PVC IN FOOD AND DRUG APPLICATIONS

BRUCE H. BORSUK

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INTRODUCTION

The regulatory status of PVC in the food and drug industry is, not surprisingly, a complicated issue. It is my general conclusion at this point that past and current regulatory inaction on the part of the FDA and other agencies has had as much impact as determing how and where PVC can be employed as any adverse regulatory action has had. A major regulatory proposal concerning the use of PVC in contact with food, for example, remains in limbo, neither finalized nor withdrawn. Vista, as a supplier of PVC, must abide not only by the regulations of the FDA, but also by the desires and interpretations of its prospective customers, who have their own standards and expectations regarding the current and future use of PVC in food contact applications.

In spite of this discouraging description of the PVC regulatory scene as being somewhat less than concrete, there are certainly some definitive rules and procedures governing the use of PVC in many applications.

Knowledge of these rules and procedures and adherence to appropriate regulation should enable us to pursue, and eventually sell to, customers who have eluded us in the past. As for the PVC applications which do not benefit from such regulatory direction, monitoring of forthcoming regulatory action as well as dialogue with prospective customers is advised prior to any major product or market development actions.

PVC FOR FOOD CONTACT AND LIQUOR BOTTLES

The Food and Drug Administration has jurisdiction over the use of PVC in food packaging, cosmetic packaging, drug packaging and as a component of medical devices, although the regulations differ for each of these areas of application.

In 1958, the Federal Food, Drug and Cosmetics Act was amended by the addition of a Food Additives Amendment, which defines a food additive but provides that the term does not include "...any substance used in accordance with a sanction or approval granted prior to the enactment of this paragraph...." PVC is such a prior-sanctioned substance. Prior to 1958, PVC had been used in flexible food contact applications as well as for the production of some rigid food-containing bottles and was generally recognized as safe for these uses. More technically, PVC resin qualifies for prior sanctioning provided it has a maximum volatility of not over 3% when heated for one (1) hour at 105°C, and an inherent viscosity of not less than 0.35.

In 1968, industry urged the Bureau of Alcohol, Tobacco and Firearms (BATF) to test the suitability of using PVC for liquor bottles. Final approval depended upon satisfaction of FDA food safety criteria, but initial authorization was one step removed, and lay within the jurisdiction of BATF. Beginning in 1968, BATF permitted the marketing of PVC liquor bottles in specific sizes on an experimental basis. Over the next three years, industry worked closely with BATF in the hopes that the experimental tag would be removed from PVC liquor bottles. In 1971, the Department of Treasury (of which BATF is a part) decided that allowing full-scale marketing of PVC liquor bottles would be "a major federal action significantly affecting the quality of the human environment". It was the opinion of the Department of Treasury that such a move would require the preparation of an Environmental Impact Statement (EIS) in accordance with the National Environmental Policy Act of 1969. The EIS was issued by BATF

in early 1973 and was very favorable to PVC manufacturers, concluding that PVC bottles are less energy intensive to produce than their glass counterparts. The EIS endorsed approval of PVC as a suitable container for use with distilled spirits.

Just a BATF was finalizing its environmental assessment of PVC liquor bottles, Schenley Distillers, Inc. surprised both industry and government with its finding that trace amounts of vinyl chloride were migrating from PVC bottles to distilled spirits such as vodka and gin. This finding was confirmed by the FDA and others and on May 11, 1973 BATF, preempting a proposed FDA regulation prohibiting the packaging of alcoholic beverages in PVC bottles, terminated the experimental use of PVC packaging for distilled spirits.

This FDA proposal, although precluding the use of PVC resin for packaging liquor bottles, would have permitted the continued use of PVC in other rigid and semi-rigid food applications. Based on data generated by OSHA concerning the toxic affects of exposure to vinyl chloride, however, the FDA in 1975 broadened its proposal and indicated an intent to ban all rigid and semi-rigid PVC products while allowing continued use of PVC for thin film and coatings or closure liners (Attachment A).

This FDA proposal, never made final or withdrawn, forms the basis of the "little black cloud" which hangs over PVC. It is unlikely that this proposal will ever become law. The FDA, on October 15, 1979, even responded in a letter to GTR that "PVC continues to be prior sanctioned for food contact purposes providing that no vinyl chloride monomer migrates to the food." In this letter the FDA also indicates that, since the 1975 proposal was published, "Manufacturers have improved their manufacturing techniques so that little or no vinyl chloride remains in the polymer".

On April 2, 1982 the FDA published an Advanced Notice of Proposed Rule Making (Attachment B) which discusses a "constituents policy" applicable to the PVC problem. It is expected that this policy will withdraw the 1975

proposal and clear the use of PVC products in contact with all foods subject to some limitation on either the residual monomer content or, more likely, the maximum concentration of vinyl chloride that may migrate.

Constituents in this area refers to substances not intended to be either direct or indirect food additives, yet unavoidably present in the additive, such as residual VCM. It seems the FDA has admitted that it will accept the presence of a carcinogen as a constituent of a non-carcinogenic additive.

According to Keller & Heckman attorney John Eldred, "Prudence suggests and most users require that PVC compounds intended for use in food-contact application be made with the lowest feasible residual monomer levels".

Both the PVC industry and BATF await this constituents policy. On September 28, 1984, Food and Drug Commissioner Frank E. Young stated in a letter that there is "no reason at the present time why a rule establishing safe conditions for use of PVC bottles and other food-contact uses of vinyl chloride polymers should not be issued". In December of 1984, Jerome Heckman of Keller and Heckman wrote to Mr. Young endorsing that statement and urged the commission to issue "without delay" such a food additive regulation. As of this writing, this has not occurred.

GOOD MANUFACTURING PRACTICES

All direct or indirect-food additives, whether prior sanctioned or granted approval through specific regulation, must be produced using "good manufacturing practices". This term is dealt with, vaguely, in the Code of Federal Regulations, Part 174 (Attachment C). This regulation is surprisingly devoid of any references to specific manufacturing practices and contains such generalities as, "any substance used as a component of articles that contact food shall be of a purity suitable for its intended use".

In September of 1983, Bill Percival of DuPont's Patents and Regulatory Affairs Department, in a response to an inquiry from SKS, offered the following interpretations of the practical meaning of good manufacturing practices:

a) When considering production facilities, keep in mind "reasonable precaution" and "prudence";

b) positive pressure enclosure for a compounding line would not be necessary;

c) we should consider

- physical separation of extruders (for compound or dryblend production) using some sort of enclosure to prevent anything from dropping from ceiling beams or walls into the resin,

- separate storage of food-grade vs. non-FDA additives (or reactants),

- use of color codes on packages to designate food-grade vs. non-food grade additives,

- use of checklists, operating instructions, etc. to absolutely minimize any chance of operator error.

- regular operator training on the importance of maintaining the food-grade product in pristine form.

In the final analysis, however, a resin is considered to have been produced using good manufacturing practices if it meets the volatility (3.0%) and I.V. (0.35) specification mentioned previously. (See Attachment D)

FDA APPROVALS AND THE MASTER FILE SYSTEM

In 1962 the Federal Food, Drug and Cosmetics Act was again amended by the passage of the New Drug Act Amendments. This new law gave the FDA the responsibility, for the first time, for passing on drug efficacy as well as safety. At about this time, plastics were gaining widespread popularity for use in drug packaging, especially bottles, and the FDA found it necessary to consider a drug's packaging when evaluating the drug's efficacy.

In order for the FDA to accomplish its evaluation as described above, it must be supplied with information concerning the drug as well as the intended packaging. Data pertaining to the drug itself, of course, comes from drug manufacturers. The drug manufacturers may also supply the information concerning the intended packaging material if such information was made available to it by the packaging suppliers. In order to keep producers of resin, compound, or bottles (in the case of PVC drug bottles for example) from having to share with their customers information generally considered trade secrets, the FDA set up a system which has come to be called Master Files. The FDA's Master Files system is completely voluntary and allows the FDA to collect and keep confidential all information necessary to pass judgement on the suitability of a particular drug's packaging. An SPI manual published in 1967, and still pertinent, states that plastics manufacturers "....usually provide FDA with lists of the components of their products, relevant details about the manufacturing process used, a description of the chemical composition and physical characteristics of their products, explanations of product designations used, and data concerning the percentage concentrations of components or formulations", for inclusion in a Master File.

There are actually two types of Master Files; a Drug Master File (DMF) and a Medical Device Master File (MDMF). Each serves the same purpose and can contain similar, if not identical, information. The difference being that

the Drug Master File is referenced by the FDA in conjunction with a New Drug Application (NDA) or Investigational New Drug Exemption Application (IND), while the Medical Device Master File is referenced by the FDA in conjunction with a Medical Device Application, as required by the New Device Statute of 1976.

PVC FOR PACKAGING DRUGS AND BIOLOGICS

As previously mentioned, containers used to package drugs are considered to be a part of the drug and, therefore, are cleared at the time the FDA issues its approval of a New Drug Application. Blood bags contain an anti-coagulant and are regulated as biologics. In both cases, it is the responsibility of the drug or biologics manufacturer to supply the FDA with information concerning its product's composition and packaging. This can best be accomplished through the Drug Master File system described above. The manufacture of resin, compound, and bottle (or flexible sheet in the case of the blood bag) may each set up DMF's at the FDA. These raw material manufacturers can then authorize the drug or biologics manufacturer to request the FDA to refer to the DMF in its review of the New Drug Application. These steps may also be followed when the drug or biologics manufacturer wishes to approve a new source of supply, although in this case the FDA's review will be cursory for a raw material such as PVC resin. It is important to the drug or biologics manufacturer that his raw material supplier have a DMF set up and be able to provide the manufacturer with its assigned DMF number.

In the case of a New Drug Application, if the FDA needs further information relevant to the packaging, a request will be made of the appropriate suppliers.

PVC AS A COMPONENT OF MEDICAL DEVICES

As with drugs and biologics, the manufacturer of a medical device is required to register and list the devices it manufactures. If Vista Polymers produces a resin or compound and markets it (them) specifically for use as a component of a medical device, Vista would incur the registration and listing obligation. If, however, we produce resin or compound for general uses which may include its employment by a device manufacturer as a component of a medical device, the registration and listing requirement is not applicable.

All medical devices are placed into one of these categories:

Class I devices are subject to general controls applicable to all devices.

Class II devices are subject to performance standards in addition to general controls.

Class III devices are those which are intended for use in supporting or sustaining human life and are subject to premarket approval similar to that required of new drugs.

These classifications are of no particular concern to us as suppliers of PVC, however potential customers sometimes state that our resin or compound must have "Class III certification", for example. Such certification for PVC does not officially exist, and any necessary approvals of our products would be handled by the FDA's Master Files procedure. The manufacturer of a device that wishes to employ a Vista PVC product as a component of a device may be required to provide FDA with information regarding the PVC component. Again, the device manufacturer, like the drug or biologics manufacturer, requests the FDA to reference Vista's Medical Device Master File identifying it by its Master File number.

A

PVC FOR COSMETICS PACKAGING

The FDA has no requirements for PVC compounds used to package cosmetics. Nevertheless, many manufacturers of shampoo as well as mouthwash require that PVC compounds used to make bottles for their products have a very low residual monomer level, essentially the same as that requested for the manufacture of food-contact products. The FDA does not seem to have any special interest in cosmetic containers and John Eldred of Keller & Heckman does not anticipate the FDA will direct any attention to this area when it releases the "constituents policy" discussed above.

MASTER FILES: ESTABLISHMENT PROCEDURE, CONTENTS, AND OTHER MATTERS

Value to Vista

The existence of a Drug Master File at the FDA is a necessity for approval of our resin(s) at Klockner who, although supplying markets for which PVC is already prior-sanctioned, require each resin supplier to communicate its DMF number as part of the resin approval process. In addition American Hoechst, who produces large volumes of pharmaceutical blister packaging using a 5265-type resin, will probably need a DMF number to approve our lowest molecular weight resin.

Both a Drug Master File and a Medical Device Master File will allow marketing and sales to develop many accounts from which we have been excluded due to FDA issues as well as due to a customer's inability to segregate FDA-approved from non-FDA approved resins. (To clarify: having "FDA-approved" resin simply refers to having the appropriate Master File and adhering to good manufacturing practices. Actual approval cannot be granted until the FDA evaluates a particular resin in combination with an intended use as evidenced by a customer's New Drug Application, Medical Device Registration, or notification of new source of supply.)

Although the medical applications market for PVC is somewhat smaller and more fragmented than our traditional markets, recent market research confirming its high growth potential, as well as the opportunity for greater-than-pipe netbacks make it a promising target for our non-pipe diversification strategy. Furthermore, the steps necessary to position our products for FDA related applications (i.e. establishment of FDA Master Files) will likely require no capital expenditure or product modification beyond that which we are already considering for the rigid calendering market. An evaluation of the FDA status of our reactor additives will be necessary, however.

Just a few potential accounts requiring "FDA-approved" resin are Johnson & Johnson (purchase 1.5-2.0MM lbs./yr. of resin for production of band-aids and medical tapes); Baxter-Travenol; Vinylex; Sherwood Medical; and various companies who produce compounds specifically for FDA applications.

Also, consider the possible value of a DMF when recalling the anticipated release of FDA standards for use of PVC in the manufacture of liquor bottles.

I recommend we begin immediately the steps necessary to establish both a DMF and an MDMF.

Number of Files

We may include information on any number of our five resins, or all five, in a DMF, the same for an MDMF, so a maximum of two FDA files will be necessary for resin. As for a Vista bottle compound, dryblend, or pellet, I suggest a separate DMF or MDMF in which we reference our own resin Master Files.

Contents of Files

The FDA advises we include at least:

1. Formulation
2. Toxicity data
3. Other applicable test data
4. Index of material submitted for the file

Jerome Heckman has advised us to include some truly confidential information as this will be necessary for the FDA to establish a file for us in the face of storage and filing space limitations. He suggests: complete formulation including the identity of the catalyst (initiator), surfactants used (if any), and molecular weight control agents (if any).

If the FDA, when evaluating our file in conjunction with a customer's application or notification, requires further data such as results of extraction studies, we may add it upon their request.

In general, the contents of our file can always be expanded or updated as our business dictates.

Confidentiality of File Contents

The FDA maintains that the contents of the files are confidential, however questions have arisen regarding the applicability of the Freedom of Information Act (FOIA). The FOIA provides specific exemptions which allow governmental agencies (such as FDA) to keep certain documents confidential. Exemption 4 of the FOIA concerns "documents containing trade secrets of commercial or financial information obtained from a person outside government and privileged or confidential". (Interestingly, a case known as Continental Oil Co. vs. Fuel Products Commission in 1975 is cited as a relevant test case of this exemption.) "Trade secret" has been defined in the courts as "... a secret, commercially viable plan, formula, process, or device that is used for making, preparing, compounding or processing trade commodities and that can be said to be product of either innovation or substantial effort." "Confidential information" is that, as to which, "disclosure would cause substantial harm to the competitive position of the party from whom the information was obtained". An FDA Master File would qualify for this exemption.

Cost

The FDA reports there is no fee charged for the establishment of a Master File. If we use the services of Keller & Heckman, charges would be "about $500.00" according to Peter de la Cruz of that firm. Keller & Heckman serves to minimize delays by hand-delivering our letter and information to the FDA, and following up "as frequently as may be necessary" until the Master File number is assigned.

What FDA Does

Initially FDA simply assigns a number to the DMF or MDMF and communicates this number to us. It is purely an administrative task which will take anywhere from "a couple of weeks" according to a recent conversation with FDA, to "4 months" according to Mr. de la Cruz of Keller & Heckman, referring to a current backlog of work at FDA.

As alluded to previously, the FDA does not "approve" the material submitted as they do not know in what type of applications the resin will be employed. As for the probability of our resin gaining approval for the applications we are already considering, I suggest we first consult the suppliers of our antioxidant, CTA, etc. as they should be able to review with us the FDA status of their products. Concurrent with this we can ask FDA for a preliminary review of the suitability of our resin for several named applications in our request for Master File establishment.

Miscellaneous

For both DMF and MDMF, one original and one duplicate original of all material must be submitted. The DMF is sent to the FDA's Drugs & Biologics Product Coordination Center; the MDMF to the Center for Devices and Radiological Health.

ATTACHMENTS

A Proposed FDA Regulation prohibiting use of PVC for production of rigid and semi-rigid food-contact articles.

B Advance Notice of Proposed Rule Making discussing a policy for regulating constituents of direct and indirect food additives.

C Part 174 - Indirect Food Additives: General including definition of Good Manufacturing Practices.

D SPI Manual "Good Manufacturing Practices" Criteria for Plastic resins "Prior Sanctioned" under the Food Additives Amendment of 1958.

ATTACHMENT A

(2) *Long varieties.* U.S. No. 2, or better grade, 1⅞ inches minimum diameter.

(3) *All varieties.* Size B, if U.S. No. 1, or better grade.

(b) *Maturity (skinning) requirements.*

(1) *Russet Burbank and Red McClure varieties.* For U.S. No. 2 grade not more than "moderately skinned" and for other grades not more than "slightly skinned."

(2) *All other varieties.* Not more than "moderately skinned."

(c) *Inspection.* (1) No handler shall handle any potatoes for which inspection is required unless an appropriate inspection certificate has been issued with respect thereto and the certificate is valid at the time of shipment. For purposes of operation under this part it is hereby determined pursuant to paragraph (d) of § 948.40, that each inspection certificate shall be valid for a period not to exceed 5 days following the date of inspection as shown on the inspection certificate.

(2) No handler may transport or cause the transportation by motor vehicle of any shipment of potatoes for which an inspection certificate is required unless each shipment is accompanied by a copy of the inspection certificate applicable thereto and the copy is made available for examination at any time upon request.

(d) *Special purpose shipments.* (1) The grade, size, maturity and inspection requirements of paragraphs (a), (b) and (c) of this section and the assessment requirements of this part shall not be applicable to shipments of potatoes for:

(i) Livestock feed;

(ii) Relief or charity; or

(iii) Canning, freezing, and "other processing" as hereinafter defined.

(2) The grade, size, maturity and inspection requirements of paragraphs (a), (b) and (c) of this section shall not be applicable to shipments of seed pursuant to § 948.6 but such shipments shall be subject to assessments.

(e) *Safeguards.* Each handler of potatoes which do not meet the grade, size, and maturity requirements of paragraphs (a) and (b) of this section and which are handled pursuant to paragraph (d) for any of the special purposes set forth therein shall,

(1) Prior to handling, apply for and obtain a Certificate of Privilege from the committee,

(2) Furnish the committee such reports and documents as requested, including certification by the buyer or receiver as to the use of such potatoes, and

(3) Bill each shipment directly to the applicable processor or receiver.

(f) *Minimum quantity.* For purposes of regulation under this part, each person may handle up to but not to exceed 1,000 pounds of potatoes without regard to the requirements of paragraphs (a), (b) and (c) of this section, but this exception shall not apply to any shipment which exceeds 1,000 pounds of potatoes.

(g) *Definitions.* The terms "U.S. No. 1," "U.S. No. 2," "slightly skinned," and "moderately skinned" shall have the same meaning as when used in the U.S. Standards for Potatoes (§§ 51.1540–51.1566 of this title, effective September 1, 1971, as amended), including the tolerances set forth therein. The term "other processing" has the same meaning as the term appearing in the act and includes, but is not restricted to, potatoes for dehydration, chips, shoestrings, starch, and flour. It includes only that preparation of potatoes for market which involves the application of heat or cold to such an extent that the natural form or stability of the commodity undergoes a substantial change. The act of peeling, cooling, slicing, dicing, or applying material to prevent oxidation does not constitute "other processing." Other terms used in this section shall have the same meaning as when used in Marketing Agreement No. 97, as amended, and this part.

(h) *Applicability to imports.* Pursuant to section 8e of the act and § 980.1, Import regulations (7 CFR 980.1), Irish potatoes of the red skinned round type, except certified seed potatoes, imported into the United States during the period September 29, 1975, through June 30, 1976, shall meet the grade, size, and quality requirements specified in paragraph (a) of this section, and during the effective date of this handling regulation through October 31, 1975, shall be not more than "moderately skinned."

Dated: August 28, 1975.

CHARLES R. BRADER,
Deputy Director, Fruit and Vegetable Division, Agricultural Marketing Service.

[FR Doc.75-23304 Filed 9-2-75;8:45 am]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 121]

[Docket No. 75N-0235]

PRIOR-SANCTIONED POLYVINYL CHLORIDE RESIN

Termination of Notice of Proposed Rulemaking

The Commissioner is withdrawing a proposal published in the FEDERAL REGISTER of May 17, 1973 (38 FR 12931) to establish a regulation under § 121.2009 (21 CFR 121.2009) to identify the criteria for the safe use of prior-sanctioned polyvinyl chloride resin as a component of food packaging material in contact with nonalcoholic food.

Since publication of the proposal, additional information has been received concerning the use of polyvinyl chloride in food packaging materials which indicates that this proposal was too narrow in its scope. Published elsewhere in this issue of the FEDERAL REGISTER are proposed regulations concerning the use of vinyl chloride polymers in contact with all types of food.

Accordingly, the Commissioner hereby withdraws the proposal published on May 17, 1973, and terminates the rule making proceeding begun by that proposal.

This action is taken pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 409, 701(a), 52 Stat. 1055, 72 Stat. 1785–1788 (21 U.S.C. 348, 371(a)) and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Effective date. This order shall be effective September 3, 1975.

Dated: August 27, 1975.

A. M. SCHMIDT
Commissioner of Food and Drugs

[FR Doc.75-23340 Filed 8-29-75;8:45 am]

[21 CFR Part 121]

[Docket No. 75N-0190]

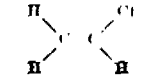
VINYL CHLORIDE POLYMERS IN CONTACT WITH FOOD

Notice of Proposed Rulemaking

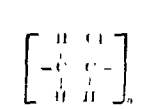
The Food and Drug Administration (FDA) is proposing regulations to restrict the uses of vinyl chloride polymers in contact with food. The proposal permits the continued use of vinyl chloride polymers in food packaging and other food-contact articles where the potential for migration of vinyl chloride is diminished to the extent that it may not reasonably be expected to become a component of food. The proposal includes an interim food additive regulation for the use of water pipe made from vinyl chloride polymers. The interim regulation would be in effect pending development of additional data to determine if vinyl chloride may reasonably be expected to be in potable water that is drawn from the tape. The proposed regulation would prohibit all other uses of vinyl chloride polymers in food-contact articles, including semirigid and rigid articles such as bottles and sheets, because in those uses vinyl chloride may reasonably be expected to become a component of food. Interested persons have until November 3, 1975 to submit comments

USE OF VINYL CHLORIDE

Vinyl chloride is a chemical with the following structure:



It has a boiling point of −14° C (6.8° F) and consequently it is ordinarily a gas. This property led to its use as a propellant for aerosol products such as cosmetics, drugs, and pesticides. Vinyl chloride is polymerized to form polyvinyl chloride in which the basic monomeric unit is repeated:



In this formula, *n* represents the number of monomeric units that may be present, a sum which normally exceeds 800 units.

Vinyl chloride homopolymers and copolymers are used in the production of articles or components of articles in-

tended to contact food, including food-packaging materials, coatings, parts for food processing equipment, flexible tubing, and water pipes.

Polyvinyl chloride has several properties that make it useful for packaging, such as clarity, resistance to water and many chemicals, capability of acting as a barrier to gas and water, capability of being sealed by heat, and capability of being molded into deep shapes. Approximately 300 million pounds of polyvinyl chloride are used each year in the packaging of food, making it (after polyethylene) the second most commonly used plastic for packaging food. The production of water pipe is one of the single largest uses of polyvinyl chloride, accounting annually for over 400 million pounds of resin. In addition, the polymers of vinyl chloride have also been found useful as packaging materials for other products within FDA's jurisdiction, including drug products, blood, and cosmetics. Vinyl chloride polymers are also used as components of certain medical devices.

Early investigatory work reviewed by Dr. A. J. Lehman, then Chief of the Division of Pharmacology, Food and Drug Administration, indicated that polyvinyl chloride was insoluble in various solvent systems used to simulate food. Consequently, there was little concern about the safety of food-contact articles made from polyvinyl chloride. In 1950, Dr. Lehman reported to the Association of Food and Drug Officials:

> We consider as the most important single physical characteristic of a film its solubility or the leaching out of any of its constituents in the common media with which the plastic may come in contact. If nothing can be extracted when tested with representative food-type solvents (lard-oil, vinegar, sodium bicarbonate, meat juice, water, etc.) under conditions somewhat more rigorous than might be experienced under practical usage, we usually have no objections to use of the film in situations where direct contact with food may result. Toxicological problems relate more to the plasticizers employed to give the film certain desirable characteristics than to the film itself. Plasticizers are legion, but to develop one which is nontoxic and yet efficient is not easy of accomplishment.

Reports of this work were published by Dr. Lehman in "Chemicals in Food: A report to the Association of Food and Drug Officials on Current Developments," *Quarterly Bulletin of the Association of Food and Drug Officials of the United States*, 15(3):82, 1951, and "Food Packaging," *Ibid.*, 20(4):159, 1956.

MIGRATION OF VINYL CHLORIDE TO FOOD

In early 1973, representatives of Schenley Distillers, Inc., Cincinnati, Ohio, reported to FDA their having found vinyl chloride in distilled alcoholic beverages, such as vodka and gin, packaged in polyvinyl chloride bottles. The findings of their migration studies were subsequently confirmed by FDA and led to a proposal concerning the use of polyvinyl chloride. This proposed regulation, published in the FEDERAL REGISTER of May 17, 1973 (38 FR 12931), would have precluded use of polyvinyl chloride resin in articles for use in contact with alcoholic foods and was based on: (1) The finding that residual vinyl chloride in polyvinyl chloride bottles was being extracted by bottled distilled spirits and wines, and (2) the fact that no available animal feeding studies established a safe level of consumption when vinyl chloride was extracted from containers into food. At that time there were no data that indicated that polyvinyl chloride articles in contact with nonalcoholic foods would result in migration of residual vinyl chloride into the food and, accordingly, there was no reason to consider restriction of such uses.

The existence of residual vinyl chloride in articles made from vinyl chloride polymers is related to the manufacturing process and the physical structure of the polymers. The gas vinyl chloride becomes the packaging material consisting of polyvinyl chloride or one of the copolymers of vinyl chloride through a series of distinct steps. The first step is the polymerization of the vinyl chloride to form a polymer, e.g., polyvinyl chloride resin. This resin is then blended with a number of other substances that may include plasticizers, stabilizers, lubricants, and processing aids to form a compounded material ordinarily referred to as a "compound," e.g., a polyvinyl chloride flexible film "compound" or a polyvinyl chloride bottle "compound." This "compound" is then used by the fabricator to produce the finished article that is used in contact with food.

The individual molecules of polyvinyl chloride may be visualized as short strands of thread. The individual molecules are attracted to each other by physical forces that tend to hold them together so strongly that the polyvinyl chloride, by itself, is rigid. The polymeric material contains an exceedingly large number of polyvinyl chloride molecules, which are intermingled and provide a number of open spaces (interstices) among the individual molecules.

The origin of the possibility that vinyl chloride may migrate to food is its incomplete polymerization into polyvinyl chloride. Estimates indicate that somewhat less than 90 percent of the vinyl chloride is converted to polyvinyl chloride. Most of the remaining 10 percent vinyl chloride is either vented to the atmosphere, or recovered by techniques, such as vacuum stripping, and reused. However, some vinyl chloride remains in the polyvinyl chloride resin following its polymerization and isolation: At one time as much as 2000 parts per million (ppm) residual vinyl chloride remained, but with new processing methods, as little as 1 to 2 ppm remain. It is theorized that the vinyl chloride becomes physically trapped among the interstices of the polymer "threads."

This model permits an explanation of the varying degrees to which vinyl chloride is removed from the different forms of the polymer. A large amount of the vinyl chloride that fails to polymerize never becomes trapped in the resin; it either finds its way out of the resin maze, due to its volatility, or can be removed by vacuum stripping. Most, if not all, of the remaining vinyl chloride may be removed in the preparation of polyvinyl chloride "compound" for such flexible plastic materials as gaskets, films, and tubing. In preparing the "compounds" the polyvinyl chloride resin is mixed and heated with as much as 50 to 60 parts of plasticizer per hundred parts of resin. The addition of the plasticizer "opens" the spaces between the polymer "threads," and the heat tends to drive out the remaining vinyl chloride molecules. Further opportunity for removal of vinyl chloride is provided during the fabrication of the "compound" into articles because heat is usually used in the process. By contrast, it is much more difficult for the vinyl chloride molecules to escape from rigid and semirigid polyvinyl chloride articles because they contain little or no plasticizer and are generally thicker than plasticized articles. Many rigid articles have been analyzed and found to contain residual vinyl chloride. However, FDA has not been able to detect vinyl chloride in any of the plasticized, flexible polyvinyl chloride products it has analyzed.

Even in the case of rigid unplasticized polyvinyl chloride, there is a loss of vinyl chloride during fabrication into articles. Once fabricated, the polyvinyl chloride articles continue to lose vinyl chloride by diffusion. Data have been developed showing a gradual loss of residual vinyl chloride from polyvinyl chloride articles during their storage prior to use. This diffusion phenomenon continues to occur when the polyvinyl chloride is used in contact with food. If vinyl chloride is present, a certain amount may be expected to migrate to the food. In the case of semirigid and rigid articles that contain high levels of residual vinyl chloride, this amount has been shown to be substantial. However, in the case of coatings, films, and other plasticized food-packaging materials in which the amount of residual vinyl chloride is extremely small, there appears to be little likelihood that vinyl chloride would reasonably be expected to be present in the food.

The migration of vinyl chloride may be viewed as a simple diffusion phenomenon: The vinyl chloride is leaving the location of highest concentration, the plastic article, and moving to a location of lower concentration, whether it be the surrounding air or the food contained in the article. This hypothesis appears to be supported by the work of scientists at Ethyl Corp. ("VCM extraction from PVC bottles," *Modern Packaging*, pp. 45–48, April 1975). Their data indicate that the vinyl chloride levels in the plastic article and its food content eventually reach a point of equilibrium. However, there continues to be a loss of residual vinyl chloride to the surrounding atmosphere so that the level in the plastic article becomes lower relative to the level in the food inside it. When this occurs, there is a migration of vinyl chloride from the food into the plastic article: This is represented by a decrease in the concentration of vinyl chloride that can be detected in the food. The ob-

vious end point indicated by this hypothesis is that there would be no vinyl chloride in the food or in the plastic article at that distant point in time when it has all migrated to the surrounding atmosphere.

A modification and extension of this hypothesis has been proposed by Professor Seymour Gilbert, Ph.D., Department of Food Science, Rutgers University, New Brunswick, N.J. Dr. Gilbert's work indicates that there are active sites in rigid polyvinyl chloride that tend to adsorb and hold on to vinyl chloride molecules. At high vinyl chloride concentrations these active sites are covered by a very small part of the total vinyl chloride and the remainder tends to migrate from the polyvinyl chloride in accordance with the usual diffusion theory. He postulates that at vinyl chloride concentrations of less than 1 ppm in the polyvinyl chloride, not all the active sites are covered and thus there are few unadsorbed vinyl chloride molecules left to migrate. His theory is supported by the results of equilbrium studies in which powdered polyvinyl chloride resins containing no vinyl chloride were added to food-simulating solvents containing known concentrations of vinyl chloride. Vinyl chloride was found to be taken up by the resin and its concentrations in the food-simulating solvents were reduced to a much greater extent than would be explained by simple diffusion or partitioning.

Schenley Distillers reported levels of vinyl chloride as high as 20 ppm in vodka and 25 ppm in gin. Confirmatory work on samples of the same material by FDA showed levels of 11 ppm vinyl chloride in vodka and 12 ppm in gin. Since that time FDA has received many additional reports of findings of vinyl chloride in various types of food packaged in polyvinyl chloride bottles. Generally, these reports have not included suitable information to evaluate accuracy, such as: an adequate description of the methodology, including chromatograms; data from recovery studies verifying the claimed sensitivities; data showing confirmation by mass spectroscopy; and identification of the plastic material. It should be noted that analysis for vinyl chloride requires careful analytical techniques to assure credible findings. The analysis becomes progressively more difficult as the concentration of vinyl chloride decreases.

The problems involved with the analysis for vinyl chloride are emphasized by the difficulties that firms have encountered in obtaining consistent results during "round-robin" studies in which a number of laboratories have analyzed the same material. FDA has developed a method for the determination of vinyl chloride in polyvinyl chloride and in food-simulating solvents. (Copies are available from the Division of Food and Color Additives, Food and Drug Administration, 200 C St., SW., Washington, D.C. 20204.) This method is considered to be capable of measuring levels of vinyl chloride in food-simulating solvents as low as 20 parts per billion (ppb) (in 50 percent ethanol) and in polyvinyl chloride as low as 0.35 ppm.

On December 20, 1973, representatives of FDA and the Society of the Plastics Industry, Inc. (SPI) met to discuss chemical information concerning vinyl chloride that SPI had submitted with its comments of October 15, 1973, on the original proposal of May 17, 1973. In response to questions raised at this and subsequent meetings, members of the SPI have obtained information about polyvinyl chloride, including analyses of various types of foods for the presence of vinyl chloride, refinement of the methodology for detection, and review of the toxicological aspects. Memoranda of these meetings and the information supplied are on public display at the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852.

Data supplied by SPI indicated that vinyl chloride could migrate to nonalcoholic foods from polyvinyl chloride bottles. Analyses of two samples of vegetable oils packed in polyvinyl chloride bottles revealed the presence of vinyl chloride at levels of 1.6 and 6.5 ppm. Reported results of analyses of additional samples of foods, drugs, and cosmetics disclosed varying levels of vinyl chloride, e.g., vinegar (5 ppb), mineral oil (74 ppb and approximately 2 ppm from two other samples), a vitamin supplement (approximately 1 ppm), and a mouthwash (174 ppb). No vinyl chloride was reported from a series of water samples using an analytical method reportedly sensitive to 50 ppb. These latter samples had been collected from operating potable water systems of various polyvinyl chloride formulations at six different building sites.

In early 1974, the British Ministry of Agriculture, Fisheries, and Food reported finding vinyl chloride in concentrations ranging from 10 to 80 ppb in fruit squashes and from 10 to 40 ppb in cooking oils. The Canadian Health Protection Branch of the Ministry of Health and Welfare reported finding vinyl chloride ranging from 0.9 to 8.4 ppm in seven samples of apple cider vinegar. It also reported vinyl chloride in samples of various wines (less than 0.025 to 0.98 ppm), gin (0.22 to 0.7 ppm), and malt vinegar (1.5 ppm).

Data from experimental work using food-simulating solvents, i.e., distilled water, 3 percent acetic acid, ethanol, and *n*-heptane, support these earlier data showing migration of vinyl chloride to types of foods other than alcoholic beverages: The data show that the use of alcohol and *n*-heptane as solvents representing alcoholic and fatty foods, respectively, results in the highest levels of vinyl chloride extractives as compared to the amounts extracted by distilled water (representing aqueous foods) and 3 percent acetic acid (representing acidic foods). All of these data are on public display in the office of the Hearing Clerk, Food and Drug Administration.

The available data indicate that certain applications of vinyl chloride do not present a realistic possibility of vinyl chloride migration. The Commissioner is unaware of any findings of vinyl chloride migration from film, cap liners, coatings, gaskets or flexible tubing. Results of analyses of extractives from such articles have shown no detectable vinyl chloride. Analyses of these plastic articles themselves have shown no detectable vinyl chloride using analytical methods reported to be capable of detecting a level as low as 1 ppm residual vinyl chloride. No residual vinyl chloride was found in FDA analysis of polyvinyl chloride blood bags and flexible tubing using a method capable of detecting 0.35 ppm residual vinyl chloride.

The lack of findings of extractable vinyl chloride from film is not surprising, for theoretical calculations indicate that if film contained residual vinyl chloride, 100 percent migration of the residual vinyl chloride from a 1 mil (0.001 inch) film would result in 2 ppb vinyl chloride in food. These calculations assume that 10 grams of food contact each square inch of film, the film weighs 20 milligrams per square inch per mil thickness, and the film contains 1 ppm residual vinyl chloride. However, these assumptions are exaggerated, e.g., the vinyl chloride will migrate into the air as well as the food, and much lower levels of migration into food would be expected to occur under actual conditions of use, to the point where they would be extremely small. The data substantiate this conclusion because the levels of extractable vinyl chloride have never been shown to approach 100 percent in those cases where actual values have been presented for article thickness, residual vinyl chloride level, and levels of extraction of vinyl chloride.

The greatest likelihood for migration of vinyl chloride appears to be from polyvinyl chloride bottles and other rigid or semirigid polyvinyl chloride articles that are intended for one-time use. A wide variety of products have been packaged in such containers, including vegetable oils, vinegar, honey, and liquid vitamin supplements. Large quantities of processed meats are packaged in rigid and semirigid containers composed of vinyl chloride polymers. Jelly, honey, and other condiments are frequently packaged in individual serving containers composed of vinyl chloride polymers. These various articles range in thickness from approximately 7 mils to 30 mils. Semirigid articles with a thickness of 7 to 12 mils were reported in a submission from the American Meat Institute to contain 0 to 180 ppm residual vinyl chloride and to yield 4 to 20 ppb vinyl chloride when extracted by *n*-heptane. Rigid articles with a thickness of 10 to 21 mils were reported by the American Meat Institute to contain 6 to 127 ppm residual vinyl chloride and to yield 2 to 237 ppb vinyl chloride when extracted by *n*-heptane.

Water pipe is a use of polyvinyl chloride that presents little likelihood that vinyl chloride will become a component of potable water. The pipe's rigid, relatively thick wall would be expected to have a potential for high levels of residual vinyl chloride; data show that the level of residual vinyl chloride attainable in water pipe may vary from less than

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10 ppm to more than 100 ppm. However, the potential for extraction of vinyl chloride from potable water pipe is greatly reduced because of the low solubility of vinyl chloride in water, the short time of contact, the large volume of water in contact with the pipe, and the comparatively low temperatures of exposure. The primary use of polyvinyl chloride potable water pipe is from water mains to buildings where a large volume of water flow occurs, and the temperature of exposure is lowered because the pipe is buried. Moreover, the small amount of vinyl chloride that might migrate into water from water pipe would be expected to dissipate during the aeration and agitation that occur at the tap.

TOXICITY OF VINYL CHLORIDE

FDA is unaware of any suitable toxicity data from animal feeding studies that demonstrate a safe level of ingestion of vinyl chloride. Results of a 90-day feeding study with rats were submitted to FDA in October 1974. However, that study was not conclusive and, furthermore, could not resolve the prime issue of safety, namely carcinogenicity, since it was a short-term feeding study. Lifetime studies are necessary to evaluate properly the potential for long-range effects, such as carcinogenicity.

Considerable data exist concerning the toxic effects of vinyl chloride from atmospheric exposures, especially by inhalation and occupational contact. As the Commissioner pointed out in his April 22, 1974, proposal (39 FR 14215) to prohibit the use of vinyl chloride as an ingredient in drug and cosmetic aerosol products:

> There is ample evidence that vinyl chloride inhalation can result in acute toxicity manifested by an array of symptoms, including unconsciousness as a result of high concentration by inhalation. Cardiac effects, bone changes, and degenerative changes in the brain, liver, and kidneys have also been reported in animals.

The results from studies by Torkelson, et al., on the chronic effects of vinyl chloride on laboratory animals (T. R. Torkelson, F. Oyen, and V. K. Rowe, "The Toxicity of Vinyl Chloride as Determined by Repeated Exposure of Laboratory Animals," *American Industrial Hygiene Association Journal*, 22(5), 354–361, 1961) indicated slight effects in rats exposed to atmospheres containing 100 and 200 ppm vinyl chloride. An exposure of 50 ppm was considered to be a "no-effect" level. Published scientific reports implicate vinyl chloride as a causative agent for "acroosteolysis" of the hands and feet as well as systemic effects among industrial workers engaged in the manufacture of vinyl chloride. Dr. P. L. Viola, in studies, exposed rats to an atmosphere containing 3 percent (30,000 ppm) vinyl chloride vapors for 4 hours per day for 5 days per week for 1 year (P. L. Viola, A. Bigotti, and A. Caputo, "Oncogenic Response of Rat Skin, Lungs, and Bones to Vinyl Chloride," *Cancer Research*, 31: 516–522, May 1971). He reported that rats subjected to such exposure developed tumors of the skin, lungs, and bones. Copies of these reports are on file with the Hearing Clerk, Food and Drug Administration.

Reporting at the February 15, 1974, fact-finding hearing, which was called by a notice that the Occupational Safety and Health Administration published in the FEDERAL REGISTER of January 30, 1974 (39 FR 3874), Dr. Cesare Maltoni discussed preliminary results from his investigations directed at clarifying the type and degree of carcinogenic effects of vinyl chloride, as previously reported by Dr. Viola. Dr. Maltoni's investigations involved various types and levels of exposure to vinyl chloride, including: (1) An attempt to reproduce the conditions of Dr. Viola's experiment using a level of 30,000 ppm; (2) experiments using atmospheric exposure to vinyl chloride vapors at levels ranging from 50 to 10,000 ppm; (3) an experiment investigating the effects upon ingestion (intubation) of vinyl chloride; and (4) experiments investigating endoperitoneal and subcutaneous routes of administration. (C. Maltoni & G. Lefemine: "Carcinogenicity Bio-assays of Vinyl Chloride," *Environmental Research*, 7:387–405, 1974 and "Le potenzialitá dei saggi sperimentali nella predizione dei rischi oncogeni ambientali. Un esempio il cloruro di vinile," *Accademia Nazionale Dei Lincei*, 56:1–11, 1974). In addition to rats, Dr. Maltoni reported that experiments were also being conducted using mice and hamsters.

At the February meeting, Dr. Maltoni discussed his preliminary findings of the development of angiosarcoma of the liver, along with other types of tumors, at levels of atmospheric exposure as low as 250 ppm. At the New York Academy of Sciences meeting, May 10–11, 1974 ("Carcinogenicity Bioassays of Vinyl Chloride: Current Results," *Annals of the New York Academy of Sciences*, 246:195–218, January 31, 1975), he subsequently reported the development of angiosarcoma of the liver and other types of tumors at levels of atmospheric exposure as low as 50 ppm. Further, he announced that additional experiments were being started; the experiments are using larger numbers of animals and lower dose levels of inhalation exposure. Inhalation exposure studies using similar low levels of vinyl chloride are also in progress at Industrial Biotest Research Laboratories (IBRL) under the sponsorship of the Manufacturing Chemists Association. In discussing these two studies in regulations, published in the FEDERAL REGISTER of October 4, 1974 (39 FR 35890), establishing standards for industrial exposure to vinyl chloride, the Occupational Safety and Health Administration stated:

> These investigators have induced angiosarcoma of the liver in rats and mice at exposure concentrations of 50 ppm and in hamsters at higher concentrations of exposure. Additional tumors involving other organs, including the kidneys, lungs, and skin of exposed animals, were also observed in frequencies much in excess of control animals.

As noted above, the Food and Drug Administration issued a proposal on April 22, 1974, concerning the use of vinyl chloride as a propellant in aerosol drugs and cosmetics. At the same time, manufacturers were requested to recall any outstanding stocks of such products from the market. A final regulation was published in the FEDERAL REGISTER of August 26, 1974 (39 FR 30830), prohibiting the use of vinyl chloride as a propellant in cosmetic aerosols and requiring an approved new drug application for the marketing of aerosol drugs containing vinyl chloride as a propellant.

In separate actions, the Environmental Protection Agency, banned the use of vinyl chloride as a propellant in certain pesticide aerosols by notice published in the FEDERAL REGISTER of April 26, 1974 (39 FR 14753), and the Consumer Product Safety Commission banned the use of other self-pressurized household products containing vinyl chloride, by a notice published in the FEDERAL REGISTER of August 21, 1974 (39 FR 30112).

Dr. Cesare Maltoni has issued a preliminary report concerning the progress of his studies investigating the effects of vinyl chloride when ingested (Cesare Maltoni, Adriano Ciliberti, Luciano Gianni, Pasquale Chieco, "Insorgenza Di Angiosarcomi In Ratti, In Sequito A Somministrazione Per Via Orale Di Cloruro Di Vinile," *Gli Ospedali della Vita*, Anno II, Numero 1, Gennaio-Febbraio 1975). Dr. Maltoni's study involves the administration to rats by intubation of vinyl chloride in an olive oil solution at dosage levels of 50 milligrams per kilogram of body weight, 16.5 milligrams per kilogram of body weight and 3.3 milligrams per kilogram of body weight. The study was initiated with 40 male and 40 female rats at each dosage level, plus a control group of the same number. After 52 weeks, the examination of those rats that had died revealed one rat in the highest dose group to have angiosarcoma of the thymus, and a rat in the 16.5 milligrams dose level was found to have angiosarcoma of the liver. No tumors were reported in the 3.3 milligrams dosage group or in the controls. The experiment is continuing with an anticipated completion date in early 1976. In addition, Dr. Maltoni has initiated an experiment using lower dosage levels.

After evaluating all the data, the Commissioner concludes that it is likely that when the Maltoni study has been completed, it will show that vinyl chloride is carcinogenic when ingested. He notes that these results are consistent with the finding that inhalation of vinyl chloride has been shown to produce cancer. The Commissioner acknowledges that the finding of angiosarcoma in one rat in each of the two highest dosage levels may be regarded by some persons as inconclusive evidence that vinyl chloride is carcinogenic when ingested. However, Dr. Maltoni reports that, to his knowledge, no spontaneous angiosarcomas of rats have been reported in the literature. Additionally, Dr. Maltoni reports that angiosarcoma of the thymus and of the liver have never occurred spontaneously in their colony of Sprague-Dawley rats. The Commissioner concludes that the preliminary data from the incomplete ingestion studies, when combined with the

her data already available concerning .e hazards of vinyl chloride, are sufficient to warrant the actions proposed in this proposal.

PROPOSED ACTION

Under section 201(s) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(s)), a substance is excluded from the definition of "food additive" if its use was sanctioned by FDA prior to September 6, 1958. A number of uses of vinyl chloride polymers were so approved and consequently are "prior sanctioned."

Subsequent to the enactment of the Food Additives Amendment of 1958, FDA issued letters stating that polyvinyl chloride resin was generally recognized as safe in specific compositions, including rigid and semirigid articles intended to contact foods. These letters were based on the premise that the uses and data cited in the Lehman articles for film and coatings could be interpreted to extend to other food-contact articles containing polyvinyl chloride.

In addition, since 1958, a variety of uses of vinyl chloride polymers in food-contact articles have been approved by the issuance of food additive regulations in 21 CFR Part 121, Subparts D and F: § 121.1179 *Coatings on fresh citrus fruit;* § 121.2507 *Cellophane;* § 121.2514 *Resinous and polymeric coatings;* § 121.-2520 *Adhesives;* § 121.2521 *Vinyl chloride-propylene copolymers;* § 121.2524 *Polyethylene phthalate polymers;* § 121.-526 *Components of paper and paperboard in contact with aqueous and fatty foods;* § 121.2543 *Packaging materials for use during the irradiation of prepackaged foods;* § 121.2545 *Textruls;* § 121.-2550 *Closures with sealing gaskets for food containers;* § 121.2569 *Resinous and polymeric coatings for polyolefin films;* § 121.2571 *Components of paper and paperboard in contact with dry food;* § 121.2591 *Semirigid and rigid acrylic and modified acrylic plastics;* § 121.2608 *Vinyl chloride-lauryl vinyl ether copolymers;* § 121.2609 *Vinyl chloride-ethylene copolymers;* § 121.2623 *Vinyl chloride-hexene-1 copolymers;* § 121.2631 *Microporous polymeric filters.*

The safety of a substance used in food-contact articles may be reevaluated at any time. Use of a prior-sanctioned substance may be prohibited or limitations may be established for its safe use under section 402(a) of the act (21 U.S.C. 342 (a)) when the Commissioner determines that such use may be injurious to health. For a substance used pursuant to a food additive regulation, under section 409 of the act (21 U.S.C. 348) approval must be revoked when a fair evaluation of the data before the Commissioner fails to establish that the substance is safe under its conditions of use. In the case of a substance that is neither prior-sanctioned nor the subject of a food additive regulation, use may continue only as long as the substance is generally recognized as safe.

The Commissioner has reviewed the uses of vinyl chloride polymers in light of (1) the available data concerning the safety of vinyl chloride and (2) the likelihood of the migration of vinyl chloride to food. Although testing for the carcinogenicity of vinyl chloride upon ingestion is not complete, the Commissioner concludes, as discussed above, that sufficient data have been accumulated to establish the likelihood that it will be shown to be carcinogenic and therefore to require appropriate action to restrict the use of vinyl chloride polymers. The Commissioner concludes that the use of vinyl chloride polymers should be prohibited where there is a reasonable expectation of any migration of vinyl chloride into food.

This conclusion is consistent with the requirements of the act for all uses of vinyl chloride polymers, whether prior-sanctioned, approved food additives, or based on the assumption that they are generally recognized as safe.

The Commissioner interprets section 402(a) of the act, which prohibits use of food-contact articles that may render food injurious to health, as requiring a showing of both possible migration and possible harm. The Commissioner concludes that the criterion of migration in section 201(s) of the act is appropriately used in applying section 402(a) of the act. Consequently, a poisonous or deleterious component of a prior-sanctioned food-contact article comes within the terms of section 402(a) of the act if it may reasonably be expected to become a component of food. Since the carcinogenic potential of vinyl chloride upon ingestion is already sufficiently well documented to warrant a determination that it may, if present, render food injurious to health, the only prior-sanctioned uses of vinyl chloride polymers that may continue to be authorized are those where there is no reasonable expectation of migration.

Because of the likelihood that vinyl chloride is a carcinogen when ingested, for uses approved by food additive regulations a fair evaluation of the data before the Commissioner fails to establish their safety wherever there is reasonable expectation that vinyl chloride will migrate from the polymers into food. Therefore, the only uses that may continue to be approved are those where there is no reasonable expectation of such migration.

For uses of vinyl chloride polymers that have been generally recognized as safe, when there is a reasonable expectation that vinyl chloride will migrate into food, the evidence of potential carcinogenicity upon ingestion requires the conclusion that general recognition of their safety does not exist. Thus, as in the uses that are prior-sanctioned or approved by food additive regulation, the only permissible uses are those where there is no reasonable expectation of such migration.

In considering whether particular food-contact articles raise a reasonable expectation of migration of vinyl chloride into food, the Commissioner has reached several tentative conclusions upon which this proposal is based.

The Commissioner concludes that there is no reasonable expectation of migration of vinyl chloride from thin plasticized film because of the method of manufacture and the thickness of most film used for wrapping food (approximately 1 mil). As discussed above, plasticizing the film results in an article essentially free of vinyl chloride, and there is no reasonable expectation that any remaining vinyl chloride actually migrates into food.

The Commissioner also concludes that there is no reasonable expectation of migration of vinyl chloride from jar and bottle cap liners and gaskets. Polyvinyl chloride cap liners and gaskets, which have almost completely replaced the rubber and cork materials formerly used, are of two major types. Some are applied in liquid form as a ring around the part of the cap in contact with the container, and others consist of a circular disc cut from film and inserted so as to cover completely the inside surface of the cap. A majority of those types are plastisols which are applied as liquid and are made from paste resins containing finely ground (1 micron or less) polyvinyl chloride and plasticizer. These plastisols contain about 100 parts polyvinyl chloride and 60 parts plasticizer. Other gaskets are made by combining these plastisols with other polyvinyl chloride resins. In addition to removal of residual vinyl chloride in the plasticizing process, additional vinyl chloride is thought to be removed when the plastisol is heated to approximately 350° F for 5 to 8 minutes during application. The small potential for residual vinyl chloride that exists after such processing, together with the fact that a gasket has only limited contact with food, leads to the conclusion that there is no reasonable expectation of migration of vinyl chloride into food. Similarly, no migration may be expected from cap inserts cut from thin plasticized film, for the reasons previously discussed. Moreover, in the case of all cap liners there will be only slight contact with food. Considering these factors, the Commissioner concludes that there is no reasonable expectation of migration of vinyl chloride from cap liners.

Can coatings containing polyvinyl chloride are primarily used on the inside of beer and soft drink cans and, to a much lesser extent, inside food cans. Most of the polyvinyl chloride used for can coatings is produced by the solution polymerization process which produces polyvinyl chloride with the lowest residual vinyl chloride content. After conversion of the resin into can coatings, no residual vinyl chloride has been reported, presumably because the thinness of the applied film and the baking it has received, at above 300° F, have caused the removal of the residual vinyl chloride. In such a case, it can be concluded that there is no reasonable expectation of migration of vinyl chloride into food.

Polyvinyl chloride flexible tubing, ranging in internal diameter from 2 to 3 thousandths of an inch to 3 to 4 inches, is highly plasticized. As previously discussed, it is thought that plasticization reduces residual vinyl chloride content to the point where there is no reasonable expectation that any will migrate into

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food. In addition, flexible tubing is generally used in applications where food contacts the tubing only briefly and the temperature of the food is often low. These circumstances further reduce the possibility of any migration of vinyl chloride.

Textryls incorporating vinyl chloride polymers in accordance with § 121.2545 (21 CFR 121.2545) are nonwoven sheets prepared from natural or synthetic fibers and bonded with fibryls. The fibryls consist of vinyl chloride-vinyl acetate copolymer resin that is prepared by solution polymerization, a process that has been shown to result in less than 1 ppm vinyl chloride in the resin. The fibryls are formed by precipitating a solvent solution of the copolymer in water and then washing the precipitate until all solvent is removed. The fibryl is commingled with fibers prepared from polyethylene terephthalate resins to facilitate sheet formation and subsequently heat cured to fuse the fibryl and effect bonding. These procedures for manufacturing textryls should result in a reduction of level of the residual vinyl chloride to the point that the Commissioner concludes that their use would not reasonably be expected to result in vinyl chloride becoming a component of food.

Microporous polymeric filters used in accordance with § 121.2631 (21 CFR 121.2631) are based on polyvinyl chloride resins produced by solution polymerization, which, as noted above, results in low levels of residual vinyl chloride. The filters are prepared by adding silicon dioxide to a solvent solution of the resins, resulting in "opening" of the resins and further loss of residual vinyl chloride. The filter is formed by extrusion and calendering followed by a hot water wash to remove solvent. Each of these steps, together with the preuse treatment required by § 121.2631, would result in a reduction of any remaining vinyl chloride to the point that the Commissioner concludes that the use of microporous polymeric filters would not reasonably be expected to result in vinyl chloride becoming a component of food.

Adhesives containing vinyl chloride polymers in accordance with § 121.2520 (21 CFR 121.2520) have no contact with food except incidentally at the edges of food-packaging materials. Because of this slight contact, the Commissioner concludes that the continued use of adhesives containing vinyl chloride polymers would not reasonably be expected to result in vinyl chloride becoming a component of food.

However, the data indicate that rigid and semirigid polyvinyl chloride articles intended to contact food (including bottles, blister packs, boxes and pipe, except as noted below for water pipe) may transmit vinyl chloride to the food they contact. Therefore, the Commissioner finds that these uses can no longer be permitted for contact with food.

The use of vinyl chloride polymers as coatings for fresh citrus fruits, which is permitted by § 121.1179 (21 CFR 121.1179), presents the possibility of ingestion of vinyl chloride because the polymers are applied directly to the fruit. Therefore, the Commissioner concludes that the available data do not demonstrate that this use is safe.

Because copolymers of vinyl chloride might also be expected to contain residual vinyl chloride capable of migrating to food, this proposal applies to vinyl chloride copolymers, as well as to the homopolymer, polyvinyl chloride.

In accordance with these conclusions, the proposed regulations take the following approach:

1. Prior-sanctioned uses of vinyl chloride homopolymers and copolymers as coatings, gaskets, cap liners, flexible tubing, and plasticized films would be identified in regulations permitting their continued use. This proposal identifies all such prior sanctions known to the Commissioner. Persons aware of other prior-sanctioned uses should submit proof of the sanctions during the period for comment on this proposal.

2. Prior-sanctioned uses of vinyl chloride homopolymers and copolymers in semirigid and rigid applications would no longer be permitted except in water pipe as discussed below. This proposal would amend § 121.106 (21 CFR 121.106) of the regulations to so provide. Once these proposed regulations become final, vinyl chloride polymers could be used in semirigid and rigid applications only after approval of a food additive petition, submitted pursuant to § 121.51 (21 CFR 121.51) of the regulations. In addition to the other required information for a food additive petition, data would be necessary to demonstrate that there is no reasonable expectation that vinyl chloride will become a component of food.

3. Uses of vinyl chloride homopolymers and copolymers as coatings, gaskets, cap liners, flexible tubing, and plasticized films that are not prior-sanctioned and that are not subject to food additive regulations are not expressly affected by this proposal. Such uses could be continued if they are otherwise generally recognized as safe. A petition to affirm such uses as generally recognized as safe may be submitted pursuant to § 121.40 (21 CFR 121.40).

4. Food additive regulations permitting the use of vinyl chloride polymers would be amended to permit the continued use of these polymers as coatings (other than those applied directly to food), gaskets, cap liners, flexible tubing, and plasticized films and to prohibit other uses except in water pipe as discussed below.

5. Food additive regulations specifically providing for the use of adjuvants in the production of food-contact articles containing vinyl chloride polymers would be amended to be consistent with the proposed restrictions on the use of vinyl chloride polymers.

At the time final regulations are issued, it may be necessary to define the classes of permitted polyvinyl chloride food-contact articles with greater particularity. Thus, based on available data and on information concerning theoretical prospects of migration of vinyl chloride, specifications for permitted articles might be established in terms of thickness, degree of plasticization, method of polymerization used, vinyl chloride content of the "compound" used, heat applied during processing, and similar criteria. Comments should include all available data and information that help to identify particular applications and specifications that assure no reasonable expectation of migration. The Commissioner advises that at the time the final regulations are issued, based on such data and information, it may be appropriate to restrict or eliminate uses that are here proposed to be continued.

Determining whether any food packaging component, such as vinyl chloride, is reasonably expected to become a component of food necessarily involves fine judgment, for which precise standards cannot be articulated. If there is no detectable vinyl chloride in a food-contact article, and there are no detectable extractives of vinyl chloride from the article into food-simulating solvents, and there is a sound theoretical basis for predicting no migration below the detectable level, *e.g.*, the article is plasticized or contact with food is slight, the Commissioner concludes that there is no reasonable expectation of migration. Where vinyl chloride is detected at a very low level in the food-contact article, it may nevertheless be possible to conclude that there is no reasonable expectation of migration into food based on theoretical considerations peculiar to the particular product and use. The Commissioner advises that the detection of vinyl chloride extractives in food-simulating solvents under testing conditions appropriate for food-contact articles indicates that the residual vinyl chloride in the article may reasonably be expected to migrate into food. The Commissioner concludes that testing conducted with food-simulating solvents is an appropriate method for ascertaining the likelihood of migration from a food-contact article to food. Because of analytical difficulties, food often cannot be reliably tested for evidence of migration. For this reason, food-simulating solvents have long been used both by industry and FDA to test food-contact articles.

The Commissioner is aware that the technology for reducing the amount of vinyl chloride in vinyl chloride polymers, or eliminating it altogether, is improving rapidly and that major advances not known to FDA may have been made within recent months. Thus, additional classes of food-contact articles may exist for which it can be concluded that there is no reasonable expectation that vinyl chloride would migrate into food. Comments on this proposal suggesting that such articles do exist should include data, analytical methodology used, and a theoretical analysis of the expectation of migration.

In the case of polyvinyl chloride potable water pipe, the Commissioner concludes that the data available at this time indicate that vinyl chloride may not reasonably be expected to be present in water drawn from a polyvinyl chloride water pipe system. Although data from the testing of polyvinyl chloride water pipe containing static water have shown

migration of vinyl chloride, no vinyl chloride has been detected in samples of water drawn from operating polyvinyl chloride potable water pipe. It is likely that static testing does not reasonably assess the likelihood of the presence of vinyl chloride in water. It is proposed that an interim period of time be provided for the continued use of polyvinyl chloride water pipe, pending development of data from tests appropriate for the determination of the potential for the presence of vinyl chloride in water drawn from a polyvinyl chloride potable water pipe system.

Under the proposal, polyvinyl chloride water pipe would be subject to the provisions of § 121.4000 (21 CFR 121.4000), concerning food additives approved on an interim basis. Within 60 days following the effective date of a final regulation, an interested person would be required to satisfy FDA that studies have been undertaken to determine whether vinyl chloride may reasonably be expected to be present in water drawn from a system containing polyvinyl chloride pipe. If no such commitment were made, or adequate and appropriate studies were not undertaken, the regulation permitting continued use of polyvinyl chloride water pipe would be revoked.

This announcement provides 60 days for public comment, after which time the comments will be reviewed and final regulations issued. The Commissioner proposes that the regulations become effective 30 days after their promulgation as final regulations. No recall of affected articles is now anticipated to be necessary. The Commissioner concludes that the hazard to the public health is not so immediate as to warrant issuance of these regulations without opportunity for public comment or to require recall and destruction of foods already packaged. The continued use of installed equipment having food-contact surfaces composed of vinyl chloride polymers would be permitted; any residual vinyl chloride is likely to have dissipated to the atmosphere during the period of service.

These proposed regulations deal only with vinyl chloride contamination of food. The Commissioner plans to issue additional announcements in the near future concerning cosmetics, drugs, and medical devices. Also, the proposed regulations would not immediately affect the status of vinyl chloride polymers used in food-contact articles in the household, food service establishments, and food dispensing equipment. Such articles are the subject of a notice published in the FEDERAL REGISTER of April 12, 1974 (39 FR 13285), and they will be evaluated in accordance with the terms of that notice.

The Commissioner has carefully considered the environmental effects of the proposed regulations and, because the proposed action would not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. The Commissioner has also carefully considered the inflation impact of the proposed regulations, and has found that the proposed action would not cause a major inflation impact as defined in OMB Circular A-107. Therefore, no inflation impact statement is required. At the time additional announcements concerning cosmetics, drugs, and medical devices are issued, these conclusions will be reevaluated. Data and information concerning environmental and inflation impact may be submitted as a comment on this proposal. Copies of the FDA environmental and inflation impact assessments are on file with the Hearing Clerk, Food and Drug Administration.

A petition to ban the use of polyvinyl chloride in food packaging was received by the Commissioner on July 7, 1975 from Public Citizen's Health Research Group, 2000 P St., NW., Washington, DC 20036, as this proposal on the use of vinyl chloride polymers was being prepared. Each of the petitioner's comments has been considered in the drafting of this document. A letter will be sent to the petitioner responding to the petition.

Copies of the reports and data referred to above are on file at the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852.

Published elsewhere in this issue of the FEDERAL REGISTER is a notice withdrawing a proposal to add § 121.2009 (21 CFR 121.2009) and terminating the rule making proceeding on the use of polyvinyl chloride resin in articles for use in contact with alcoholic foods, which was begun on May 17, 1973 (38 FR 12931).

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 402, 409, 701, 52 Stat. 1042, 1046-1047 as amended, 1049, 1055 (21 U.S.C. 321(s), 342, 348, 371)) and under authority delegated to him (21 CFR 2.120), the Commissioner proposes to amend Part 121, as follows:

1. In § 121.106 by adding new paragraph (e)(4) as follows:

§ 121.106 Substances prohibited from use in human food.

* * * * *

(e) * * *

(4) ***Vinyl chloride.*** (i) Vinyl chloride has the molecular formula C_2H_3Cl. It is a synthetic chemical not found in natural products and has been used in the production of polymeric substances that may contact food.

(ii) Food containing any added or detectable level of vinyl chloride is deemed to be adulterated in violation of the act.

(iii) The use in food-contact articles of vinyl chloride homopolymers and copolymers is prohibited, except that such use is not prohibited:

(*a*) In coatings, gaskets, cap liners, flexible tubing, and plasticized films if such use is otherwise in accordance with the requirements of the act and this chapter; or

(*b*) If specifically permitted in this part.

§ 121.1179 [Amended]

1a. In § 121.1179 *Coatings on fresh citrus fruit* by deleting and reserving paragraph (b)(3), and deleting the reference to paragraph (b)(3) from paragraph (b)(4).

2. By adding the following new section to Subpart E, to read as follows:

§ 121.2009 Vinyl chloride polymer resins.

Polyvinyl chloride resins consist of basic resins produced by the polymerization of vinyl chloride. Polyvinyl chloride basic resins have a maximum volatility of not over 3 percent when heated for 1 hour at 105° C, as determined by ASTM Method D 3030-72,[1] and an inherent viscosity of not less than 0.35 as determined by ASTM Methods D 1243-66.[1] Vinyl chloride copolymer resins are the polymers produced by the copolymerization of vinyl chloride with other monomeric substances. Vinyl chloride homopolymers and copolymers may be safely used as follows:

(a) *Coatings.* (1) Polyvinyl chloride for use as a can enamel.

(2) Vinyl chloride-vinyl acetate copolymer for use as a can enamel.

(3) Vinyl chloride-butadiene-acrylonitrile copolymer for use as a component of conveyer belts intended for use with fresh fruits, vegetables, and fish, and as a component of coatings of paper and paperboard in contact with meat and lard.

(4) Vinyl chloride-vinylidene chloride copolymer for use as a liner, i.e., coating, for steel pipe.

(b) *Plasticized films.* (1) Polyvinyl chloride for use in plasticized film in contact with food.

(2) Vinyl chloride-butadiene-acrylonitrile copolymer for use in plasticized film in contact with oleomargarine.

(3) Vinyl chloride-vinylidene chloride copolymer for use in plasticized film in contact with food.

(4) Vinyl chloride-vinyl acetate copolymer for use in plasticized film in contact with food.

3. In § 121.2507, by amending paragraph (c) by revising the entry in the list of substances for "polyvinyl chloride" to read as follows:

§ 121.2507 Cellophane.

* * * * *

(c) * * *

* * * * *

Limitations * * *

* * * * *

Polyvinyl chloride..	As the basic polymer for use only in coatings.

* * * * *

4. In § 121.2511, by amending paragraph (b) by revising the listing entries for "dicyclohexyl phthalate" and "diphenyl phthalate" to read as follows:

§ 121.2511 Plasticizers in polymeric substances.

* * * * *

(b) * * *

[1] Copies may be obtained from: American Society for Testing and Materials, 1916 Race St., Philadelphia, PA 19103.

ATTACHMENT B

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Chapter I

[Docket No. 81N-0281]

Policy for Regulating Carcinogenic Chemicals in Food and Color Additives; Advance Notice of Proposed Rulemaking

AGENCY: Food and Drug Administration.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is considering proposing a new policy for use in assuring the safe use of food additives and color additives that contain minor amounts of carcinogenic chemicals. This policy would replace the current case-by-case approach to regulating such additives with an approach that applies consistent standards. This advance notice describes the scientific and regulatory problems confronting the agency with respect to such additives and explains the need to consider a change in FDA's present approach. This advance notice also discusses the alternatives that the agency is considering.

FDA is publishing this advance notice so that the agency will have the benefit of a broad range of views early in the rulemaking process, and so that interested persons will have an opportunity to express their opinions. Detailed regulations for implementing any policy that the agency may adopt will be proposed in a future issue of the Federal Register after consideration of comments received in response to this advance notice.

Elsewhere in this issue of the Federal Register, the agency is publishing a final rule listing D&C Green No. 6 for use in externally applied drugs and cosmetics. That rule further explains and illustrates how FDA has applied the approach set forth in this advance notice of proposed rulemaking. This document also discusses alternative theories for implementing the approach that the agency applied in the decision on D&C Green No. 6.

DATE: Comments by July 1, 1982.

ADDRESS: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: For information relating to the policy under consideration and regulations to be proposed: Terry C. Troxell, Bureau of Foods (HFF-334), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-472-5690.

For information relating to risk assessment procedures: Alan M. Rulis, Bureau of Foods (HFF-334), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-472-5676.

SUPPLEMENTARY INFORMATION:

I. Background

Like all chemicals, no food additive or color additive can be produced absolutely pure. Each additive, even a highly purified one, consists of an array of chemical entities, both functional and nonfunctional. For example, a color additive may contain one primary and a number of secondary colors, all of which are somewhat functional in the final additive. A polymer resin used in food packaging may contain a continuum of chemicals from monomer and dimer to high molecular weight polymers, only some of which are functional. Finally, all chemical substances, including those used as additives, contain numerous impurities such as residual reactants, intermediates, manufacturing aids, and products of side reactions and degradation.

In the early 1950's Congress became concerned about the safety of the chemicals being used in increasing amounts in foods. Under the adulteration provisions of the law, in order to prevent the use of such chemicals in food, FDA was required to prove in court that a food bore or contained a poisonous or deleterious substance which may render it injurious to health (21 U.S.C. 342(a)(1)). This process was cumbersome and time-consuming. More important, it did not adequately protect the consumer, because FDA had the burden of proving that the substance used in food had some potential for causing injury. Manufacturers also disliked the system because it prohibited the use of any amount of a chemical substance if that chemical had the potential for causing injury.

Accordingly, in response to these mounting concerns from consumers and manufacturers alike, Congress passed the Food Additives Amendment to the Federal Food, Drug, and Cosmetic Act (the act) in 1958. (21 U.S.C. 321(s) and 348.) That amendment set up a premarketing safety clearance system requiring that a food additive be shown to be safe for its intended use by the sponsor and be approved by FDA before it is used in food. The legislation also established safety standards to apply to the evaluation of the additive.

The Food Additives Amendment defines a food additive as:

> * * * any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use) * * *

21 U.S.C. 321(s).

Thus, the amendment covers both direct additives (substances intended for direct use in foods) and indirect additives (substances that through use in food packaging or for other food-contact purposes might become or might reasonably be expected to become components of food).

The legislative history makes it clear that Congress intended the amendment to protect consumers from unsafe food additives while at the same time permitting manufacturers to use food additives at safe levels (H.R. Report No. 2284, 85th Cong., 2d Sess. (1958)). This intent is reflected in the standard for approval called the "general safety clause," that Congress inserted into the law:

> No such regulation shall issue if a fair evaluation of the data before the Secretary-
> (A) fails to establish that the proposed use of the food additive, under the conditions of use to be specified in the regulation, will be safe * * *

U.S.C. 348(c)(3)(A).

The safety of a food additive must be demonstrated by properly conducted and evaluated scientific tests, but the additive need not be shown to be absolutely safe. Congress recognized the impossibility of proving the safety of an additive beyond any doubt and under any conditions of use. Reflecting the viewpoint of the various scientists who testified in support of a reasonable standard for the safety of an additive, the House of Representatives Report on the amendment states:

> The concept of safety used in this legislation involves the question of whether a substance is hazardous to the health of man or animal. Safety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive. It does not—and cannot—require proof beyond any possible doubt that no harm will result under any conceivable circumstance * * *

H.R. Report No. 2284, 85th Cong., 2d Sess. 1, 1958.

FDA regulations governing the safety assessment of food additives have incorporated that language. Under 21 CFR 170.3(i), safety of a food additive means that there is a reasonable

certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.

Because of particular concerns about cancer, Congress added the anticancer clause, or Delaney Clause, to the Food Additives Amendment. This Clause establishes a flat rule "[t]hat no additive shall be deemed be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal * * *" (21 U.S.C. 348(c)(3)).

Although the Department of Health, Education, and Welfare (HEW) (now the Department of Health and Human Services) did not object to the inclusion of the Delaney Clause in the act, the Assistant Secretary for Health made it clear that, in the view of HEW and FDA, "the (food additives amendment) reads and means the same with or without the inclusion of the (Delaney) clause * * *." H.R. Rept. No. 2422, 85th Cong., 2d Sess., pp. 10–11. The Department held this view because of the prevalent scientific conviction in 1958 that the state of the art would not permit scientists to establish a tolerance for a carcinogen. Thus, it was impossible to determine reliably a level of exposure to a carcinogen below which one can be assured that there is no significant increase in the risk of developing cancer. In other words, scientists lacked the technology to assess adequately the risk presented by a particular chemical. (See Food Additives: Bills to Amend the Federal Food, Drug, and Cosmetic Act with Respect to Chemical Additives in Food: Hearings Before the Subcomm. of the House Comm. on Interstate and Foreign Commerce, 85th Cong., 1st Sess., 369, 1957 (statement of W.C. Heuper, M.D.).)

The Color Additive Amendments of 1960 (21 U.S.C. 321(t) and 376) establish standards for the safety of a color additive that are virtually identical to those set forth in the food additive provisions except that they contain a slightly different version of the Delaney Clause for noningested color additives (21 U.S.C. 376(b)(5)(B)). In addition, the Color Additive Amendments provide for the premarket approval of color additives in drugs, devices, and cosmetics as well as food through a mechanism called listing. For a discussion of the Color Additive Amendments, see the final rule published elsewhere in this issue of the Federal Register listing D&C Green No. 6 for use in externally applied drugs and cosmetics.

II. Regulatory History

During the two decades that FDA has administered the food and color additive provisions, the agency has, with a few exceptions, interperted the food and Color Additive Amendments to ban the use of any additive that was found to contain or was suspected of containing minor amounts of carcinogenic chemicals, even if the additive as a whole had not been found to cause cancer (noncarcinogenic additives).

For example, FDA terminated the provisional listings of carbon black (41 FR 41857; September 23, 1976) and graphite (42 FR 60734; November 29, 1977) because the agency suspected that these colors could contain polynuclear aromatic hydrocarbons (PNA's), some of which are carcinogenic. The agency removed Ext. D&C Yellow No. 1 from the provisional list (42 FR 62478; December 13, 1977) because of the possibility that it might contain as impurities 4-aminobiphenyl and benzidine, both of which have been shown to be carcinogenic in humans. FDA terminated the provisional listing of D&C Red Nos. 10, 11, 12, and 13 because the agency suspected that they might contain low levels of -naphthylamine, a known human carcinogen (42 FR 62475; December 13, 1977).

The agency has also proposed to restrict the uses of polyvinyl chloride (PVC) materials in contact with food (40 FR 40529; September 3, 1975) because of a finding that vinyl chloride monomer, a known human carcinogen, could migrate in small amounts into food from PVC bottles.

The agency has approved the use of food and color additives that contain or may contain minor amounts of lead and arsenic, proven carcinogens. Those chemicals are ubiquitous environmental contaminants, routinely found in food and water as well as in chemicals used to manufacture food and color additives. Their pervasiveness is such that no food or color additive can realistically be manufactured without the possibility of some lead or arsenic contamination. Thus, because the alternative would be to prohibit the use of all additives, the agency has minimized the amount of the chemicals and thus the risk attendant to the use of such additives by setting specifications for lead and arsenic in many food and color additive regulations. FDA does not regard these exceptional situations as constituting a true departure from its traditional regulatory approach described in the examples listed above. In sum, the agency has generally concluded that a safe level could not be established for a carcinogenic chemical in a food or color additive and has consistently taken regulatory action against additives that contain carcinogenic chemicals.

In an early administrative interpretation shortly after the enactment of the Color Additive Amendments, the agency construed the Delaney Clause as being triggered only if tests of the color additive as a whole revealed that the color caused cancer. (Discussion of Sec. 8.36, Digest of Objections to January 24, 1961, proposed color additive regulations.) See the final rule published elsewhere in this issue of the Federal Register listing D&C Green No. 6 for use in externally applied drugs and cosmetics. It is not clear, however, to what extent, if any, this interpretation was applied in subsequent agency decisions on specific color additives.

III. Context in which Regulatory Alternatives are Presented

Recent scientific and legal developments have convinced FDA that it may now be necessary and appropriate for the agency to reconsider how it determines whether there has been an adequate demonstration of the safety of a food additive or color additive that contains a carcinogenic constituent but that is not itself carcinogenic.

Over the past 20 years, there have been rapid developments in analytical capabilities that make it possible to decrease by orders of magnitude the levels at which the components of a substance such as a food additive or color additive are detectable and identifiable. Many chemicals now can be identified and quantified at levels around one part per billion.

Coupled with this development has been a large increase in the number of substances that have been studied for carcinogenicity in animal bioassays. For example, Tomatis has reported that 828 chemical substances were under test for cancer throughout the world in 1975 (Ref. 1). Many of these bioassays have resulted in positive findings for carcinogenesis.[1] The Occupational Safety and Health Administration has reported (Ref. 2) that about 17 percent of 7,000 test chemicals on a Public Health Service list are tumorigenic. Griesmer and Cueto have reported that 52 percent of the chemicals that have been studied in the National Cancer Institute (NCI)

[1] The percentage of positive bioassay results in the reports cited is high partly because the chemicals selected for evaluation are often those that are suspected of being carcinogenic. Scientists select these chemicals on the basis of available information, such as molecular structure-activity relationships, genotoxicity studies, and epidemiological evidence.

bioassay program are carcinogenic (Ref. 3). A National Toxicology Program report indicated that 41 percent of 95 tests completed showed that the tested substances are carcinogenic (Ref. 4).

As the number of chemicals that are found to cause cancer in animals has grown, and as scientists' ability to detect the components of a substance has become more acute, the chances that a food additive or color additive will be found to contain a carcinogenic chemical entity increase. It is the agency's frank expectation that a growing number of additives will be found to contain a carcinogenic chemical in future years. If FDA continues to implement the regulatory approach that it has followed in recent years, it will be forced to refuse to approve or to terminate the approval of the use of each of these additives, even though they themselves may be safe.

However, the agency believes that there are alternatives to its current policy that will adequately protect the public health. Not all of the additives that have been or will be found to contain carcinogenic chemicals will themselves be shown to induce cancer in appropriate tests (e.g., D&C Green No. 6). The agency believes that a distinction can be drawn between additives that contain a carcinogenic chemical but that have not themselves been shown to be carcinogenic. Two recent developments support the agency's belief that such a distinction is appropriate.

One development was the 1979 decision by the United States Court of Appeals for the District of Columbia in *Monsanto* v. *Kennedy*, 613 F. 2d 947 (D.C. Cir. 1979). In discussing whether a substance that migrates into food is a food additive, that court expressed the view that there is "administrative discretion, inherent in the statutory scheme, to deal appropriately with *de minimis* situations." *Id.* at 955. If FDA has discretion to disregard low-level migration into food of substances in indirect additives because the migration of the particular additive presents no public health concern, then the agency may also disregard, after appropriate tests, a carcinogenic chemical in a noncarcinogenic food additive or color additive, if FDA determines that there is a reasonable certainty of no harm from the chemical.

Second, the agency is now confident that it possesses the capacity, through the use of extrapolation procedures, to assess adequately the upper level of risk presented by the use of a noncarcinogenic additive that contains a carcinogenic chemical. FDA has been reluctant to use these procedures for regulatory decisionmaking. Many theoretical models have been developed to extrapolate from animal experimental data to the relatively low levels of possible human exposure, but they can vary widely in the risk values that they predict. Thus, knowledge of the true risk at relatively low exposures is elusive.

Nevertheless, even though there is an inadequate scientific basis for confidence in the accuracy of predictions of actual risk by these procedures, there has been a growing recognition in the scientific community that by using certain conservative extrapolation models it is possible to estimate an upper limit of risk. (See e.g., "Chemical Compounds in Food-Producing Animals" (44 FR 17070; March 20, 1979) and FDA's decision on lead acetate (45 FR 72112; Ocober 31, 1980 and 46 FR 15500; March 6, 1981).) The estimate of the risk may be exaggerated by these conservative extrapolation models. Because the estimated risk will not be understated, however, such risk assessment techniques can be used with confidence to determine whether, under the general safety clause, there is a reasonable certainty that no harm will result from the intended use of an additive.

IV. Regulatory Approach

A. Introduction

In the decision on D&C Green No. 6 published elsewhere in this issue of the Federal Register, FDA is approving a color additive that has not been shown to be a carcinogen in appropriate tests, even though it contains a carcinogenic impurity. In this advance notice of proposed rulemaking, FDA is announcing its intent to formally adopt the principles on which that decision is based as the general policy of the agency. Therefore, FDA is soliciting comments on whether it should do so, or whether it should adopt some other approach to the problem. To facilitate such comments, the remainder of this document will describe the general policy that FDA is considering.

The policy consist of three elements:

1. Clarifying exactly what an "additive" is;

2. Interpreting the Delaney Clause to apply only when the additive itself has been shown to cause cancer; and

3. Using risk assessment as one of the tools for determining whether the additive is safe under the general safety clause.

FDA believes that the act and its legislative history, as well as subsequent judicial and administrative interpretations, support such a general policy.

B. Construction of the Term "Additive"

Conceivably, each chemical in the complex mixture that constitutes a food additive could itself be considered to be a food additive. Each of these chemicals in some sense becomes a component of the Food of which the additive is a part.

For example, in the case of an indirect food additive used in food packaging or the like, any chemical impurity that migrates from the indirect additive into food could be considered to be an additive. In the *Monsanto* case, the agency argued that the food additive definition applied to the residual acrylonitrile monomer used to fabricate the final bottle, as well as to the bottle itself, because the monomer was intended for use and was used to manufacture the copolymer bottle. (Government's Brief, pp. 63, 67.) However, the *Monsanto* court held that the statute does not compel the Commissioner of Food and Drugs to declare that each chemical in an additive is itself an additive. *Monsanto*, id. at 954, 955.

FDA has reexamined the issue of when a chemical should be considered to be a food or color additive, and has developed three alternative but not mutually exclusive interpretations to address the problem. Each of these interpretations is presented here. FDA has worked out the first of these, the constituents approach, more extensively than the others, but the agency wishes to emphasize that, at this time, it does not view any legal theory as being preeminent. Indeed, FDA may conclude that one, all, or some other combination of approaches may be appropriate. The overall risk assessment policy outlined in this notice, however, would be the same under each interpretaton.

1. *The constituents approach.* This approach distinguishes between the additive as a whole and its constituents for the purpose of determining when the Delaney Clause is triggered. Using this approach, the food additive would be the substance that is actually intended for use in food or for food contact. All nonfunctonal chemicals present in that substance would be called the "constituents" of the additive. Similarly, the term "color additive" would mean only those substances intended for use as a dye, pigment, or other substance that is capable of imparting color. (See 21 U.S.C. 321(t).) Any other chemical present in a color additive but not intended for use as described above would be a constituent of the color additive. The constituents would include residual reactants, intermediates, and manufacturing aids, as well as products

of side reactions and chemical degradation. A constituent, although part of the additive as a whole, would not itself be considered to be an additive for regulatory purposes because it is not intended for use in food or for food contact, or for imparting color in food, drugs, devices, or cosmetics. In fact, no one wants such a constituent to be present in the final additive. In an ideal world all chemical reactions invariably would run to completion, and troublesome side reactions or chemical degradation or decomposition could be avoided. Unfortunately, chemical synthesis does not operate that way, and these constituents, although they can probably be reduced, simply cannot be eliminated under current scientific techniques.

In the case of a direct food additive, the identity of the additive is unambiguous: it is the substance including all its constituents that the food processor deliberately puts into the food. Similarly for color additives the additive is the dye, pigment, or other substance including all its constituents that the manufacturer deliberately incorporates into the food, drug, device, or cosmetic for the purpose of imparting the intended color.

Some examples may clarify how various substances in direct food additives or color additives would be classified under the constituents approach. A substance intended for use in the processing of any food would be considered a food additive even though that substance may essentially be removed from the food in subsequent processing steps. Thus, extraction solvents employed in food processing would continue to be food additives because they are intended for use in a food. Such products are distinguishable from the residual reaction products such as *p*-toluidine present in D&C Green No. 6, because *p*-toluidine is not intended for use in the final color additive but only in the manufacture of the additive.

In the case of an indirect food additive, the constituents approach would regulate as indirect food additives only those substances actually intended for use in food contact. All other chemicals present in the indirect food additive would be treated as constituents.

Food packaging materials are examples of indirect additives that are complex and that often contain a number of substances, each of which is intended to have a specific physical or technical effect. For example, one type of plastic food wrap contains slip agents and antioxidants that are blended with polyolefin resin and incorporated into the final polyolefin film. All three of these substances would be considered to be additives, because they are all intended for use in the final food-contact preparation. Conversely, a chemical used in the manufacture of the polyolefin resin and remaining in the additive as an impurity resulting from an incomplete chemical reaction would be treated as a constituent.

The constituents approach takes into account the state of the art of scientific detection techniques. Although it generally is possible to detect or predict migration to food of at least one constituent from an additive used in a food-contact surface and although the number of migrating constituents which are detectable continually increases with advances in analytical methods, it is not currently possible to identify completely all the constituents that become components of food as a result of the use of an indirect additive. The detection, or prediction by sound scientific methods, of migration of one or more constituents of an intended substance is an indication that all of its ingredients may become components of food to some extent, however slight.

The constituents approach also recognizes that the only practical way for the agency to ensure that constituents of the indirect additive, which become components of food, do not exceed safe limits, is to issue a regulation that prescribes safe conditions of use for the indirect food additive as a whole, not merely for the migrating portions.

Two additives intentionally blended together for use in food, for food contact, or for imparting color, would remain additives; the physical mixing would not change one of the component additives into a constituent.

The focus under the constituents approach, as in *Monsanto*, is on the safety of the additive as a whole. FDA believes that, although it differs in construct from the *de minimis* migration approach discussed below, the constituents approach is supported by the reasoning in *Monsanto*.

2. *De minimis migration approach.* A second approach, somewhat different from the constituents approach, is based directly on the *Monsanto* decision. The court, recognizing the difficulties posed by a strict literal interpretation of the statute, declared that "there is latitude inherent in the statutory scheme [of the Federal Food, Drug, and Cosmetic Act] to avoid literal application of the statutory definition of 'food additive' in those *de minimis* situations that, in the informed judgment of the Commissioner, clearly present no public health or safety concern." *Id.* at 954.

The *Monsanto* decision permits the Commissioner to exempt from treatment as indirect food additives chemicals that migrate at low levels into food, if the migration of that particular chemical at the level in question poses no threat to the public health. Under this decision, it appears that the Commissioner may also take the position that the Delany Clause is not triggered by the presence of a carcinogenic chemical that occurs in a noncarcinogenic direct food additive or color additive, if the agency can conclude that there is a reasonable certainty of no harm from the presence of the chemical. Under this narrow reading of *Monsanto*, called here for convenience the *de minimis* migration approach, FDA would set a fixed upper limit on the absolute amount of a carcinogenic chemical that could be present. The existence of "reasonable certainty of no harm" from the presence of that chemical is predicated on the fact that only a minute amount of it is present. That is, the risk from the *de minimis* migration of carcinogenic chemicals into food from an indirect additive (or the *de minimis* presence of such chemicals in a direct additive) is trivial because the amount of the chemical is so low, and the resulting potential human exposure to it is thus trivial.

A policy based on the *de minimis* migration approach as set forth here would be narrower than one based on the constituents approach. It would not permit the agency to approve the marketing of additives containing carcinogenic chemicals that are present in food in more than trivial amounts, even though the risk from the use of the additive falls below an acceptable upper limit as determined by an appropriate risk assessment evaluation. If the fixed upper limit of exposure to a compound (based on its concentration in a particular additive and its prevalence in other additives) is set relatively low, as *Monsanto* suggests it should be, then this policy would permit the continued use of very few additives with carcinogenic constituents and would result in few regulatory decisions that would differ from those that could be reached under the present policy.

3. *Sensitivity of the method (SOM) approach.* FDA believes that an approach analogous to that proposed for use in regulating the residues of carcinogenic drugs administered to food-producing animals may also justify a policy for regulating carcinogenic chemicals present in minor amounts in food additives and color additives that are not themselves carcinogenic.

A proviso in the Delaney Clause for chemical compounds administered to food-producing animals (21 U.S.C. 348(c)(3)(A), 360b(d)(1)(H), 376(b)(5)(B)) allows the use in such animals of a chemical that is a carcinogen, provided that no residue of the chemical is found in edible portions by methods prescribed or approved by FDA. If a compound for use in food-producing animals is a carcinogen, the agency has proposed procedures referred to as the SOM (see 44 FR 17070; March 20, 1979) governing the collection of data showing whether the proviso has been complied with; i.e., capable of showing what residues may safely be allowed to go undetected.

Applied to food additives and color additives, a policy based on the SOM approach would permit the Commissioner to decline to classify as an additive a carcinogenic chemical thought to be present in the additive, but undetectable by a specified method, as long as the risk of cancer posed by that concentration of the carcinogen fell below a certain "acceptable" or "insignificant" level. That is, the detection of a carcinogenic chemical becomes the ultimate inquiry. If the chemical cannot be detected and if its hypothetical presence below the detection level does not exceed an acceptable risk of cancer, the chemical need not be regulated as an additive.

The SOM approach is the narrowest of the three approaches described and would result in the least change from current policy.

C. Interpretation of the Delaney Clause

The Delaney Clause requires the disapproval of any food additive that has been shown to be a carcinogen in appropriate testing. It states:

> That no additive shall be deemed to be safe if it [the additive] is found to induce cancer when ingested by man or animal, or if it [the additive] is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal * * *
>
> 21 U.S.C. 348(c)(3)(A).

However, it does not state that an additive shall not be deemed safe if the additive "or any of the chemicals present in the additive" is found to induce cancer. Addition of the quoted language to 21 U.S.C. 348(c)(3)(A) would change the meaning of this provision. A natural reading of the language that does appear in the statute establishes that the Delaney Clause does not apply to a carcinogenic chemical in a food additive absent a finding, after appropriate tests, that the additive as a whole induces cancer. Similar reasoning would apply to the Delaney Clause in the color additive provisions of the act. (21 U.S.C. 376.)

The legislative histories of the Food Additives Amendment and Color Additive Amendments are silent on this question. However, the agency's contemporaneous interpretation of the Color Additive Amendments supports the interpretation of the Delaney Clause set forth above, as explained in the preamble to the D&C Green No. 6 regulation.

D. Proof of Safety Under the General Safety Clause

As discussed in Section III above, FDA believes that risk assessment may be appropriately used to determine whether, under the general safety clause, there is a reasonable certainty that no harm will result from the proposed use of the additive. The risk assessment techniques under consideration are similar to those used by the agency and discussed in its evaluation of the safety of D&C Green No. 6 published elsewhere in this issue of the Federal Register. Interested persons are referred to that discussion for an example of how a safety determination using risk assessment would proceed.

Because carcinogens vary widely in potency, and because human exposure to carcinogens usually occurs at levels several orders of magnitude below that at which compound-related human tumor incidence can be detected by scientific studies, it has been necessary for scientists to develop quantitative extrapolation procedures to estimate the levels of risk to humans of exposure to carcinogens at very low levels. Several quantitative risk assessment models such as the one-hit model (Ref. 5), the Crump modified multistage model (Ref. 6), and the linear proportional model (Ref. 7) are available to extrapolate animal bioassay data to human exposure. Any one of these models can be used to estimate the upper limits of potential risk created by exposure to the chemical. The agency has not determined which extrapolation model is the most appropriate one to use, and requests comments on this issue.

After relevant animal data have been generated and analyzed, an appropriate risk assessment procedure would then calculate an acceptable maximum exposure level to the chemical based on a suitable risk standard. This level would be calculated by extrapolating from an upper confidence limit of bioassay data, using procedures that would include an evaluation of pharmacodynamic data, including any human studies available, epidemiological evidence, and studies of the mechanism of action of the carcinogen. FDA is requesting comments on what risk standard would be appropriate for use in implementing the policy.

Once FDA has determined a maximum acceptable level of exposure to a carcinogenic chemical, the agency would then consider whether the amount of actual exposure to the chemical from food additives and color additives is within the acceptable level. If necessary, the agency would develop specifications for such chemicals in individual additive regulations, taking into account total estimated exposures.

Under the general safety clause, an additive must meet the agency's toxicological requirements for food additives and color additives. The risk assessment procedures discussed in this advance notice would not modify currently applied requirements under the general safety clause other than to provide a procedure for determining whether a noncarcinogenic additive that contains minor amounts of a proven carcinogenic chemical is safe. The risk assessment procedure would provide a method for estimating the levels of such chemicals that meet the general safety clause standard of safety. The upper limit of acceptable exposure would be determined by carcinogen potency and risk extrapolation by the best current scientific methods available. FDA believes that any risk assessment procedure should yield such low acceptable levels that nothing but minor levels of carcinogenic chemicals would be able to pass the screen.

Risk assessment of carcinogens is currently not completely rigorous from a biological viewpoint, but it does provide, at minimum, a scientifically based means to evaluate the health concerns of a series of chemicals. Its weakness stems from the substantial assumptions which are employed. However many of these same assumptions are endemic to toxicology evaluations in general. In order to calculate a given risk level, a dose-response relationship is extrapolated to doses several orders of magnitude lower than the tested dose. Furthermore, the risk assessment assumes that humans will be no more sensitive to the carcinogen than were the most sensitive animals tested (Ref. 8).

If the policy is implemented, it is FDA's current view that the risk assessment procedure should be conservative to compensate for the weakness in scientific rigor, should use a model that is likely to overestimate the

risk, and should contain a low risk
lard.

.A believes that this general policy is a sensible, scientific means of limiting the circumstances in which it will be necessary for the government to act to ban the use of a food additive or color additive, without compromising the public health protection afforded by the act. This policy, if finally adopted, is intended to be implemented solely in those instances (e.g., in the case of D&C Green No. 6) where data demonstrate that there is a reasonable certainty that no harm will result from the use of an additive that contains a carcinogenic chemical.

E. Alternative Policies

As this advance notice explains, FDA is considering formalizing an approach that will assure the safe use of food additives and color additives that contain minor amounts of carcinogenic chemicals, and requests comments on that approach. In considering how best to develop a policy on this issue, the agency has followed the line of reasoning set forth in this notice. The agency recognizes, however, that a number of different approaches might also deal with the problem, and requests that interested persons submit any
native policies to FDA as
ments.

FDA is also aware that the three approaches (constituents, *de minimis* migration, and sensitivity of the method (SOM)) discussed above support regulatory decisions of varying breadth. In general, if used alone the constituents approach would be the broadest, and the SOM approach would be the narrowest. The agency requests comments on which of the three approaches or combination of approaches would be the most workable from a legal, scientific, and procedural perspective. Further, FDA is interested in receiving comments on any other approaches—either based on, or different from, the three that are discussed in this advance notice.

Finally, FDA would like to receive comments on whether an across-the-board rule incorporating the suggested approaches should be issued or whether, instead, the agency should continue handling carcinogenic chemicals in food and color additives on a case-by-case basis.

An agency is free to choose between evolving an approach to a regulatory problem through a series of individual
ions, on the one hand, and issuing
neral regulation to be applied in
ecific cases, on the other. Both methods have advantages and disadvantages, and the choice of which to use is generally within the discretion of the agency. See *Securities and Exchange Comm.* v. *Chenery Corp.*, 332 U.S. 194 (1947); *NLRB* v. *Bell Aerospace Co.*, 416 U.S. 267, 294 (1974); *Chisholm* v. *FCC*, 538 F.2d 348, 364–366, *cert. denied*, 429 U.S. 890 (1976). In this advance notice, FDA requests comments on how its discretion should be exercised in developing an approach to the handling of carcinogenic chemicals in food and color additives. The agency has a number of such issues before it in addition to D&C Green No. 6, on which there is a pressing need to take action. The agency does not view the existence of an ongoing rulemaking proceeding as posing any bar to specific regulatory actions. The agency emphasizes that it will continue to make regulatory decisions on the food and color additives that come before it in the ordinary course of business. In making such decisions, the agency may use one or more of the approaches discussed herein, as appropriate.

V. Economic and Environmental Impact

The risk assessment policy under consideration may have economic consequences for individual industries. In some cases, the policy should produce positive economic benefits that would result from preventing a ban of an additive containing a carcinogenic constituent. The agency is not aware of any significant negative economic effects of this policy. If proposed regulations are to be issued after FDA considers the comments received on this advance notice, then FDA will be required by Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96–354) to access the economic consequences. However, the agency does not now possess the data that would permit a detailed assessment of the economic impact. Therefore, the agency requests that interested persons submit information that will aid the agency in making an economic impact assessment.

FDA also is required to consider the potential environmental effects of the actions to be proposed. The agency believes that issuance of any regulations as a result of this advance notice would not significantly affect the quality of the human environment. FDA requests comments on the potential environmental consequences of implementing the policy discussed in this notice.

References

The following information has been placed on display in the Dockets Management Branch, Food and Drug Administration, and may be seen from 9 a.m. to 4 p.m., Monday through Friday.

1. Tomatis, L., "The Value of Long-Term Testing for Implementation of Primary Prevention," *in* "Origins of Human Cancer," Edited by Hiatt, H. H., et al., Cold Spring Harbor Laboratory, NY, pp. 1339–1357, 1977.

2. Occupational Safety and Health Administration, Final rule to add 29 CFR Part 1990, "Identification, Classification, and Regulation of Potential Occupational Carcinogens," Federal Register, January 22, 1980 (45 FR 5001).

3. Griesemer, R. A. and C. Cueto, Jr., "Toward a Classification Scheme for Degrees of Experimental Evidence for the Carcinogenicity of Chemicals for Animals," *in* "Molecular and Cellular Aspects of Carcinogen Screening Tests," Edited by Montesano, R., et al., International Agency for Research on Cancer, Lyon, France, pp. 259–281, 1980.

4. National Toxicology Program, Fiscal Year 1980 Annual Plan, Washington, DC: Department of Health, Education, and Welfare, Public Health Service, 1980.

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6a. Crump, K. S., "An Improved Procedure for Low-Dose Carcinogenic Risk Assessment From Animal Data," *Journal of Environmental Pathology and Toxicology*, in press.

b. Environmental Protection Agency, Notice of Availability: Water Quality Criteria Documents, Federal Register, Appendix C, November 28, 1980 (45 FR 79318, 79347).

7a. Hoel, D. G., et al., "Estimation of Risks of Irreversible, Delayed Toxicity," *Journal of Toxicology and Environmental Health*, 1:133–151, 1975.

b. Food and Drug Administration, Proposal to amend 21 CFR Parts 70, 500, 514 and 571, "Chemical Compounds in Food-Producing Animals," Federal Register, March 20, 1979 (44 FR 17070).

c. Gaylor, D. W. and R. L. Kodell, "Linear Interpolation Algorithm for Low Dose Risk Assessment of Toxic Substances," *Journal of Environmental Pathology and Toxicology*, 4:305–312, 1980.

8a. Williams, G. M., A. Leff, and J. H. Weisburger, "A Species to Species Comparison of Carcinogenicity Data, with Human Extrapolation," Final Report to the National Institute of Environmental Health Sciences (Contract No. 1–ES–6–2130), July 1978.

b. National Academy of Sciences, "Pest Control: An Assessment of Present and Alternative Technologies," Contemporary Pest Control Practices and Prospects, Vol. I, pp. 54–101, 1975.

c. Crouch, E. and R. Wilson, "Interspecies Comparison of Carcinogenic Potency," *Journal of Toxicology and Environmental Health*, 5:1095–1118, 1979.

Interested persons may, on or before July 1, 1982, submit to the Dockets

ATTACHMENT C

§ 173.385 Sodium methyl sulfate.

Sodium methyl sulfate may be present in pectin in accordance with the following conditions.

(a) It is present as the result of methylation of pectin by sulfuric acid and methyl alcohol and subsequent treatment with sodium bicarbonate.

(b) It does not exceed 0.1 percent by weight of the pectin.

§ 173.395 Trifluoromethane sulfonic acid.

Trifluoromethane sulfonic acid has the empirical formula CF_3SO_3H (CAS Reg. No. 1493-13-6). The catalyst (Trifluoromethane sulfonic acid) may safely be used in the production of cocoa butter substitute from palm oil (1-palmitoyl-2-oleoyl-3-stearin) (see § 184.1259 of this chapter) in accordance with the following conditions:

(a) The catalyst meets the following specifications:

Appearance. Clear liquid.
Color. Colorless to amber.
Neutralization equivalent. 147-151.
Water. 1 percent maximum.
Fluoride ion. 0.03 percent maximum.
Heavy metals (as Pb). 30 parts per million maximum.
Arsenic (as As). 3 parts per million maximum.

(b) It is used at levels not to exceed 0.2 percent of the reaction mixture to catalyze the directed esterification.

(c) The esterification reaction is quenched with steam and water and the catalyst is removed with the aqueous phase. Final traces of catalyst are removed by washing batches of the product three times with an aqueous solution of 0.5 percent sodium bicarbonate.

(d) No residual catalyst may remain in the product at a detection limit of 0.2 part per million fluoride as determined by the method described in "Offical Methods of Analysis of the Association of Official Analytical Chemists," sec. 25.046, 12th Ed. (1975), which is incorporated by reference. Copies are available from the Division of Food and Color Additives, Bureau of Foods (HFF-330), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, or available for inspection at the Office of the Federal Register, 1100 L St. NW., Washington, DC 20408.

[43 FR 54237, Nov. 11, 1978, as amended at 47 FR 11639, Mar. 19, 1982]

PART 174—INDIRECT FOOD ADDITIVES: GENERAL

§ 174.5 General provisions applicable to indirect food additives.

(a) Regulations prescribing conditions under which food additive substances may be safely used predicate usage under conditions of good manufacturing practice. For the purpose of this part and Parts 175, 176, and 177 of this chapter, good manufacturing practice shall be defined to include the following restrictions:

(1) The quantity of any food additive substance that may be added to food as a result of use in articles that contact food shall not exceed, where no limits are specified, that which results from use of the substance in an amount not more than reasonably required to accomplish the intended physical or technical effect in the food-contact article; shall not exceed any prescribed limitations; and shall not be intended to accomplish any physical or technical effect in the food itself, except as such may be permitted by regulations in Parts 170 through 189 of this chapter.

(2) Any substance used as a component of articles that contact food shall be of a purity suitable for its intended use.

(b) The existence in the Subchapter B of a regulation prescribing safe conditions for the use of a substance as an article or component of articles that contact food shall not be construed to relieve such use of the substance or article from compliance with any other provision of the Federal Food, Drug, and Cosmetic Act. For example, if a regulated food-packaging material were found on appropriate test to impart odor or taste to a specific food product such as to render it unfit within the meaning of section 402(a)(3) of the act, the regulation would not be construed to relieve such use from compliance with section 402(a)(3).

(c) The existence in this Subchapter B of a regulation prescribing safe conditions for the use of a substance as an

article or component of articles that contact food shall not be construed as implying that such substance may be safely used as a direct additive in food.

(d) Substances that under conditions of good manufacturing practice may be safely used as components of articles that contact food include the following, subject to any prescribed limitations:

(1) Substances generally recognized as safe in or on food.

(2) Substances generally recognized as safe for their intended use in food packaging.

(3) Substances used in accordance with a prior sanction or approval.

(4) Substances permitted for use by regulations in this part and Parts 175, 176, 177, 178 and § 179.45 of this chapter.

(Sec. 409, 72 Stat. 1785, 1786, as amended (21 U.S.C. 348, 371))

[42 FR 14534, Mar. 15, 1977]

PART 175—INDIRECT FOOD ADDITIVES: ADHESIVE COATINGS AND COMPONENTS

Subpart A—[Reserved]

Subpart B—Substances for Use Only as Components of Adhesives

Sec.

Subpart C—Substances for Use as Components of Coatings

AUTHORITY: Secs. 409, 701, 52 Stat. 1055-1056 as amended, 72 Stat. 1785-1788 as amended (21 U.S.C. 348), unless otherwise noted.

SOURCE: 42 FR 14534, Mar. 15, 1977, unless otherwise noted.

Subpart A—[Reserved]

Subpart B—Substances for Use Only as Components of Adhesives

§ 175.105 Adhesives.

(a) Adhesives may be safely used as components of articles intended for use in packaging, transporting, or holding food in accordance with the following prescribed conditions:

(1) The adhesive is prepared from one or mor of the optional substances named in paragraph (c) of this section, subject to any prescribed limitations.

(2) The adhesive is either separated from the food by a functional barrier or used subject to the following additional limitations:

(i) *In dry foods.* The quantity of adhesive that contacts packaged dry food shall not exceed the limits of good manufacturing practice.

(ii) *In fatty and aqueous foods.* (a) The quantity of adhesive that contacts packaged fatty and aqueous foods shall not exceed the trace amount at seams and at the edge exposure between packaging laminates that may occur within the limits of good manufacturing practice.

(b) Under normal conditions of use the packaging seams or laminates will remain firmly bonded without visible separation.

(b) To assure safe usage of adhesives, the label of the finished adhesive container shall bear the statement "food-packaging adhesive".

(c) Subject to any limitation prescribed in this section and in any other regulation promulgated under section 409 of the act which prescribes safe conditions of use for substances that may be employed as constituents of adhesives, the optional substances used in the formulation of adhesives may include the following:

(1) Substances generally recognized as safe for use in food or food packaging.

ATTACHMENT D

THE SOCIETY OF THE PLASTICS INDUSTRY
INCORPORATED

SPI

FOOD PACKAGING MATERIALS BULLETIN

"GOOD MANUFACTURING PRACTICES" CRITERIA FOR PLASTIC RESINS "PRIOR SANCTIONED" UNDER THE FOOD ADDITIVES AMENDMENT OF 1958

We suggest that you keep this bulletin among your permanent reference material.

(March, 1963)

PREFACE

This Bulletin has been prepared by the Food Packaging Materials Committee of The Society of the Plastics Industry, Inc. in the hope that it will provide helpful information in a compact form to those who supply plastics materials for food packaging and processing applications. A great deal of the credit for this work is due the Technical Information Subcommittee of the Food Packaging Materials Committee for the more than two years of effort that went into preparation of this publication. The data included was screened and placed in its present form by the Subcommittee after all known producers of the plastics covered were painstakingly contacted and afforded a full opportunity to supply information about their products. Thereafter this material was circulated in draft form and ultimately finalized as it now appears.

We also acknowledge with gratitude the cooperation given the Society by the Department of Agriculture in supplying the two letters reproduced herein attesting to the acceptability of the listed materials for use in Federally inspected meat and poultry plants.

It is believed that this Bulletin will prove a valuable reference for all those making food packaging or processing materials or components thereof. Its publication is not intended however, as any express or implied warranty as to the general fitness of the products covered for all specific uses; this is a matter which must necessarily be left to case-by-case determination dependent on the nature of each intended application.

The Society of the Plastics
Industry, Inc.

"GOOD MANUFACTURING PRACTICES" CRITERIA FOR PLASTIC RESINS "PRIOR SANCTIONED" UNDER THE FOOD ADDITIVES AMENDMENT OF 1958

On July 22, 1960, the Food and Drug Administration, by means of a letter directed to our Counsel, reaffirmed the "prior sanctioned" status of the major plastic polymers now in use in food contact applications, and not specifically covered by Food Additives Regulations. This landmark letter had this effect as a result of its reference to an article entitled "Food Packaging" by Dr. A. J. Lehman, Chief of FDA's Division of Pharmacology, which appeared in a widely disseminated publication in 1956[1]. In the introduction to this article Dr. Lehman stated:

> "That class of materials loosely referred to as plastics are currently being exploited widely for food-packaging purposes..... Our purpose now is to discuss these new developments and bring up-to-date our listing of materials for food packaging which we have reason to regard as acceptable."

The reaffirmation of the status of these materials is of vital significance to the plastics industry because materials recognized as "prior sanctioned" are exempt from the coverage of the Food Additives Amendment of 1958 and, hence, clearance of these substances by means of Food Additives Regulations is not required. For the information of those who may not have seen copies of the FDA letter, a copy is included in this publication. Reference to the letter, as well as reference to the Lehman article upon which it comments, will demonstrate that the approvals or "prior sanctions" are limited by the condition that the "resins" covered be made "in accordance with good manufacturing practice, for use in food" applications.

Since criteria for determining whether a polymer on the Lehman List has been made in accordance with "good manufacturing practice" have not been available in a single source heretofore, the SPI Food Packaging Materials Committee has collected data from which it has been able to compile definitions based on materials characteristics so that the industry in general may have a more concrete concept of what is involved insofar as individual polymers are concerned. The listings and descriptions in this publication are designed for this purpose.

As will be noted, the listings herein deal only with those basic resins or polymers covered in the Lehman List.[2] There are undoubtedly other materials which are "prior sanctioned" by virtue of letters sent to individual companies prior to the enactment of the Food Additives Amendment. This publication does not purport to cover other such materials, nor is it intended to encompass the adjuvants or optional ingredients which may be employed in finished or intermediate formulations of products made from the Lehman List, or any other substances.

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[1] Lehman, A. J., Quart. Bull. Assn. Food and Drug Officials of the United States, XX, No. 4, p. 159-168, October, 1956.

[2] It should be noted that the following resins originally listed by Dr. Lehman are not included in the coverage of this publication:

- Condensate dimethyl terephthelate and ethylene glycol (Regulation 121.2524)
- Polyvinyl alcohol (Petition FAP No. 209)
- Polyethylene (high and low pressure types)(Regulations 121.2508 and 2510)
- Regenerated cellulose (Regulation 121.2507)
- Terephthalic acid-ethylene glycol copolymer (Regulation 121.2524)
- Styrene butadiene copolymer (Petition FAP No. 602 and 662)
- Styrene isobutylene
- Polystyrene (normal and rubber modified)(Petitions FAP Nos. 602 and 662)

All of these polymers with the exception of styrene isobutylene are the subject of new Food Additives regulations or pending petitions for regulations so that it appeared inappropriate and unnecessary to further define "good manufacturing practices" for them. In those cases where Petitions are in the pending status, the materials involved remain "prior sanctioned" of course. The same may be said to be true as to those now covered by Regulations since the Food and Drug Administration has not exercised its power to withdraw any such sanctions.

Generally speaking, such adjuvants or optional ingredients may be employed provided they are among those considered "prior sanctioned", "generally recognized as safe", or for which an appropriate Food Additives Regulation exists. Likewise, if it can be concluded that a substance may not "reasonably be expected to become a component of food," *i.e.* it will not transfer from a plastic to food, it may be used in conjunction with any of the polymers.

The following paragraphs describe the end characteristics of significance to a determination of whether the resins or polymers covered are made in accordance with good manufacturing practice for food packaging or processing applications and are, therefore, "prior sanctioned."

1. **Polyvinyl Butyral**
   Viscosity is 2-500 cps, determined as follows:

Classification by Viscosity Level and Hydroxyl Content				Solvent Concentration
HiV-HiH	HV-LoH	LV-HH	LV-LH	
50-500 cps	–	up to 50 cps	–	Methanol 7.5%
20-200	–	up to 20	–	Methanol 6.0%
50-500	100-500	up to 50	up to 100	Ethanol 5.0%

   Up to 30% unreacted polymeric hydroxyl (calculated as polyvinyl alcohol) is generally present and permits crosslinking via phenol- or urea-formaldehyde resins or by other means. Some grades contain up to 30% of polyvinyl acetate, as determined by ASTM Method D-1396-58.

2. **Polyvinyl Chloride**
   Maximal volatility is not over 3.0% (1 hr. at 105°C) and inherent viscosity not less than 0.35 as determined by ASTM D-1243-60, Method A.

3. **Polyvinyl Acetate**
   Maximal volatility is not over 3.0% (45 min. at 135°C) and viscosity not less than 1.35 centipoise at 20°C in benzene solution (4.3 gm. resin/50 ml.).

4. **Polyvinyl Chloride-Acetate**
   Maximal volatility is not over 3.0% (1 hr. at 105°C) and inherent viscosity not less than 0.30 as determined by ASTM D-1243-60, Method A.

5. **Polyvinylidene Chloride**
   Viscosity is within the range of 0.50-1.50 centipoise at 120°C (2% solution in o-dichlorobenzene [which is Dow BS-SB-B method in Appendix A. Questions on the method, especially those on item 5 "Viscometer Calibration" may be referred directly to Dow]).

6. **Cellulose Acetate**
   Maximal free acid of cellulose ester "flake" after washing and drying is no more than 0.02% by weight (ASTM D-817-57)[3].

7. **Butadiene-Acrylonitrile Synthetic Rubber**
   In plastics, butadiene-acrylonitrile (as is butadiene styrene) is used to modify or "toughen" other polymers, principally polystyrene. The rubber's contribution to the resultant plastic depends on th molecular weight and monomer ratio of the rubber, measurable by ASTM D-1646-59T and Kjeldahl determination for nitrogen content (indicative of bound acrylonitrile in the rubber) respectively. There need be no restrictions on these factors because the commercially available butadiene-acrylonitrile rubbers have not significant extractables.

[3] The ester "flake" is never used other than as a component of a formulation, all of the components of which must someway be cleared or exempt from the Food Additives Amendment as suggested in the opening paragraphs of this article.

The above limitations are believed to apply to cellulose acetobutyrate and cellulose proprionate; as to cellulose nitrate, a nitrogen content of 10.9% to 12.2% was prior sanctioned for food packaging purposes.

A

8. **Ethyl Cellulose**
Viscosity is within the range of 3-5000 cps (25°C, 5% solution in 80:20 toluene: ethanol [ASTM D-914-50]). Ethoxyl content is within the range 43-51.5%.

9. **Rubber Hydrochloride**
Chlorine content is within the range of 30-32%. One mil films of the unmodified product are to have a volatile content of no more than 0.5% (4 hrs. at 75°C) and a hexane extract of no more than 2.0% (2 hrs. reflux).

10. **Polyester Resin-Ethylene Terephthalate and Ethylene Isophthalate**
Maximum volatility is no more than 0.5% when heated at 60°C for 12 hrs. at a pressure less than 10 mm of mercury. Hexane-soluble content (2 hrs. reflux) is less than 1.0%.

11. **Butadiene-Acrylonitrile-Styrene**
Total residual monomer is primarily styrene and is less than 1.0%, determined by the SPI method (Appendix B)* for rubber modified polystyrenes, using chloroform as solvent.

12. **Polymer of 2-Chloro-Butadiene**
Maximal volatility of the dried coating is not over 0.5% (4 hrs. at 75°C) and hexane extraction is not over 2.0% (2 hrs. reflux).

13. **Polymer of Melamine-Formaldehyde**
The resin is cured at selected time-temperature conditions which will evaporate solvents and produce insolubility by crosslinking.

14. **Polymer of Urea-Formaldehyde**
(Includes unmodified resins, and those reacted with selected amines, to develop solubility in water sufficient for application purposes.) The resin is cured at selected time-temperature conditions which will evaporate solvents and produce insolubility by crosslinking.

15. **Polymer (Fluid) of Dimethylpolysiloxane**
The polymer is clear, has a maximal acid number not exceeding 0.5 (MIL-S-21568A, paragraph 4.6.8) and has the following additional physical properties:

Nominal Viscosity (Centistokes)	Maximum Volatility (%) (48 hrs. at 200°C) (ASTM D-972-48T)	Maximal Color (ASTM D-1209-54)
350*	2	40

*Prior sanctions for higher viscosity types are believed to exist.

*The shaking-time requirement in Section 6b (page iv) should be extended from 3 to 24 hours to insure complete removal of styrene monomer.