chromosomal aberrations were detected in 20% of metaphases) of 0.0065 and 0.0096 mg/ml, respectively.

Chromosome aberration tests were performed to examine the mutagenic potential of methyl acrylate (Sofuni et al. 1984a). Chinese hamster cells were exposed to 0.8 to 5.0 ml/h (60 to 378 ppm) gaseous methyl acrylate in distilled water for 1 hour with a 23-hour recovery and to 0.375 to 0.15 mg/ml liquid methyl acrylate for 24 or 48 hours with no recovery. In the gaseous phase, mutagenic effects were seen with 1.7 and 2.5 ml/h (128 and 189 ppm) methyl acrylate; the frequency of aberrant cells was 70% and 100%, respectively. In the liquid phase with a 24-hour exposure time, 0.075 and 0.15 mg/ml methyl acrylate were mutagenic, with an aberrant cell frequency of 18% and 98%. With a 48-hour exposure time in the liquid phase, a dose of 0.075 was "±," with 7% aberrant cells.

A AS52/XPRT assay using CHO cells was performed without metabolic activation to evaluate the mutagenic potential of methyl acrylate (Oberly et al. 1993). Methyl acrylate, tested at concentrations of 10 to 25 $\mu\text{g/ml}$, was not mutagenic in this assay.

Splenocytes from male C57BL/6 mice were used in an in vitro test to determine the effect of ethyl acrylate on SCE and chromosomal aberrations (Kligerman et al. 1991). The cells were treated for 4 hours with 10 to 80 and 10 to 30 $\mu\text{g/ml}$ ethyl acrylate in DMSO. In order to expose blast-transformed (cycling) cells, the cultures were exposed to 1 to 20 $\mu\text{g/ml}$ ethyl acrylate at 23 hours after culture initiation for 21 to 25 hours. Exposure of splenocytes in the G_0 phase to ethyl acrylate for 4 hours did not result in an increase in the frequency of SCEs or chromosomal aberrations. Ethyl acrylate was very toxic at concentrations $\geq 30 \mu\text{g/ml}$. After blast transformation (G_1 -S), exposure of splenocytes to 2 or 5 $\mu\text{g/ml}$ resulted in an increase in the frequency of cells with chromatid-type aberrations and a slowing of the cell cycle. SCE frequency was increased in a nonsignificant manner. Ethyl acrylate, 10 $\mu\text{g/ml}$, was toxic.

The genotoxic potential of acrylic acid and *n*-butyl acrylate in DMSO was determined in UDS, micronucleus, and in vitro transformation assays using Syrian hamster embryo (SHE) fibroblasts without metabolic activation (Wiegand, Schiffmann, and Henschler 1989). Concentrations of 1 to 300 (acrylic acid) and 1 to 400 (*n*-butyl acrylate) $\mu\text{g/ml}$ were used in the UDS assay, 0.5 to 10 $\mu\text{g/ml}$ were used in the micronucleus assay, and 5 to 50 (acrylic acid) and 5 to 15 (*n*-butyl acrylate) $\mu\text{g/ml}$ in the transformation assay. Appropriate positive controls were used. Acrylic acid and *n*-butyl acrylate were not genotoxic in these assays.

n-Butyl acrylate was tested for mutagenic potential without metabolic activation in an in vitro micronucleus test and a cell transformation assay using SHE cells (IARC 1999). Butyl acrylate was not mutagenic at a dose of 10 $\mu\text{g/ml}$ (HID).

The mutagenic potential of acrylic acid was determined in vitro in cytogenetic and UDS assays (McCarthy et al. 1992). Acrylic acid was tested at concentrations of 2846 to 5000 and 1615 to 3769 nl/ml without and with metabolic activation, respectively, in the cytogenetic assay using CHO K1 cells and at concentrations of $\leq 0.6 \mu\text{l/ml}$ in the UDS assay using primary rat hepatocytes. Acrylic acid was mutagenic in the cytogenetic assay using CHO K1 cells and nonmutagenic in the UDS assay.

Methyl methacrylate was nonmutagenic without and with metabolic activation in a *Salmonella* assay (Zeiger et al. 1990). Methyl methacrylate was positive without and with metabolic activation in a chromosomal aberration assay and SCE assay, and was positive without metabolic activation in a mouse lymphoma assay.

The clastogenic potential of methyl acrylate was determined in vivo in a micronucleus test using male Balb C mice (Przybojewska et al. 1984). Four animals per group were given two IP doses, 24 hours apart, of 37.5 to 300 mg/kg methyl acrylate, and the animals were killed following the last dose. A negative and a positive control was used. At all doses tested, methyl acrylate significantly increased the percent of polychromatic erythrocytes with micronuclei (MPEs), and at all doses except the lowest, the ratio of polychromatic erythrocytes (PCEs) to normochromatic erythrocytes (NCEs) was significantly decreased compared to the negative control. Methyl acrylate was clastogenic.

A micronucleus test was also performed using ddY mice that were exposed via inhalation to 1300 or 2100 ppm methyl acrylate for 3 hours (Sofuni et al. 1984b). In this study, methyl acrylate was not clastogenic.

Methyl acrylate was assayed in another in vivo micronucleus test using bone marrow cells from ddy mice dosed once orally with 250 mg/kg (IARC 1999). The results were negative.

The clastogenic potential of ethyl acrylate was determined in vivo in a micronucleus test using male Balb C mice (Przybojewska et al. 1984). Four animals per group were given two IP doses, 24 hours apart, of 112.5 to 1800 mg/kg ethyl acrylate, and the animals were killed following the last dose. (In the high-dose group, the dose was toxic to two animals; therefore, results from the high-dose group used two animals.) A negative and a positive control was used. At all doses except the lowest, ethyl acrylate significantly increased the percent MPEs. At all doses, the ratio of PCEs to NCEs was significantly decreased compared to the negative control. Ethyl acrylate was clastogenic.

Ashby, Richardson, and Tinwell (1989) performed four micronucleus assays using C57B16J Aplk or BALB/c mice to determine the mutagenic potential of ethyl acrylate (Ashby, Richardson, and Tinwell 1989). In the first assay, groups of five male and female C57B16 mice were given a single IP injection of 738 mg/kg ethyl acrylate in corn oil; sampling was done after 48 hours for one group of males and one group of females and after 72 hours for another group of males. In the second assay, 10 male C57B16 mice were given IP injections of 738 mg/kg in

distilled water at 0 and 24 hours, and sampling was done 6 hours later. In the third and fourth assays, groups of 10 male BALB/c mice were given two IP injections of 812 mg/kg, and sampling was done after 30 hours. Positive results were only observed in the third assay. A significant increase in MPEs was observed, due to two animals having "a marginally elevated MPE incidence," and the ratio of PCEs to NCEs was significantly different from controls. These results were not reproduced in the fourth assay. The researchers concluded that ethyl acrylate "is inactive as a micronucleus-inducing agent in bone marrow of both C57B1J and BALB/c mice."

Female homozygous Tg.AC transgenic mice were treated dermally on a shaved area of the back three times per week for 20 weeks with 200 μ l of 60, 300, or 600 μ M ethyl acrylate in acetone (Tice, Nylander-French, and French 1997). Positive controls were treated with 12-*O*-tetradecanoylphorbol-13-acetate (TPA) and negative controls were treated with vehicle. Blood samples were collected from the tail at 4, 8, 12, 16, and 20 weeks; micronucleus effects were examined after 20 weeks while DNA migration was evaluated with each sample. After 20 weeks of dosing, the frequency of MPEs and NCEs was not increased in treated mice, nor was the percentage of PCEs altered. Additionally, the researchers determined the extent of DNA damage in peripheral blood leukocytes. Ethyl acrylate did not significantly alter the extent of DNA migration in leukocytes or the dispersion of migrating DNA among leukocytes.

The effect of ethyl acrylate on DNA damage in forestomach squamous epithelium was determined in an alkaline elution assay (Morimoto et al. 1990). No DNA damage was observed in male F344 rats given a single oral dose of 0.1% to 4.0% ethyl acrylate.

The effect of ethyl acrylate on chromosomal aberrations and SCEs was examined using groups of five male C57BL/6 mice that were dosed intraperitoneally with 125, 250, 500, or 1000 mg/kg ethyl acrylate in saline (Kligerman et al. 1991). Negative controls were dosed with saline and positive controls were dosed with 100 mg/kg acrylamide in saline. The spleens of the animals were removed 24 hours after dosing. Ethyl acrylate administration did not result in an increase in SCE frequency or percentage of cells with chromosomal aberrations in splenocytes. Also, ethyl acrylate did not slow the cell cycle in splenocytes.

Chromosomal aberration assays were performed using male and female Chinese hamsters and Sprague-Dawley rats to determine the effect of butyl acrylate on chromosomes (Engelhardt and Klimisch 1983). The hamsters and rats, which were housed one animal per cage and two to three animals per cage during dosing, respectively, were exposed to 817 and 820 ppm butyl acrylate, respectively, for three 6-hour and one 5-hour exposures. Butyl acrylate, although toxic to the animals, did not cause increased chromosomal aberrations in either species.

A chromosomal aberration assay was also performed using rat bone marrow cells to determine the mutagenic potential of *n*-butyl acrylate (IARC 1999). The animals were given one IP

dose of 300 mg/kg. Butyl acrylate was mutagenic when given by IP administration.

The mutagenic potential of acrylic acid was determined in vivo in *Drosophila* sex-linked recessive lethal, cytogenetic, and mouse dominant lethal assays (McCarthy et al. 1992). Acrylic acid was tested at a concentration of 2%, given by feeding or injection, in the *Drosophila* sex-linked recessive assay, as a single dose of 100 to 1000 mg/kg by gavage or 2000 or 5000 ppm in the drinking water for 5 days in the cytogenetic assay using Sprague-Dawley rats, and as a single dose of 32 to 324 mg/kg or five daily doses of 16 to 162 mg/kg by gavage in the mouse dominant lethal assay using CD-1 mice. Acrylic acid was non-mutagenic in all assays.

In tests using *Drosophila melanogaster*, ethyl acrylate (inhibited) was not mutagenic following feeding of 40,000 ppm or injection of 20,000 ppm (Valencia et al. 1985).

Reactions of acrylic acid with 2'-deoxyadenosine, 2'-deoxycytidine, 2'-deoxyguanosine, and thymidine at pH 7.0 and 37°C for 40 days resulted in the formation of 2-carboxyethyl (CE) adducts via Michael addition (Segal et al. 1987). 1-CE-adenosine (1-CE-Ade), N⁶-CE-Ade, 7-CE-guanine, and 3-CE-thymine were isolated after in vitro reaction of acrylic acid with calf thymus DNA at pH 7.0 and 37°C for 40 days.

CARCINOGENICITY

Dermal

Acrylates/VA Copolymer. 2-Ethylhexyl acrylate is a component of Acrylates/VA Copolymer. An 86.5% solution of 2-ethylhexyl acrylate in acetone was applied to the clipped dorsal skin of 40 mice throughout their lifetime (Rohm and Haas Co. 1983). Two test animals developed malignant skin carcinomas, and four had benign growths. One animal in the control group exposed to acetone only had a skin carcinoma.

A group of 40 male C3H/HeJ mice, housed 5 animals per cage, were dosed on a clipped area of the back three times per week with "one brushful" of 75% 2-ethylhexyl acrylate in acetone (approximate dose of 20 mg per application) (DePass, Maronpot, and Weil 1985). The dose was determined in a 2-week preliminary study and was the greatest concentration that "resulted neither in grossly observable irritation nor reduced weight gain." All animals were examined daily. Dosing resulted in two animals with squamous cell carcinomas and four with squamous cell papillomas on treated skin. The first tumor was observed after 11 months. A significant increase in the frequency of chronic nephritis was observed in treated animals compared to vehicle controls. The researchers stated that "treatment with EHA [2-ethylhexyl acrylate] may have exacerbated the onset and development of this condition which is normally seen in aged mice." 2-Ethylhexyl acrylate was "oncogenic."

The carcinogenic potential of 2.5%, 21%, 43%, and 86.5% 2-ethylhexyl acrylate in acetone was determined using groups of 80 male C3H mice (Wenzel-Hartung, Brune, and Klimisch 1989). Twenty-five microliters of the test article were applied to

a clipped area of the interscapular region of the animals three times per week throughout their lifetime, with the exception of the 43% concentration. For this concentration, application was discontinued after 24 weeks of dosing and the animals were observed until they died. Control groups were untreated or received applications of acetone only. All animals were observed twice daily for signs of toxicity. Body weights were measured weekly. A slight but statistically significant increase in body weights was observed for all test groups. All concentrations induced visible scale and/or eschar formation. Within 7 weeks after discontinuation of dosing with 43% 2-ethylhexyl acrylate, the skin appeared normal. The skin of the animals of the 2.5% group was normal after the 11th week of dosing. Application of 21% and 86.5% 2-ethylhexyl acrylate produced encrusted and keratinized nodules at the site of application. Hyperkeratosis and scabbing in the cutis, thickened and pigmented subcutaneous tissue, dermal hyperplasias, papillomas, and cornified squamous cell carcinomas, malignant melanomas, and fibrosarcomas were observed at microscopic examination in animals of the 21% and 86.5% dose groups. To a "small extent," the groups treated with 2.5% and 43% 2-ethylhexyl acrylate had hyperkeratosis and scabbing in the cutis. 2-Ethylhexyl acrylate had a "clearly carcinogenic effect" in the animals of the 21% and 86.5% dose groups. Skin tumor induction times were not significantly different between these groups. No neoplasias were seen in the animals of the 2.5% and 43% dose groups. The researchers stated that "the most essential finding of this study demonstrates that there is an association between severe skin-irritation symptoms and the occurrence of benign and malignant tumors."

The carcinogenic potential of 21.5%, 43%, and 85% (w/w) 2-ethylhexyl acrylate in acetone was determined in a 2-year study using groups of 80 male CRL:NMRI BR mice. In a preliminary study, NMRI mice were more resistant than C3H/HeJ mice to the irritant effects of 2-ethylhexyl acrylate (Mellert et al. 1994). The test substance was applied to the clipped interscapular area. Benzo[a]pyrene (B[a]P), 25 μ l at a concentration of 0.015%, was used as a positive control. At 3 months, two animals per group were killed and skin from the test site was examined microscopically. After 7 months, the groups were divided into two subgroups; subgroup A continued the original treatment and subgroup B was untreated for 2 months and then received applications of 5 μ g TPA in 0.1 ml acetone twice weekly for 20 weeks. Subgroup B animals with skin lesions that persisted during the nontreatment period (eight animals from the 21.5% group and three from the 85% group) were excluded from TPA treatment. Surviving animals in both subgroups were killed 2 years after the initiation of dosing. Body weights were determined weekly until week 14, and then monthly. All mice were examined daily for signs of toxicity, and skin effects and onset of tumors were recorded weekly.

Dosing with 2-ethylhexyl acrylate did not affect mean body weights. Mean survival was not affected by dosing with or without TPA. In the animals killed after 3 months, focal skin le-

sions were observed in one animal from each treated group; microscopy reported hyperkeratosis, hyperplasia (acanthosis), and increased numbers of macrophages. One animal of the high-dose group (as well as one positive-control animal) had ulceration and crust formation. No skin lesions were seen in the control animals. Animals of subgroup A had focal or multifocal skin lesions at the application site, the frequency of which was not dose-dependent. In the test groups, crust formation and ulcerations occurred to a slight or moderate degree; this was dose-related. No subgroup A animals developed skin tumors. Similar skin lesion and tumor results were observed in subgroup B. One squamous cell papilloma occurred at each dose in subgroup B. None of the animals of subgroup B excluded from TPA treatment developed skin tumors.

IARC determined that "there is inadequate evidence in humans" and "there is limited evidence in experimental animals for the carcinogenicity of ethylhexyl acrylate" (IARC 1994). The overall evaluation was "ethylhexyl acrylate is not classifiable as to its carcinogenicity to humans."

Acrylic Acid and Ethyl and Butyl Acrylates. Groups of 40 male C3H/HeJ mice were used to determine the carcinogenic potential of acrylic acid, butyl acrylate, and ethyl acrylate (DePass et al. 1984). Dermal applications of 25 μ l of 1% acrylic acid, 1% butyl acrylate, or undiluted ethyl acrylate (doses of 0.20, 0.20, or 23 mg, respectively) were made to a clipped area on the back of each animal three times weekly throughout its lifespan. Negative (vehicle-acetone) and positive controls (vehicle-methylcholanthrene) were used. The animals were housed in groups of five; animals of the ethyl acrylate test group were housed individually after 13 months because of early mortality. All animals were examined daily, and the onset and progress of neoplasms was recorded monthly. The dorsal skin and lesions from all animals that died were collected for microscopic examination. No skin irritation was observed during the study. No significant difference was found in survival time among the test and negative-control groups. Acrylic acid, butyl acrylate, and ethyl acrylate were not carcinogenic; one animal of the butyl acrylate group had a fibrosarcoma that appeared after 665 days of dosing. At microscopic examination, animals dosed with ethyl acrylate had epidermal necrosis (4), keratin necrosis (6), dermal fibrosis (6), hyperkeratosis (12), and dermatitis (5). One animal in each of the acrylic acid and butyl acrylate groups had epidermal hyperplasia.

The carcinogenic potential of acrylic acid was studied using groups of 30 female mice (Cote et al. 1986a, 1986b). Acrylic acid, 4% in acetone, was applied to dorsal skin three times per week for 1.5 years. A second group of mice was initiated with DMBA prior to application of acrylic acid. Acetone or DMBA followed by acetone were applied to control animals. Two squamous cell carcinomas were observed in the animals of the acrylic acid group, and one squamous cell carcinoma and three papillomas were observed in the DMBA/acrylic acid group. The researchers concluded that acrylic acid was a "complete although weak carcinogen."

The researchers reported that acrylic acid also produced an increase in leukemia, stating that the incidence of leukemia was 86% in test animals and 30% in controls. However, an independent review (Arthur D. Little, Inc. 1986) did not confirm the reported incidence. The independent reviewer stated that "although the numbers of lymphomas were elevated in one of the treatment groups, inconsistent patterns of tumor occurrence from organ to organ would strongly suggest that the lymphomas were not treatment related."

Groups of 50 C3H/HeN Hsd BR and Hsd:(ICR)BR mice were treated topically with 25 or 100 μ l of 1% acrylic acid in acetone for 6 weeks or 21 months (Hoechst Celanese 1990). Negative-control groups were treated with acetone and positive control groups were treated with B[a]P. No definitive carcinogenic effect was observed in male and female ICR and male C3H mice; an increase in the frequency of lymphosarcomas was observed for female C3H mice. Acrylic acid was not carcinogenic.

Oral

Acrylic Acid and Ethyl Acrylate. Groups of 50 male and 50 female Wistar rats were given 120, 400, or 1200 ppm acrylic acid in the drinking water for 26 (males) or 28 (females) months (Hellwig, Deckardt, and Freisberg 1993). A control group was given untreated water. Feed and water consumption and body weights were determined weekly for the first 3 months; feed and water consumption was then determined every 3 months and body weights were measured every 4 week. The animals were examined daily and palpated weekly. Blood samples were taken from 10 males and 10 females per group after 12, 18, 24, 26, and 28 months. At study termination, the animals were killed and necropsied and selected tissues were examined microscopically.

The actual concentrations in the test solutions were 96% to 106%, 94% to 103%, and 92% to 102% of the target concentrations of 120, 400, and 1200 ppm, respectively, corresponding to a daily mean intake of approximately 8, 27, and 78 mg/kg acrylic acid, respectively. Significant differences in feed or water consumption or in body weights were not observed between the test and control animals. Clinical signs of toxicity were not observed, and differences in mortality were not observed between the test and control animals. Treatment-related changes in hematologic parameters were not found. Non-neoplastic tissue changes were similar to those of controls. A "slightly increased incidence in hepatocellular fatty deposits" in males of the high dose group could be treatment-related. The incidence and organ distribution of neoplasms did not differ between test and control animals. "No clear toxic or oncogenic effects" were found upon administration of 120 to 1200 ppm acrylic acid in the drinking water.

Groups of 50 male and 50 female F344N rats and B6C3F₁ mice were dosed by gavage with 100 or 200 mg/kg ethyl acrylate in corn oil five times per week for 103 weeks (NTP 1986). Control groups of 50 male and 50 female rats and mice were given corn oil by gavage. Survival was similar for test and control animals, and signs of systemic toxicity was not observed. Squamous

cell papillomas and squamous cell carcinomas of the nonglandular stomach occurred at the site of chemical deposition in both male and female rats and mice in a dose- and concentration-dependent manner. Ethyl acrylate also caused irritation of the gastric nonglandular stomach mucosa in male and female rats and mice. Ethyl acrylate was carcinogenic to F344/N rats and B6C3F₁ mice, causing squamous cell carcinomas in male rats and male mice, squamous cell papillomas in male and female rats and male mice, and squamous cell papillomas or carcinomas (combined) in male and female rats and mice.

Groups of 18 to 23 male F344 rats were dosed 5 days per week with 200 mg/kg ethyl acrylate in corn oil (dose volume of 5 ml/kg) for 6 or 12 months; a control group of 21 rats was dosed with corn oil for 12 months (Ghanayem et al. 1993). Five animals per group were killed 24 hours after dosing; the remaining animals of the low-dose group were killed 15 months and of the control and high-dose groups were killed 9 months after dose termination. All of the test animals killed 24 hours after dose termination had mucosal hyperplasia, but no squamous cell papillomas or carcinomas were observed. None of the 18 and 16, respectively, surviving 15-month and control recovery animals had any lesions, whereas 8 of 13 of the 12-month recovery animals had mucosal hyperplasia and 4 had squamous cell papillomas and carcinomas.

Inhalation

Methyl, Ethyl, and Butyl Acrylates. Groups of 86 male and 86 female Sprague-Dawley rats were exposed to air containing 15, 45, or 135 ppm methyl (58, 173, or 519 mg/m³, respectively) or *n*-butyl acrylate (86, 258, or 773 mg/m³, respectively) for 6 hours per day, 5 days per week for 2 years (Reininghaus et al. 1991). Control animals breathed untreated air. Animals exposed to *n*-butyl acrylate were observed for 6 months after the termination of dosing. Some animals of each group were killed after 12 and 18 months of dosing, and some of the animals exposed to *n*-butyl acrylate were killed after 24 months. A decrease in body weight gain was temporarily observed for animals of the 135-ppm methyl acrylate group. Local effects of irritation at the nasal mucosa were observed in the nasal turbinates. Dose-related atrophy of the neurogenic portion of the olfactory epithelium with proliferation of the reserve cells to a multilayered epithelium was reported. Regeneration was observed in the *n*-butyl acrylate recovery animals. Dose-related corneal opacity and ocular vascularization was observed with methyl acrylate and 135 ppm butyl acrylate.

Groups of 115 male and 115 female Fischer 344 rats and 105 male and 105 female B6C3F₁ mice were exposed 6 hours per day to air containing 25 or 75 ppm (0.10 or 0.31 mg/l, respectively) ethyl acrylate for 27 months or to 225 ppm (0.92 mg/l) for 6 months followed by a 21-month recovery period (Miller et al. 1985). Control groups of rats and mice were exposed to untreated air for 27 months. Some animals from each groups were killed for interim necropsy. The animals were observed daily for signs of toxicity. Body weights were initially determined

weekly, and were then determined biweekly or monthly. The mean body weight gains of rats and mice of the 75- and 225-ppm groups were statistically significantly decreased throughout the study; 225 ppm was determined to be in excess of the MTD based on the decreased weight gain. No other toxicologically significant changes were observed. In the test animals, tissues from 71 to 76 male and 70 to 78 female Fischer 344 rats and 69 to 75 male and 66 to 78 female B6C3F₁ mice were examined microscopically. No neoplasms were observed in rats or mice. In rats, concentration-dependent non-neoplastic lesions of the olfactory portion of the nasal mucosa were observed for test groups. In mice, lesions were concentration-dependent and consisted of replacement of the olfactory neuroepithelium by ciliated respiratory epithelium accompanied by submucosal glandular epithelium. In both rats and mice, only the areas of nasal mucosa normally lined by olfactory epithelium was altered.

Parenteral

Acrylic Acid. Groups of 30 female Hsd:(ICR)Br mice were dosed with 20 μ mol (1.4 mg) acrylic acid in 0.05 ml trioctanoin or vehicle only subcutaneously into the left flank once weekly for 52 weeks; the animals were then observed for an additional 93 days (450 total days on study) (Segal et al. 1987). An untreated control group of 100 animals was observed for 450 days. Twenty-eight test and vehicle-control animals and 94 untreated controls survived until study termination. Two animals of the test group had sarcomas at the site of injection. None of the vehicle- or untreated-control animals had neoplasms.

IARC (1999) gave the following carcinogenic evaluations for acrylic acid, methyl acrylate, ethyl acrylate, and *n*-butyl acrylate. "No epidemiological data" and "no experimental data relevant to the carcinogenicity of acrylic acid were available"; "acrylic acid is not classifiable as to its carcinogenicity to humans." "No epidemiological data relevant to the carcinogenicity of methyl acrylate were available" and "there is inadequate evidence in experimental animals for the carcinogenicity of methyl acrylate"; "methyl acrylate is not classifiable as to its carcinogenicity in humans." "No epidemiological data relevant to the carcinogenicity of ethyl acrylate were available" and "there is sufficient evidence in experimental animals for the carcinogenicity of ethyl acrylate"; "ethyl acrylate is possibly carcinogenic to humans." "No epidemiological data relevant to the carcinogenicity of *n*-butyl acrylate were available" and "there is inadequate evidence in experimental animals for the carcinogenicity of *n*-butyl acrylate"; "*n*-butyl acrylate is not classifiable as to its carcinogenicity in humans."

IARC (1994) gave the following evaluation for methyl methacrylate: "There is inadequate evidence in humans for the carcinogenicity of methyl methacrylate. There is evidence suggesting lack of carcinogenicity of methyl methacrylate in experimental animals." Overall, "methyl methacrylate is not classifiable as to its carcinogenicity to humans."

CLINICAL ASSESSMENT OF SAFETY -- --

Irritation and Sensitization -- --

Predictive

Acrylates Copolymer. A repeated insult patch test was completed using 47 subjects, 7 males and 40 females, to determine the irritation and sensitization potential of a 25% dilution of Acrylates Copolymer (supplied as a cloudy white liquid) using distilled water (percent solids not specified) (Consumer Product Testing Co. 1996). Semioclusive patches containing approximately 0.2 ml of the test material were applied for 24 hours to the upper back of each subject three times per week for a total of 10 applications. The test sites were scored 24 to 48 hours after patch removal. Following a 14-day nontreatment period, a challenge patch was applied for 24 hours to the test site on the back and to a previously unpatched site on the volar forearm. The challenge sites were scored immediately and 24 hours after patch removal. Reactions were not observed during induction or at challenge, and Acrylates Copolymer was neither a dermal irritant nor a sensitizer.

An assay of the irritation and sensitization potential of Acrylates Copolymer, 30% solids and pH 7 to 7.4, and Acrylates Copolymer, 100% solids, as a 15% solution in ammonia water (pH 7.95) and as a 25% acetone solution, was completed using 49 patients (BFGoodrich Specialty Chemicals 1997). The test article was applied under an occlusive patch for 24 hours. The test site was scored for irritation upon patch removal and 3, 6, 10, and 14 days after application. After a 1-week nontreatment period, a challenge application was made and scored for the following 4 days. Acrylates Copolymer, 30% solids, was neither an irritant nor a sensitizer. Both Acrylates Copolymer, 100% solids, solutions did not produce an irritant response. The Acrylates Copolymer acetone solution produced a reaction upon challenge, but the ammonia water solution did not; the researchers stated that the reaction was probably due to the acetone.

Sodium Polyacrylate. The irritation and sensitization potential of Sodium Polyacrylate was determined using 50 subjects (Finnegan and Dienna 1953). A 1/4 inch square of cotton cloth was saturated with undiluted Sodium Polyacrylate, placed on the inner surface of the forearm, covered with aluminum foil, and held in place for 48 hours. The patch was then removed and the site was examined for irritation. Two weeks after patch application, the procedure was repeated on the opposite arm. Irritation and sensitization were not observed.

Provocative

Acrylates/VA Copolymer. 2-Ethylhexyl acrylate is a component of Acrylates/VA Copolymer. A total of 243 patients with a history of exposure to (meth)acrylates were patch tested with a (meth)acrylates series (Kanerva, Jolanki, and Estlander 1997). An occlusive patch containing 0.1% to 0.5% 2-ethylhexyl acrylate was applied to the back for 24 hours. None of the patients were sensitized by 2-ethylhexyl acrylate.

Ethyl Acrylate, Butyl Acrylate, and Methacrylate Monomers. Adams and Maibach (1985) reported on a 64-month study (during the years 1977 to 1983) involving 12 dermatologists that researched patient reactions to cosmetics. Of an estimated number of 281,100 patients seen, an estimated number of 13,216 patients had contact dermatitis and in 713 of those patients, it was related to cosmetics. Patch tests were performed according to the methods of the North American Contact Dermatitis Group (NACDG) on 56% of the subjects. There was one cutaneous reaction to unspecified methacrylate monomer and five to ethyl methacrylate.

Patch tests using the Finn-chamber method, which used nonocclusive tape and involved at least three readings, were performed to determine sensitization to acrylates (methyl methacrylate: 10% in petrolatum; remainder: 1% in petrolatum) (Kanerva, Estlander, and Jolanki 1988). Prior to 1982, testing was only done with methyl methacrylate; no patients were sensitized to this monomer. From 1982 to 1985, 12 of 22 patients did not react to (meth)acrylates, 10 had an irritation response to ethyl acrylate, 9 had irritation to butyl acrylate, and none reacted to methyl methacrylate. From 1985 to 1986, 12 of 24 patients did not react to (meth)acrylates, 6 had an irritation response to ethyl acrylate, and 2 had an irritation response to butyl acrylate.

In one case study, a patient was sensitized to a nail laquer that contained 9% methyl acrylate, and the patient had an allergic reaction when patch tested with 1.5% methyl acrylate in petrolatum (Kanerva et al. 1995). In another case study, a patient was sensitized to methyl acrylate from photobonded nail gel, methyl and ethyl methacrylate from nail liquid, and butyl methacrylate from nail hardener (Kanerva et al. 1996a). The patient did not react to patch testing with 0.1% 2-ethylhexyl acrylate or 0.1% to 1% methacrylic acid.

Workplace Exposure/Effects

The Finnish Register of Occupational Diseases reported that five of 815 cases of occupational contact urticaria (0.6%) were due to ethylhexyl acrylate (Kanerva et al. 1996b). All cases occurred in females.

Respiratory system observations, including pulmonary function testing (PFT) and chest x-rays, were made for 190 people who worked in the Spray Drier department from 1966 to 1983; these workers were exposed to a variety of acrylic polymer dusts as well as other materials (Rohm and Haas Co. 1984c). Twenty-five percent of the workers who had worked in this department had left before PFT was fully validated or x-rays were retained. The remainder of the plant workforce was used for the unexposed group. Chest x-rays were obtained for 109 exposed employees; controls were selected from the unexposed group by matching age, year hired, and smoking habit. The PFT results and the smoking habits, age, sex, race, and height were determined for 123 exposed employees; the latter four parameters and the prediction equations of Crapo, Morris, and Gardner (1981) were used to determine the predicted normal value for the forced vital capacity, the forced expiratory volume in the first second, and

the forced expiratory flow rate over the middle half of the expirogram for each individual. Exposed employees did not have an excess of chest x-ray abnormalities, especially alterations suggestive of diffuse pulmonary fibrosis, and did not have an excess of PFT abnormality.

Threshold Limit Value

The threshold limit value–time weighted average (TLV-TWA) for Acrylic Acid is 10 ppm of contaminated air by volume at 25°C and 760 torr (American Conference of Governmental Industrial Hygienists [ACGIH] 1986) and 5.9 mg/m³ in air (IARC 1999). The recommended TLVs for occupational exposure to methyl and ethyl acrylate in workplace air are 7 and 20 mg/m³, respectively. The 8-hour TLV-TWA for occupational exposure to *n*-butyl acrylate in workplace air is 52 mg/m³. Rohm and Haas Co. (1985) reported a TWA of 2 mg/m³ for an acrylic polymer that had a molecular weight of approximately 1,000,000 and that contained approximately 35% respirable ($\leq 5 \mu$) dust.

NTP REPORT ON CARCINOGENS

Ethyl Acrylate. In 1998, the Basic Acrylic Monomer Manufacturers, Inc., petitioned the NTP Board of Scientific Counselors' Report on Carcinogens Subcommittee to delist ethyl acrylate from NTP's *Report on Carcinogens* based on the assumption that "significant human exposure is unlikely" (NTP 1998). Ethyl acrylate was first listed in the 5th Annual Report on Carcinogens as "reasonably anticipated to be a human carcinogen" based on the NTP gavage study. During the discussion, it was noted that ethyl acrylate was rapidly metabolized by carboxylesterases and by conjugation with GSH, and that it had a half-life in the rodent forestomach of 94 minutes. It was also noted that ethyl acrylate was mutagenic in some in vitro tests but was not genotoxic under in vivo physiological conditions, possibly due to its "rapid metabolism."

Mechanistic studies related to forestomach tumor response were conducted to examine the association of irritation and sustained cell proliferation. A dose of 200 mg/kg, which produced forestomach tumors in the NTP assay, induced "substantial cell proliferation" in the forestomach mucosa within hours of dosing.

"A premise of the petition [was] that humans would not ingest ethyl acrylate, rather inhalation and dermal would be the primary routes of human exposure, and, further, humans do not possess forestomachs." It was voted (7-2 and 6-1) that ethyl acrylate should be delisted from the *Report on Carcinogens*. Following further discussion of the proposal, it was voted that ethyl acrylate be delisted from the Report (8-2-2). One of the abstentions cited the reason that "there was important information on cell transformation" that were not accessible.

SUMMARY

Copolymers

This report reviews the safety of a large number of polymers that contain acrylic or methacrylic acid or one of their salts or

esters. Linear polymers of acrylic acid are produced by combining the monomer with a free-radical initiator, which is generally largely consumed by the reaction. However, some unreacted monomer and catalysts can remain. Additionally, hydroquinone and monomethyl ester of hydroquinone are often incorporated into acrylic acid and its esters as an inhibitor. 2-Ethylhexyl acrylate is a component of Acrylates/VA Copolymer.

One company reported that it manufactured Acrylates Copolymer and Ammonium Acrylates Copolymer using emulsion and solution polymerization. One company reported that it produces Acrylates Copolymer as 30% solids at a pH of 3.0 and Ammonium Acrylates Copolymer as a 30% solution in propylene glycol and water at a pH of 7.5.

Ten companies representing the majority of the production of polymers sold for cosmetic use indicated that residual acrylic acid concentrations in polymers are typically between 10 and 1000 ppm, with an upper limit of 1500 ppm.

One source reported Acrylates Copolymer can contain residual amounts of ≤ 20 ppm ethyl acrylate, methyl methacrylate, methacrylic acid, and acrylic acid; another source reported that three samples analyzed using GC contained < 0.2 to 0.8 ppm acrylic acid, 0.8 to 2.6 ppm methyl methacrylate, and 1.3 to 3.9 ppm ethylene glycol dimethacrylate. Additionally, it was reported to CIR that two polymers, both defined as Acrylates Copolymer, contained different residual monomers; the first contained 36, 20, and 45 ppm *n*-butyl acrylate, methyl methacrylate, and methacrylic acid, respectively, and the second contained 1500 and 200 ppm stearyl acrylate and methacrylic acid, respectively. Acrylates/VA Copolymer can contain, as reported by two polymer producers, 100 to 1000 ppm residual 2-ethylhexyl acrylate. However, the 10 respondents of the survey described previously reported that they did not produce acrylate polymers with 2-ethylhexyl acrylate for use in the cosmetic industry. Using UV spectroscopy with a limit of detection of 300 mg/kg (ppm), acrylic acid was detected in Polyacrylic Acid at 195 nm. A 90,000-Da molecular weight sodium hydroxide-neutralized Polyacrylic Acid contained 77.5% Sodium Polyacrylate, 3.3% free acrylic acid, and 18.1% water, whereas a 4500-Da molecular weight compound contained 43.3% solids and 0.09% residual monomer.

The ingredients reviewed in this report have one or more of the following functions in cosmetic formulations: binder, film former, hair fixative, suspending agent, viscosity-increasing agent, emulsion stabilizer. Acrylates polymers used in final cosmetic products are typically used at concentrations of 2.5% to 6.0%, with a maximum of 7.5% to 25%, in binders, film formers, and fixatives and at a concentration of 0.5%, with a maximum of 2.0%, in viscosity-increasing agents, suspending agents, and emulsion stabilizers. It has been reported that Acrylates Copolymers is used at 3% to 22% and a mixture containing 30% Ammonium Acrylates Copolymer is used at 2% to 15%.

Polyacrylic Acid had an immunosuppressive effect on the response of mice to sheep red blood cells. Effects of Polyacrylic Acid-immunoglobulin G (PAIGP) complex on human

polymorphonuclear leukocytes was examined; PAIGP stimulated chemiluminescence, released superoxide anion, and was a weak inducer of elastase release.

The following LD₅₀ values were reported for Acrylates Copolymer: > 16 g/kg (dermal, rabbits), > 16 ml/kg (dermal), > 9 g/kg (dermal), 9 g/kg (dermal, rats), > 5.2 mg/l (rats). Ethylene/Acrylic Acid Copolymer had a low order of acute toxicity following dermal and oral administration to rats; the oral LD₅₀ was > 5 g/kg. The oral LD₅₀ for rats of an ammonium salt of Ethylene/Acrylic Acid was 41.50 ml/kg. In an acute inhalation study, 0 of 6 rats exposed to an aqueous emulsion of the ammonium salt of Ethylene/Acrylic Acid polymer died; the IP LD₅₀ for rats of the emulsion was 8.57 ml/kg. The dermal LD₅₀ for rabbits and the oral LD₅₀ for rats of Vinyl Acetate/Maleate/Acrylate Copolymer solution was > 5 g/kg. For rats, the oral LD₅₀ values of Polyacrylic Acid and Sodium Polyacrylate were 2.5 and > 40 g/kg, respectively; and 0.34 and 2.59 ml/kg, respectively, for male rats. Copolymers of acrylic acid and *N*-vinyl pyrrolidone containing 25% to 45% and 69% to 70% acrylic acid were non- and slightly toxic, respectively. In a subchronic inhalation toxicity study of Acrylates Copolymer, alveolar histiocytosis was observed at a dose of 30 mg/m³. Pulmonary lesions were observed in rats used in short-term and subchronic inhalation studies of acrylic acid polymers. In a chronic inhalation study of respirable polyacrylate particles, compound-related pulmonary lesions were not observed.

In dermal irritation studies using rabbits, Acrylates Copolymer was non- to mildly irritating. In one study, it produced signs of an irritant property. However, in a study in which the patches adhered to the skin, very slight to well-defined erythema, and severe erythema in one animal, were observed at 72 hours. A mixture containing 30% Ammonium Acrylates Copolymer was practically nonirritant, and an aqueous emulsion of the ammonium salt of an Ethylene/Acrylic Acid polymer produced minor irritation. Acrylates/VA Copolymer produced moderate to severe but reversible dermal irritation, Vinyl Acetate/Maleate/Acrylate Copolymer solution had a primary irritation index of 4.4. Sodium Polyacrylate did not produce irritation. Acrylates Copolymer was not a sensitizer to guinea pigs in maximization studies or a Buehler sensitization test. In ocular irritation studies using rabbits, Acrylates Copolymer was generally non- to mildly irritating. In two other studies, Acrylates Copolymer was an eye irritant but not corrosive. A mixture containing 30% Ammonium Acrylates Copolymer was practically nonirritating. An aqueous emulsion of the ammonium salt of an Ethylene/Acrylic Acid polymer produced trace corneal injury, Acrylates/VA Copolymer produced severe but reversible ocular irritation, and Vinyl Acetate/Maleate/Acrylate Copolymer solution produced moderate to severe but reversible ocular irritation. In a Draize test, the greatest tolerated concentration of Sodium Polyacrylate was 13% to 20% and 20% to 30% for unrinsed and rinsed eyes, respectively. In an irritant threshold test, the greatest concentration of Sodium Polyacrylate that did not produce irritation in three or more of five rabbits was 2%.

In *in vitro* studies, Acrylates Copolymer was non- to mildly irritating.

Reproductive effects were not observed in a study in which rats were dosed orally with 4500- or 90,000-Da molecular weight Sodium Polyacrylate.

Acrylates Copolymer was not mutagenic in Ames tests. A mixture containing 30% Ammonium Acrylates Copolymer was not mutagenic in a modified Ames test. Sodium Polyacrylate was not mutagenic in an Ames assay, a plate test, a mouse lymphoma assay, chromosomal aberration assays, a UDS assay, or an *in vivo* mouse micronucleus assay.

In clinical studies, Acrylates Copolymer and Sodium Polyacrylate did not produce irritation or sensitization. In examining the effects of workplace exposures, employees exposed to a variety of acrylic polymer dusts (as well as other materials) did not have an excess of chest x-ray abnormalities, especially those suggestive of diffuse pulmonary fibrosis, and they did not have an excess of PFT abnormality.

Monomers

Acrylic acid and methyl acrylate were administered dermally to rats and mice and to guinea pigs, respectively. Following dermal administration of acrylic acid, the radioactivity was recovered mostly in the skin trap, and then in expired carbon dioxide. Following dermal administration of methyl acrylate, radioactivity was found in the SC tissues and throughout the body. 2-Ethylhexyl acrylate, acrylic acid, methyl acrylate, ethyl acrylate, and butyl acrylate were administered orally to rats and/or mice. In most cases, the dose was generally excreted in expired air. When rats were exposed to acrylic acid via inhalation, most of the radioactivity was found in the head and snout, with relatively large amounts also being recovered in the upper respiratory tract. 2-Ethylhexyl acrylate and methyl and butyl acrylate were given intraperitoneally. Again, most of the dose was excreted in expired air.

The dermal LD₅₀ of acrylic acid was 295 to 950 mg/kg for rabbits. The oral LD₅₀ was 2100 to 3200 mg/kg for rabbits and for rats and 0.34 ml/kg for male rats. The oral LD₅₀ of glacial acrylic acid was 193 to 350 mg/kg for rats. Acute oral administration of acrylic acid and methyl, ethyl, and butyl acrylate produced gastric lesions. The acute LC₅₀ of acrylic acid was 3600 mg/m³ for rats. Short-term oral administration of ethyl acrylate to rats produced gastric lesions, primarily in the forestomach. In short-term inhalation studies, nasal lesions were produced by acrylic acid but not ethyl acrylate. Butyl acrylate produced toxicity. In subchronic dermal studies using acrylic acid, 4% produced toxic effects in mice. Subchronic oral administration of acrylic acid, ≤750 mg/kg, also produced toxic effects, and ≤200 mg/kg ethyl acrylate produced lesions in the forestomachs of rats. Methyl and butyl acrylate were not toxic to rats when given orally. Rats and/or mice were exposed to acrylic acid and ethyl and butyl acrylate in subchronic inhalation studies; nasal lesions were observed. In chronic oral studies, acrylic acid given in drinking

water did not produce lesions in rats and ethyl acrylate did not produce lesions in rats or dogs. Acrylic acid, 4%, was irritating to the skin of mice, and a 1% solution caused significant injury to the rabbit eye.

In oral and inhalation reproductive studies, acrylic acid was not teratogenic, and 2-ethylhexyl, methyl, ethyl, butyl, 2-hydroxyethyl, and hydroxypropyl acrylate were not teratogenic when administered via inhalation. In a reproductive study in which groups of gravid rats were dosed by IP injection with 0.002 to 0.008 ml/kg acrylic acid or 0.13 to 0.44 ml/kg methyl methacrylate, 0.12 to 0.41 ml/kg ethyl methacrylate, 0.23 to 0.76 ml/kg *n*-butyl methacrylate, 0.14 to 0.4 ml/kg isobutyl methacrylate, or 0.25 to 0.82 ml/kg isodecyl methacrylate monomers, the incidence of gross abnormalities significantly increased in all dose groups, except for dams of the acrylic acid and methyl methacrylate low-dose groups and of the *n*-butyl methacrylate low- and mid-dose groups. Also, the incidence of skeletal malformations was significantly increased in the acrylic acid high-dose group.

2-Ethylhexyl acrylate was not mutagenic in a microbial mutagen test, Ames test, mammalian cell transformation test, micronucleus test, monolayer or suspension assay, CHO assay, or *in vivo* cytogenetic assay; it was mutagenic in a mouse lymphoma forward mutation assay with metabolic activation, equivocally mutagenic in mutation and aberration assays, and weakly mutagenic in SCE and UDS assays. Acrylic acid was not mutagenic in plate incorporation, liquid preincubation, UDS, micronucleus, *in vitro* transformation, CHO/HGPRT, *in vivo* cytogenetic, *Drosophila* sex-linked recessive, or mouse dominant lethal assays. Acrylic acid was mutagenic in mouse lymphoma assays and in a CHO/HGPRT and *in vitro* cytogenetic assay. Methyl acrylate was not mutagenic in an Ames, *Salmonella*/microsome, spot, liquid incubation, monolayer, suspension, or AS52/XPRT assay; it was mutagenic in mouse lymphoma and chromosomal aberration assays. Methyl acrylate was positive in one and negative in two micronucleus tests. Ethyl acrylate was not mutagenic in an Ames, *Salmonella*/microsome, liquid incubation, monolayer, chromosomal aberration, SCE, or *Drosophila* assay; ethyl acrylate did induce chromosomal mal-segregation and mitotic recombination using *S. cerevisiae*, and it was mutagenic in a mouse lymphoma and chromosomal aberration assay. Ethyl acrylate was positive in one and negative in one micronucleus assay. *n*-Butyl acrylate was not mutagenic in a *Salmonella*/microsome, liquid incubation, UDS, micronucleus, or *in vitro* transformation assay; it was nonmutagenic in one and mutagenic in another chromosomal aberration assay. Methacrylic acid was not mutagenic in a *Salmonella*/microsome test. Methyl methacrylate was not mutagenic in a *Salmonella*/microsome or liquid incubation assay; it was mutagenic in a chromosomal aberration, SCE, and mouse lymphoma assay. Ethyl and butyl methacrylates were not mutagenic in a *Salmonella*/microsome test.

2-Ethylhexyl acrylate was carcinogenic when applied dermally to mice; the carcinogenic response may be associated

with the severe skin irritation induced by the chemical. IARC determined that “there is inadequate evidence in humans” and “there is limited evidence in experimental animals for the carcinogenicity of ethylhexyl acrylate.” In one study, 1% acrylic acid, undiluted ethyl acrylate, and 1% butyl acrylate were not carcinogenic. In another, 4% acrylic acid in acetone was a complete but weak carcinogen. Acrylic acid was not carcinogenic to rats when administered in the drinking water, but oral administration by gavage of ethyl acrylate in corn oil was carcinogenic to male and female rats and mice. Methyl, ethyl, and butyl acrylate were not carcinogenic in mice in inhalation studies, and acrylic acid was not carcinogenic when injected subcutaneously to mice.

IARC (1999) gave the following carcinogenic evaluations for acrylic acid, methyl, ethyl, and *n*-butyl acrylate, and methyl methacrylate: “no epidemiological data” and “no experimental data relevant to the carcinogenicity of acrylic acid were available”; “acrylic acid is not classifiable as to its carcinogenicity to humans.” “No epidemiological data relevant to the carcinogenicity of methyl acrylate were available” and “there is inadequate evidence in experimental animals for the carcinogenicity of methyl acrylate”; “methyl acrylate is not classifiable as to its carcinogenicity in humans.” “No epidemiological data relevant to the carcinogenicity of ethyl acrylate were available” and “there is sufficient evidence in experimental animals for the carcinogenicity of ethyl acrylate”; “ethyl acrylate is possibly carcinogenic to humans.” “No epidemiological data relevant to the carcinogenicity of *n*-butyl acrylate were available” and “there is inadequate evidence in experimental animals for the carcinogenicity of *n*-butyl acrylate”; “*n*-butyl acrylate is not classifiable as to its carcinogenicity in humans.” “There is inadequate evidence in humans for the carcinogenicity of methyl methacrylate. There is evidence suggesting lack of carcinogenicity of methyl methacrylate in experimental animals.” Overall, “methyl methacrylate is not classifiable as to its carcinogenicity to humans.” NTP has voted to delist ethyl acrylate from its *Report on Carcinogens*.

Case studies have been reported regarding sensitization reactions to methyl, ethyl, and butyl acrylate and ethyl methacrylate.

DISCUSSION

The CIR Expert Panel recognized that there are a large number of ingredients in this safety assessment and that these polymers are comprised of many different monomeric building blocks. Nonetheless, these polymers are uniformly large molecules and are produced in chemical reactions that leave very little residual monomer. The most recent information available indicates that, although residual acrylic acid may be as high as 1500 ppm, typical levels are 10 to 1000 ppm. The Panel was convinced that these low levels are routinely attained based on the information provided, which described significant odor if residual monomers are present. For these reasons, the Panel concluded that it is reasonable to consider these ingredients as a group.

Upon review of the available data, the Panel was primarily concerned with unreacted monomers and/or other residual chemicals such as plasticizers or catalysts. Irritation and sensitization tests on several of these polymers found very little irritation, suggesting that there are small enough levels of monomers, etc., so as not to cause irritation or sensitization. Because of the minimal irritation that was seen in some ingredients, the skin and ocular toxicity seen with Acrylates/VA Copolymer, and the strong irritancy exhibited by the monomers, it was concluded that a caveat regarding irritation should be included.

The principle concern regarding the use of these polymer ingredients is the presence of toxic residual monomers. In particular, although 2-ethylhexyl acrylate was not genotoxic, it was carcinogenic when applied at a concentration of 21% to the skin of C3H mice. Lower concentrations (2.5%) and stop-dose studies at high concentrations (43%) were not carcinogenic. 2-Ethylhexyl acrylate was not carcinogenic in studies using NMRI mice. If it is assumed that 2-ethylhexyl acrylate is present as a residual monomer at a concentration of 1000 ppm, it was reasoned that this could be compared to the 210,000 ppm (21%) used in the C3H mouse study discussed above, resulting in several orders of magnitude safety factor.

Whether in the mouse strain where an increase in carcinogenesis was seen or in the strain where no such effect was seen, there was evidence of severe dermal irritation in these 2-ethylhexyl acrylate studies. Although the Panel acknowledged that none of these copolymers in current use contains 2-ethylhexyl acrylate itself, its severe irritancy reinforced the Panel's concern about skin irritation.

Another concern regarding residual monomers was inhalation toxicity. Although the acrylic acid monomer is a nasal irritant, exposure to the monomer from use of these polymers in cosmetic formulations would always be less than the established TLVs for nasal irritation.

Although again recognizing that there is a huge variation in the mix of monomers used in the synthesis of these polymers, the Panel believes that they are similar in that the polymers, except for dermal irritation, are not significantly toxic, and residual monomer levels are kept as low as possible. Although the monomers may be toxic, the levels that would be found in cosmetic formulations are not considered to present a safety risk. Accordingly, these Acrylate Copolymers are considered safe for use in cosmetic formulations when formulated to avoid irritation.

CONCLUSION

On the basis of the available information, the CIR Expert Panel concludes that Acrylates Copolymer, Ammonium Acrylates Copolymer, Ammonium VA/Acrylates Copolymer, Sodium Acrylates Copolymer, Ethylene/Acrylic Acid Copolymer, Ethylene/Calcium Acrylate Copolymer, Ethylene/Magnesium Acrylate Copolymer, Ethylene/Sodium Acrylate Copolymer, Ethylene/Zinc Acrylate Copolymer, Ethylene/Acrylic Acid/VA

Copolymer, Acrylates/PVP Copolymer, Acrylates/VA Copolymer, Steareth-10 Allyl Ether/Acrylates Copolymer, Acrylates/Steareth-50 Acrylate Copolymer, Acrylates/Steareth-20 Methacrylate Copolymer, Acrylates/Ammonium Methacrylate Copolymer, Styrene/Acrylates Copolymer, Styrene/Acrylates/Ammonium Methacrylate Copolymer, Ammonium Styrene/Acrylates Copolymer, Sodium Styrene/Acrylates Copolymer, Acrylates/Hydroxyesters Acrylates Copolymer, Methacryloyl Ethyl Betaine/Acrylates Copolymer, Lauryl Acrylate/VA Copolymer, VA/Butyl Maleate/Isobornyl Acrylate Copolymer, Ethylene/Methacrylate Copolymer, Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer, Sodium Acrylates/Acrolein Copolymer, PVP/Dimethylaminoethylmethacrylate Copolymer, AMP-Acrylates Copolymer, Polyacrylic Acid, Ammonium Polyacrylate, Potassium Aluminum Polyacrylate, Potassium Polyacrylate, and Sodium Polyacrylate are safe for use in cosmetics when formulated to avoid skin irritation.

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