EVALUATION OF THE HEALTH ASPECTS OF MONOMERIC AND
POLYMERIC ETHYL ACRYLATE AND METHYL ACRYLATE
AS THEY MAY MIGRATE TO FOODS FROM PAPER AND
PAPERBOARD USED IN FOOD PACKAGING

1977

Prepared for

Bureau of Foods
Food and Drug Administration
Department of Health, Education, and Welfare
Washington, D.C.

Contract No. FDA 223-75-2004
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Life Sciences Research Office
Federation of American Societies
For Experimental Biology
9650 Rockville Pike
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NOTICE

This report is one of a series concerning the health aspects of using the Generally Recognized as Safe (GRAS) or prior sanctioned food substances as food ingredients, being made by the Federation of American Societies for Experimental Biology (FASEB) under contract no. 223-75-2004 with the Food and Drug Administration (FDA), U.S. Department of Health, Education, and Welfare. The Federation recognizes that the safety of GRAS substances is of national significance, and that its resources are particularly suited to marshalling the opinions of knowledgeable scientists to assist in these evaluations. The Life Sciences Research Office (LSRO), established by FASEB in 1962 to make scientific assessments in the biomedical sciences, is conducting these studies.

Qualified scientists were selected as consultants to review and evaluate the available information on each of the GRAS substances. These scientists, designated the Select Committee on GRAS Substances, were chosen for their experience and judgment with due consideration for balance and breadth in the appropriate professional disciplines. The Select Committee's evaluations are being made independently of FDA or any other group, governmental or nongovernmental. The Select Committee accepts responsibility for the content of each report. Members of the Select Committee who have contributed to this report are named in Section VII.

Tentative reports are made available to the public for review in the Office of the Hearing Clerk, Food and Drug Administration, after announcement in the Federal Register, and opportunity is provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the substances covered by the report. The data, information, and views presented at the hearing are considered by the Select Committee in reaching its final conclusions. Reports are approved by the Select Committee and the Director of LSRO, and subsequently reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures the reports are approved and transmitted to FDA by the Executive Director of FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of all of the individual members of its constituent societies.

[Signature]

Kenneth D. Fisher, Ph.D., Director
Life Sciences Research Office
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I. INTRODUCTION

This report concerns the health aspects of using monomeric and polymeric ethyl acrylate and methyl acrylate as they may migrate to foods from paper and paperboard used in food packaging. It has been based partly on the information contained in a scientific literature review (monograph) furnished by FDA (1), which summarizes the world’s scientific literature from 1920 through 1974.* To assure completeness and currency as of the date of this report, this information has been supplemented by searches of over 30 scientific and statistical reference sources and compendia that are generally available; use of new, relevant books and reviews and the literature citations contained in them; consideration of current literature citations obtained through computer retrieval systems of the National Library of Medicine; recent literature searches by the Toxicology Information Response Center, Oak Ridge, Tennessee; searches for relevant data in the files of FDA; and by the combined knowledge and experience of members of the Select Committee and the LSRO staff. In addition, an announcement was made in the Federal Register of September 2, 1977 (42 FR 44284-44285) that opportunity would be provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information and views on the health aspects of using monomeric and polymeric ethyl acrylate and methyl acrylate as they may migrate to foods from paper and paperboard used in food packaging. The Select Committee received no requests for such a hearing on monomeric and polymeric ethyl acrylate and methyl acrylate.

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321(s)], GRAS substances are exempt from the prem­marketing clearance that is required for food additives. It is stated in the Act and in the Code of Federal Regulations (2) [21 CFR 170.3 and 170.30] that GRAS means general recognition of safety by experts qualified by scientific training and experience to evaluate the safety of substances on the basis of scientific data derived from published literature. These sections of the Code also indicate that expert judgment is to be based on the evaluation of results of credible toxicological testing or, for those substances used in food prior to January 1, 1958, on a reasoned judgment founded in experience with common food use, and is to take into account reasonably anticipated patterns of consumption, cumulative effects in the diet, and safety factors appropriate for the utilization of animal experimentation data. FDA (2) recognizes further that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

*The document (PB-234 889/7) is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.
The Select Committee on GRAS Substances of LSRO is making its evaluations of these substances in full recognition of the foregoing provisions. In reaching its conclusions on safety the Select Committee, in accordance with FDA's guidelines, is relying primarily on the absence of substantive evidence of, or reasonable grounds to suspect, a significant risk to the public health. While the Select Committee realizes that a conclusion based on such reasoned judgment is expected even in instances where the available information is qualitatively or quantitatively limited, it recognizes that there can be instances where, in the judgment of the Select Committee, there are insufficient data upon which to base a conclusion. The Select Committee is aware that its conclusions will need to be reviewed as new or better information becomes available.

In this context, the LSRO Select Committee on GRAS Substances has reviewed the available information on monomeric and polymeric ethyl acrylate and methyl acrylate and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of these substances under the Federal Food, Drug, and Cosmetic Act.

II. BACKGROUND INFORMATION

Ethyl acrylate, \( \text{CH}_2=\text{CH-COOCH}_3 \), and methyl acrylate, \( \text{CH}_2=\text{CH-COOCH}_3 \), are both colorless, volatile, lacrimatory liquids. They easily polymerize on standing, but the monomers are stable when maintained below +10°C (3). Ethyl acrylate is miscible in all proportions with alcohol or ether, and is slightly soluble in water (4). It occurs in such fruits as pineapples and raspberries (5-7), and has an intense, penetrating, fruity odor. Methyl acrylate has an unpleasant, acrid odor and is not known to occur naturally. Both compounds are readily synthesized by several different processes (3). The Food Chemicals Codex (4) specifies that food grade ethyl acrylate assay not less than 99.5 percent, have a specific gravity of 0.916 to 0.919, have not more than 0.005 percent acidity (as acrylic acid), and contain not more than 0.022 percent antioxidant. The Codex lists no specifications for methyl acrylate or for polymeric ethyl or methyl acrylates.

Ethyl and methyl acrylates are listed in the Code of Federal Regulations (2) as GRAS substances that may migrate to foods from paper and paperboard products used in food packaging [21 CFR 182.90]. Methyl acrylate, polymerized, is a prior sanctioned food ingredient for use in the manufacture of paper and paperboard products used in food packaging [21 CFR 181.30]. Polymers of both monomers in the form of latex, are used in or on food packaging papers, principally as adhesives and binders.
The polymer latex may be incorporated in the manufacturing process, where it becomes essentially an integral part of the paper, or may be added as a coating, with or without pigments, to the finished paper. The monomer content of the polymer latex is about 100 to 500 ppm (8). The health aspects of using polymeric ethyl and methyl acrylates and the associated monomeric ethyl and methyl acrylates as ingredients of paper used in food packaging as currently practiced, are evaluated in this report.

The Code of Federal Regulations (2) contains several additional references [21 CFR 175.210, 175.300, 176.180, and 177.1320] to the use of polymer formulations that may contain homopolymers of ethyl or methyl acrylic acid, or their copolymers with a variety of other substances, as food packaging materials. This report does not concern such copolymers or formulations. It is also to be noted that ethyl acrylate is listed in the Code (2) as a synthetic flavoring substance or adjuvant [21 CFR 172.515]. Its use for this purpose is not evaluated in this report.

III. CONSUMER EXPOSURE DATA

Ethyl and methyl acrylate polymers and associated monomers are among the components of the food-contact surface of paper and paperboard that are regulated under the Code of Federal Regulations (2) [21 CFR 176.170], and accordingly, are subject to the extractive limitations prescribed in paragraph (c) as determined by methods described in paragraph (d) of that should not exceed 0.5 mg per sq. in. of food contact surface. The results of several actual extraction tests performed by industry as specified in the Code on a variety of polymers, copolymers, and formulations consisting of mixed polymers that are used as ingredients or coatings of paper and paperboard food packaging materials, have been made available to the Select Committee by the Food and Drug Administration (9). Tests made on polymeric paper coatings made only from methyl and/or ethyl acrylates and applied to paper at the maximum practical rate (3 lbs per 1000 sq. ft. of paper), showed that the total amount of polymer and monomer extracted was 0.38 mg per sq. in. of food contact surface, a value that is well within the 0.5 mg per sq. in. permitted under the Code. On this basis, a kilogram of food in contact with 1 sq. ft. of acrylate-containing paper could contain a combined total of as much as 55 mg of the polymers and their monomers. A 60 kg adult consuming the kilogram of exposed food in one day would be receiving the polymers and/or monomers at a dose of less than 1 mg per kg body weight per day.
IV. BIOLOGICAL STUDIES

Absorption, distribution, biotransformation, and excretion

Ethyl and methyl acrylates are absorbed from the gastrointestinal tract of rabbits (10); the respiratory tract of man, rats, rabbits, guinea pigs, and monkeys (3, 10); and the intact skin of rabbits (10-13). However, no information was found in the literature available to the Select Committee concerning the distribution, biotransformation, or excretion of either substance, or their polymers.

Acute toxicity

Data on the acute toxicity of monomeric ethyl and methyl acrylates are summarized in Table I. Pozzani et al. (14) reported that sluggishness, prostration and narcosis preceded death and that most deaths of experimental animals occurred within 24 hours after oral administration of lethal doses of monomeric ethyl acrylate. Gross pathological findings were pale liver, kidneys, and spleen; "irritated gastrointestinal tract"; and pulmonary congestion. When Treon et al. (10) orally administered lethal doses of either monomeric ethyl or methyl acrylate to rabbits, the signs of intoxication that preceded death included lethargy, distention of ear veins, running movements of the legs, tremors, spasms of the diaphragm, labored breathing and cyanosis. A decrease in body temperature and an increase in packed red blood cell volume were observed in all animals with greatest effects in the animals that succumbed. Survivors were sacrificed after two months, and examination revealed hepatocellular degeneration and degeneration of the renal tubules. The oral toxicity of monomeric ethyl acrylate in rabbits appears to be less than that of monomeric methyl acrylate.

In rabbits receiving an LD$_{50}$ dose of monomeric ethyl acrylate percutaneously (1,790 mg per kg) gross pathological findings included congestion and hemorrhage of lungs and kidneys and mottling of the liver (14). In the percutaneous rabbit studies of monomeric methyl acrylate by Smyth and Carpenter (11) antemortem and postmortem findings were not reported.

No acute oral toxicity studies of polymeric ethyl or methyl acrylate have been found.

The Select Committee has found no studies of the possible hydrolysis of ethyl or methyl acrylate polymers in vivo. Should this occur, possible products besides the ester monomers are acrylic acid, ethanol and methanol. The oral LD$_{50}$ of acrylic acid in the rat is 340 mg per kg; the lowest lethal oral dose of methanol in man is 350 mg per kg; the lowest lethal oral dose of ethanol in man is 6.0 g per kg (17).
TABLE I

Acute Toxicity of Monomeric Ethyl Acrylate and Methyl Acrylate in Animals

<table>
<thead>
<tr>
<th>Substance</th>
<th>Species</th>
<th>Sex, number per dose level</th>
<th>Route</th>
<th>Measurement</th>
<th>Dosage mg/kg</th>
<th>Ref.</th>
</tr>
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<tbody>
<tr>
<td>Ethyl acrylate</td>
<td>rat</td>
<td>M/10</td>
<td>p. o.</td>
<td>LD$_{50}$</td>
<td>1020</td>
<td>14</td>
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<tr>
<td></td>
<td>rat</td>
<td>Not given</td>
<td>p. o.</td>
<td>LD$_{50}$</td>
<td>2080</td>
<td>13</td>
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<tr>
<td></td>
<td>rat</td>
<td>F/5</td>
<td>p. o.</td>
<td>LD$_{50}$</td>
<td>830</td>
<td>16</td>
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<tr>
<td></td>
<td>rabbit</td>
<td>F/2 to 4</td>
<td>p. o.</td>
<td>MLD</td>
<td>280-420</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>rabbit</td>
<td>F/10</td>
<td>p. c.</td>
<td>LD$_{50}$</td>
<td>1790</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>rabbit</td>
<td>Sex not indicated/</td>
<td>p. c.</td>
<td>MLD</td>
<td>4400-5400</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 (total)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>mouse, CF$_1$</td>
<td>M/5+</td>
<td>p. o.</td>
<td>LD$_{50}$</td>
<td>1800</td>
<td>15</td>
</tr>
<tr>
<td>Methyl acrylate</td>
<td>rat, Wistar</td>
<td>MF/10</td>
<td>p. o.</td>
<td>LD$_{50}$</td>
<td>300</td>
<td>11</td>
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<tr>
<td></td>
<td>rabbit</td>
<td>F/1 to 4</td>
<td>p. o.</td>
<td>MLD</td>
<td>180-280</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>rabbit</td>
<td>Sex not indicated/</td>
<td>p. c.</td>
<td>LD$_{50}$</td>
<td>1300</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>mouse, CF$_1$</td>
<td>M/5+</td>
<td>p. o.</td>
<td>LD$_{50}$</td>
<td>840</td>
<td>15</td>
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* p. o. = oral administration; p. c. = percutaneous application
Short-term studies – monomers

Treon et al. (10) administered orally by rubber catheter to each of two rabbits, five days per week for 35 days, 31.5 mg monomeric ethyl acrylate per kg for a total of 25 doses, and to each of two other rabbits five days per week for 33 days, 23 mg of monomeric methyl acrylate per kg for a total of 24 doses. A slight retardation of growth was observed during the period of administration. Growth rate was normal during the two months following the last dose. There were no reported significant gross or microscopic changes in the tissues examined at the end of the experiment. It was concluded that there were no cumulative effects following repeated oral dosing of the two esters. Methyl acrylate applied in doses of 0.95 to 4.8 g, 6 to 18 times per day for one to two days, and ethyl acrylate applied in a dose of 4.6 g, 3 to 38 times per day for one to two days to the skin of rabbits, caused transitory local irritation and edema in all animals. One of the above animals that received applications of methyl acrylate was sacrificed after two months, and no evidence of abnormality was reported.

Short-term studies – polymers

In subacute toxicity tests conducted on three groups of just weaned albino rats, consisting of 17 male and 17 female animals, each group was fed a diet containing polyethyl acrylate; one group received 1 percent polyethyl acrylate, the second group 5 percent, and the control group received only the base food and water. Over the eight-week period of the study, the animals fed at the 1 percent level consumed a total of 9.6 g of acrylate and those fed at the 5 percent level consumed a total of 46.5 g of acrylate, amounting to doses of about 1.1 and 5.5 g per kg body weight per day, respectively, at the mid-point of the experiment. There were no deaths among the 102 animals comprising the eight-week study, no evidence of toxicity, and no observed pathology in organs at necropsy (18).

A polymer used as a paper ingredient, consisting (prior to polymerization) of a mixture of ethyl acrylate and methacrylic acid was fed to Carworth Farms, Nelson strain rats for six months and to beagle dogs for 106 days at levels of 1 percent and 5 percent of the diet (9). In the rat experiments, 25 males and 25 females were fed at each dose level (500 mg and 2.5 g per kg body weight) and 25 of each sex served as controls. No deaths occurred, all animals maintained normal appearance, and there was no effect on body weight gain for either sex at either dose level. Hemoglobin, hematocrit, and total and differential leucocyte counts remained normal throughout the experiment. At autopsy no significant differences were found in mean liver and kidney weights, expressed as organ to body weight ratios, between animals in the test groups and the controls. There was no effect of the experimental diets on weights of thyroid, heart, adrenals, spleen or pituitary. Microscopic examination of 23 tissues per animal performed
on five males and five females fed at the 5 percent level revealed no pathological effects due to feeding the polymer. In the dog experiments, two males and two females were fed at each dose level (200 mg and 1,000 mg per kg body weight) and two animals of each sex served as controls. The same measurements and observations made in the rat experiments, performed on all dogs, revealed no adverse effects. In addition, plasma alkaline phosphatase, glucose, and urea nitrogen measurements made prior to and towards the end of the feeding period failed to show any significant changes between preexposure and postexposure values.

Long-term studies

Monomeric ethyl acrylate, carried in corn oil in gelatin capsules, was administered to male and female beagle dogs daily for two years at levels of 10, 100, and 1000 ppm (about 0.25 to 25 mg per kg body weight per day at the mid-point of the study). The monomer contained 10 ppm of t-butylhydroquinone methyl ether as polymerization inhibitor. Because the 1000 ppm level initially caused emesis, the dose was lowered and gradually increased until a level of 1000 ppm was retained after 16 weeks and maintained through the rest of the study. No differences were observed between experimental animals and controls in hematologic values, urine protein and reducing substances, organ to body weight ratios, and histopathology (19).

Male and female albino Wistar rats received ethyl acrylate in the drinking water for four months at levels of 6, 60, and 2000 ppm, followed by levels of 7, 70, and 2000 ppm for an additional 20 months. The latter levels provided intakes of about 1 to 280 mg per kg body weight per day at the midpoint of the study. Mortality was unaffected. The only adverse effects reported were decreased food intake paralleled by lower weight gain in the rats at the 2000 ppm level. No differences were observed between experimental animals and controls with respect to the parameters indicated above in the dog experiments (19).

Special studies

Inhalation studies in which animals were exposed for seven hours 2 to 130 times during a period of about 200 days to air containing 25 to 2600 ppm of methyl or ethyl acrylate, showed that the highest levels of methyl acrylate that failed to give microscopic evidence of injury were 237, 95, and 95 ppm for rats, guinea pigs, and rabbits, respectively; the least concentrations which gave rise to injury were 578, 237, and 237 ppm, respectively (10). Parallel inhalation studies with ethyl acrylate in the same three species showed that the highest levels failing to give evidence of injury were 272, 75, and 75 ppm, respectively; the least concentrations that gave rise to injury were 501, 272, and 272 ppm, respectively. The investigators did not indicate dose levels achieved in mg per kg body weight but the following estimate can be made. A guinea pig having tidal volume of 0.13 liters per
min. (20) would inspire 55 liters of air in one seven-hour period. If the inspired air contained 75 ppm (0.300 mg per liter) of ethyl acrylate (a level at which no adverse effects were observed) and all were absorbed, the animal would be receiving 16.4 mg of acrylate that day amounting to a dose rate of about 25 mg per kg body weight per day for an adult guinea pig.

No reports were found by the Select Committee in which direct studies have been made of possible carcinogenic, mutagenic, or teratogenic effects of orally administered monomeric ethyl or methyl acrylate or their polymers. However, the following non-oral studies of the two related monomers have been noted: Singh et al. (21) reported that the intraperitoneal administration of acryl acid (a possible hydrolytic product of ethyl and methyl acrylates) was not teratogenic to rats at a level of 2.4 mg per kg but caused 6 percent resorptions and 6 percent fetal deaths at a level of 7.9 mg per kg. Monomeric methyl methacrylate was found not to be carcinogenic when painted on the back of the neck of 10 rats three times a week for four months (22).

It is to be noted that certain acrylate and methacrylate polymers have applications as surgical implants (23).

V. OPINION

The amounts of monomeric and polymeric methyl and ethyl acrylates that may migrate to foods from paper and paperboard used in food packaging are limited by regulation. Measurements made under severest conditions of extraction, show that human exposure to these substances from food packaged in materials containing them is less than 1 mg per kg body weight per day, and is probably considerably less than this figure under usual conditions.

While it has been shown that both monomers are absorbed from the gastrointestinal and respiratory tracts and from the skin, no absorption studies of the polymers have been made and the metabolic fate of the monomers and polymers has not been elucidated. However, no adverse effects have been observed and no pathological changes encountered in animals consuming up to 23 mg per kg of the methyl monomer for 33 days, or up to 280 mg per kg of the ethyl monomer for two years.

Polyethyl acrylate, but not polymethyl acrylate, has been fed for eight weeks at a dose of 5.5 g per kg body weight and a formulation containing both polyethyl acrylate and polymethacrylate has been fed for six months at a dose of 2.5 g per kg body weight without appearance of toxic or pathological effects.

The biological data on the monomers and on polyethyl acrylate, when related to estimates of human exposure that might occur due to migration of these substances from packaging materials, raise no concern about the safety
of current practices. However, no biological studies upon which evaluation of the methyl polymer can be based have been reported.

In light of these considerations, the Select Committee concludes that:

There is no evidence in the available information on monomeric ethyl acrylate, monomeric methyl acrylate, or polymeric ethyl acrylate that demonstrates or suggests reasonable grounds to suspect, a hazard to the public when they are used in paper and paperboard food packaging materials as now practiced, or as they might be expected to be used for such purposes in the future.

In view of the deficiency of relevant biological studies, the Select Committee has insufficient data upon which to base an evaluation of polymeric methyl acrylate when it is used as an ingredient of food packaging materials.
VI. REFERENCES CITED


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Report submitted by:

December 12, 1977

Date

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Select Committee on GRAS Substances