

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration

21 CFR Part 176

[Docket No. 95F-0065]

**Indirect Food Additives: Paper and Paperboard Components**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Final rule.

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**SUMMARY:** The Food and Drug Administration (FDA) is amending the food additive regulations to provide for the safe use of polyamidoamine-ethyleneimine-epichlorohydrin resin for use as a retention aid in the manufacture of paper and paperboard intended for use in contact with aqueous and fatty food. This action is in response to a petition filed by BASF Corp.

**DATES:** This rule is effective [*insert date of publication in the Federal Register*]. Submit written objections and requests for a hearing by [*insert date 30 days after date of publication in the Federal Register*].

**ADDRESSES:** Submit written objections to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

**FOR FURTHER INFORMATION CONTACT:** Vivian M. Gilliam, Center for Food Safety and Applied Nutrition (HFS-215), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-418-3094.

**SUPPLEMENTARY INFORMATION:**

**I. Background**

In a notice published in the **Federal Register** of April 13, 1995 (60 FR 18845), FDA announced that a food additive petition (FAP 5B4452) had been filed by BASF Corp., 1609 Biddle

Ave., Wyandotte, MI 48192. The petition proposed to amend the food additive regulations in § 176.170 *Components of paper and paperboard in contact with aqueous and fatty foods* (21 CFR 176.170) to provide for the safe use of a polyamide-ethyleneimine-epichlorohydrin resin as a component of paper and paperboard in contact with aqueous and fatty food.

Subsequent to the filing of the petition, the petitioner obtained a new Chemical Abstracts Service (CAS) Registry number for the additive under the following name: Polyamidoamine-ethyleneimine-epichlorohydrin resin prepared by reacting hexanedioic acid, *N*-(2-aminoethyl)-1,2-ethanediamine, (chloromethyl)oxirane, ethyleneimine (aziridine), and polyethylene glycol, partly neutralized with sulfuric acid, CAS Reg. No. 167678-45-7. In this document, polyamidoamine-ethyleneimine-epichlorohydrin resin will be referred to as the additive.

In its evaluation of the safety of this additive, FDA has reviewed the safety of the additive itself and the chemical impurities that may be present in the additive resulting from its manufacturing process. Although the additive itself has not been shown to cause cancer, it has been found to contain minute amounts of unreacted ethylene oxide, 1,4-dioxane, epichlorohydrin, and ethyleneimine, which are carcinogenic impurities resulting from the manufacture of the additive. Residual amounts of reactants and manufacturing aids, such as ethylene oxide, 1,4-dioxane, epichlorohydrin, and ethyleneimine are commonly found as contaminants in chemical products, including food additives.

## **II. Determination of Safety**

Under the general safety standard of section 409(c)(3)(A) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 348(c)(3)(A)), a food additive cannot be approved for a particular use unless a fair evaluation of the data available to FDA establishes that the additive is safe for that use. FDA's food additive regulations (21 CFR 170.3(i)) define safe as "a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use."

The food additives anticancer, or Delaney, clause of section (409(c)(3)(A)) of the act provides that no food additive shall be deemed safe if it is found to induce cancer when ingested by man or animal. Importantly, however, the Delaney clause applies to the additive itself and not to impurities in the additive. That is, where an additive itself has not been shown to cause cancer, but contains a carcinogenic impurity, the additive is properly evaluated under the general safety standard using risk assessment procedures to determine whether there is a reasonable certainty that no harm will result from the intended use of the additive. (*Scott v. FDA*, 728 F.2d 322 (6th Cir. 1984).)

### **III. Safety of Petitioned Use of the Additive**

FDA estimates that the petitioned use of the additive, polyamidoamine-ethyleneimine-epichlorohydrin resin, will result in exposure to no greater than 650 parts per billion (ppb) of the additive in the daily diet (3 kilograms (kg)) or an estimated daily intake (EDI) of 2.0 milligrams per person per day (mg/p/d) (Ref. 1).

FDA does not ordinarily consider chronic toxicological studies to be necessary to determine the safety of an additive whose use will result in such low exposure levels (Ref. 2), and the agency has not required such testing here. However, the agency has reviewed the available toxicological data on the additive and concludes that the estimated small dietary exposure resulting from the petitioned use of the additive is safe.

FDA has evaluated the safety of this additive under the general safety standard, considering all available data and using risk assessment procedures to estimate the upper-bound limit of lifetime human risk presented by ethylene oxide, 1,4-dioxane, epichlorohydrin, and ethyleneimine, the carcinogenic chemicals that may be present as impurities in the additive. The risk evaluation of ethylene oxide, 1,4-dioxane, epichlorohydrin, and ethyleneimine has two aspects: (1) Assessment of the exposure to the impurities from the petitioned use of the additive; and (2) extrapolation of the risk observed in the animal bioassay to the conditions of exposure to humans.

### A. Ethylene oxide

FDA has estimated the exposure to ethylene oxide from the petitioned use of the additive as a component of paper and paperboard to be no more than 0.7 parts per trillion (pptr) of the daily diet (3 kg), or 2 nanograms (ng)/p/d (Ref. 1). The agency used data from a carcinogenesis bioassay, in female rats, on ethylene oxide conducted by the Institute of Hygiene, University of Mainz, Germany (Ref. 3), to estimate the upper-bound limit of lifetime human risk from exposure to this chemical resulting from the petitioned use of the additive. The authors reported that the test material caused significantly increased incidence of squamous cell carcinomas of the forestomach and carcinomas in situ of the glandular stomach.

Based on the agency's estimate that exposure to ethylene oxide will not exceed 2 ng/p/d, FDA estimates that the upper-bound limit of lifetime human risk from the petitioned use of the subject additive is  $3.7 \times 10^{-9}$ , or 3.7 in a billion (Ref. 4). Because of the numerous conservative assumptions used in calculating the exposure estimate, the actual lifetime-averaged individual exposure to ethylene oxide is likely to be substantially less than the estimated exposure, and therefore, the probable lifetime human risk would be less than the upper-bound limit of lifetime human risk. Thus, the agency concludes that there is reasonable certainty that no harm from exposure to ethylene oxide would result from the petitioned use of the additive.

### B. 1,4-Dioxane

FDA has estimated the exposure to 1,4-dioxane from the petitioned use of the additive as a component of paper and paperboard to be no more than 31 pptr of the daily diet (3 kg), or 94 ng/p/d (Ref. 1). The agency used data from a carcinogenesis bioassay, in mice and rats, on 1,4-dioxane, conducted by the National Cancer Institute (Ref. 5), to estimate the upper-bound limit of lifetime human risk from exposure to this chemical resulting from the petitioned use of the additive. The authors reported that the test material induced squamous cell carcinomas of the nasal turbinates in male and female rats, hepatocellular adenomas in female rats, and hepatocellular carcinomas in male and female mice.

Based on the agency's estimate that exposure to 1,4-dioxane will not exceed 94 ng/p/d, FDA estimates that the upper-bound limit of lifetime human risk from the petitioned use of the subject additive is  $3.4 \times 10^{-9}$ , or 3.4 in a billion (Ref. 4). Because of the numerous conservative assumptions used in calculating the exposure estimate, the actual lifetime-averaged individual exposure to 1,4-dioxane is likely to be substantially less than the estimated exposure, and therefore, the probable lifetime human risk would be less than the upper-bound limit of lifetime human risk. Thus, the agency concludes that there is reasonable certainty that no harm from exposure to 1,4-dioxane would result from the petitioned use of the additive.

### *C. Epichlorohydrin*

FDA has estimated the exposure to epichlorohydrin from the petitioned use of the additive as a component of paper and paperboard to be no more than 1.3 pptr of the daily diet (3 kg), or 4 ng/p/d (Ref. 1). The agency used data from a carcinogenesis bioassay, in male rats, on epichlorohydrin conducted by Konishi et al. (Ref. 6), to estimate the upper-bound limit of lifetime human risk from exposure to this chemical resulting from the petitioned use of the additive. The authors reported that the test material caused increased incidences of forestomach hyperplasia, papillomas, and carcinomas in the rats.

Based on the agency's estimate that exposure to epichlorohydrin will not exceed 4 ng/p/d, FDA estimates that the upper-bound limit of lifetime human risk from the petitioned use of the subject additive is  $1.9 \times 10^{-10}$ , or 1.9 in 10 billion (Ref. 4). Because of the numerous conservative assumptions used in calculating the exposure estimate, the actual lifetime-averaged individual exposure to epichlorohydrin is likely to be substantially less than the estimated exposure, and therefore, the probable lifetime human risk would be less than the upper-bound limit of lifetime human risk. Thus, the agency concludes that there is reasonable certainty that no harm from exposure to epichlorohydrin would result from the petitioned use of the additive.

#### *D. Ethyleneimine*

FDA has estimated the exposure to ethyleneimine from the petitioned use of the additive as a component of paper and paperboard to be no more than 0.03 pptr of the daily diet (3 kg), or 0.1 ng/p/d (Ref. 1). The agency used data from a carcinogenesis bioassay, in mice, on ethyleneimine conducted by Innes et al. (Ref. 7), to estimate the upper-bound limit of lifetime human risk from exposure to ethyleneimine resulting from the petitioned use of the additive. The authors reported that the test material caused significantly increased incidence of lung and liver tumors in both male and female mice.

Based on the agency's estimate that exposure to ethyleneimine will not exceed 0.1 ng/p/d, FDA estimates that the upper-bound limit of lifetime human risk from the petitioned use of the subject additive is  $3.2 \times 10^{-8}$ , or 32 in a billion (Ref. 4). Because of the numerous conservative assumptions used in calculating the exposure estimate, the actual lifetime-averaged individual exposure to ethyleneimine is likely to be substantially less than the estimated exposure, and therefore, the probable lifetime human risk would be less than the upper-bound limit of lifetime human risk. Thus, the agency concludes that there is reasonable certainty that no harm from exposure to ethyleneimine would result from the petitioned use of the additive.

#### *E. Need for Specifications*

The agency also has considered whether specifications are necessary to control the amount of ethylene oxide, 1,4-dioxane, epichlorohydrin, and ethyleneimine as impurities in the polyamidoamine-ethyleneimine-epichlorohydrin resin. The agency finds that specifications are not necessary for the following reasons: (1) Because of the low level at which ethylene oxide, 1,4-dioxane, epichlorohydrin, and ethyleneimine may be expected to remain as impurities following production of the additive, the agency would not expect the impurities to become components of food at other than extremely low levels; and (2) the upper-bound limits of lifetime human risk from exposure to ethylene oxide, 1,4-dioxane, epichlorohydrin, and ethyleneimine are very low, 3.7 in a billion, 3.4 in a billion, 1.9 in 10 billion, and 32 in a billion, respectively.

#### **IV. Conclusion**

FDA has evaluated data in the petition and other relevant material. Based on this information, the agency concludes that the petitioned use of the additive as a retention aid in the manufacture of paper and paperboard intended for use in contact with aqueous and fatty food is safe, and that the additive will achieve its intended technical effect. Therefore, the agency concludes that the regulations in § 176.170 should be amended as set forth below.

In accordance with § 171.1(h) (21 CFR 171.1(h)), the petition and the documents that FDA considered and relied upon in reaching its decision to approve the petition are available for inspection at the Center for Food Safety and Applied Nutrition by appointment with the information contact person listed above. As provided in § 171.1(h), the agency will delete from the documents any materials that are not available for public disclosure before making the documents available for inspection.

#### **V. Environmental Impact**

The agency has carefully considered the potential environmental effects of this action. FDA has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

#### **VI. Paperwork Reduction Act of 1995**

This final rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

#### **VII. Objections**

Any person who will be adversely affected by this regulation may at any time file with the Dockets Management Branch (address above) written objections by *[insert date 30 days after date*

of publication in the **Federal Register**]. Each objection shall be separately numbered, and each numbered objection shall specify with particularity the provisions of the regulation to which objection is made and the grounds for the objection. Each numbered objection on which a hearing is requested shall specifically so state. Failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held. Failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. Three copies of all documents are to be submitted and are to be identified with the docket number found in brackets in the heading of this document. Any objections received in response to the regulation may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

### VIII. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Memorandum from the Chemistry Review Team (HFS-246) to the Division of Petition Control (HFS-215) entitled "FAP 5B4452, BASF Corp. Polyamide-ethyleneimine-epichlorohydrin resin, Polymin SKA, as a retention agent in the production of paper. Memorandum of correction," dated October 22, 1997.

2. Kokoski, C. J., "Regulatory Food Additive Toxicology," in *Chemical Safety Regulation and Compliance*, edited by F. Homburger, J. K. Marquis, and published by S. Karger, New York, NY, pp. 24-33, 1985.

3. Dunkelberg, H., "Carcinogenicity of Ethylene Oxide and 1,2-Propylene Oxide Upon Intra-gastric Administration to Rats," *British Journal of Cancer*, 46: pp. 924-933, 1982.

4. Memorandum from the Division of Petition Control (HFS-215) to the Executive Secretary, Quantitative Risk Assessment Committee (QRAC) (HFS-308) entitled “Estimation of upper-bound limit of lifetime risk from ethyleneimine (EI), epichlorohydrin (ECH), ethylene oxide (EO), and 1,4-dioxane (DX), FAP 5B4452 (BASF Corp.),” dated October 5, 1999.

5. “Bioassay of 1,4-Dioxane for Possible Carcinogenicity,” National Cancer Institute, NCI-CG-TR-80, 1978.

6. Konishi, Y. et al., “Forestomach Tumors Induced by Orally Administered Epichlorohydrin in Male Wistar Rats,” *Gann* 71:922-923, 1980.

7. Innes, J. R. M. et al., “Bioassay of Pesticide and Industrial Chemicals for Tumorigenicity in Mice: A Preliminary Note,” *Journal of the National Cancer Institute*, 42, No. 6, 1101-14, 1969.

**List of Subjects in 21 CFR Part 176**

Food additives, Food packaging.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 176 is amended as follows:

**PART 176—INDIRECT FOOD ADDITIVES: PAPER AND PAPERBOARD COMPONENTS**

1. The authority citation for 21 CFR part 176 continues to read as follows:

**Authority:** 21 U.S.C. 321, 342, 346, 348, 379e.

2. Section 176.170 is amended in the table in paragraph (a)(5) by alphabetically adding an entry under the headings “List of Substances” and “Limitations” to read as follows:

**§ 176.170 Components of paper and paperboard in contact with aqueous and fatty foods.**

\* \* \* \* \*

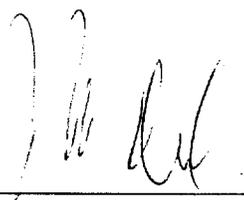
(a) \* \* \*

(5) \* \* \*

List of Substances	Limitations
Polyamidoamine-ethyleneimine-epichlorohydrin resin prepared by reacting hexanedioic acid, <i>N</i> -(2-aminoethyl)-1,2-ethanediamine, (chloromethyl)oxirane, ethyleneimine (aziridine), and polyethylene glycol, partly neutralized with sulfuric acid (CAS Reg. No. 167678-45-7).	For use only as a retention aid employed prior to the sheet-forming operation in the manufacture of paper and paperboard at a level not to exceed 0.12 percent resin by weight of the finished dry paper or paperboard.

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Dated: 3/3/00  
 March 3, 2000

  
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 Margaret M. Dotzel  
 Acting Associate Commissioner for Policy

[FR Doc. 00-???? Filed ??-??-00; 8:45 am]

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