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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Display Date	11/16/99
Publication Date	11/17/99
Certifier	J. M. [Signature]

Food and Drug Administration

21 CFR Part 178

[Docket No. 98F-0492]

Indirect Food Additives: Adjuvants, Production Aids, and Sanitizers

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the food additive regulations to provide for the expanded safe use of *N,N*-bis (2-hydroxyethyl) alkyl (C₁₃-C₁₅) amine as an antistatic agent in polypropylene homo- and copolymers intended for contact with food. This action is in response to a petition filed by ICI PLC.

DATES: This regulation is effective (*insert date of publication in the Federal Register*); 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: Ellen M. Waldron, Center for Food Safety and Applied Nutrition (HFS-215), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-418-3089.

SUPPLEMENTARY INFORMATION: In a notice published in the **Federal Register** of July 7, 1998 (63 FR 36699), FDA announced that a food additive petition (FAP 8B4602) had been filed by ICI PLC, c/o ICI Surfactants, P.O. Box 8340, Wilmington, DE 19803-8340. The petition proposed to amend the food additive regulations in § 178.3130 *Antistatic and/or antifogging agents in food-*

packaging materials (21 CFR 178.3130) to provide for the expanded safe use of *N,N*-bis (2-hydroxyethyl) alkyl (C₁₃-C₁₅) amine as an antistatic agent in polypropylene homo- and copolymers intended for contact with food.

In its evaluation of the safety of this food additive, FDA has reviewed the safety of the additive itself, the starting materials used, 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 1,4-dioxane and ethylene oxide, which are carcinogenic impurities resulting from the manufacture of the additive. Residual amounts of impurities, such as 1,4-dioxane and ethylene oxide, are commonly found as contaminants in chemical products, including food additives.

I. Determination of Safety

Under the general safety standard 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 the act (21 U.S.C. 348(c)(3)(A)) 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).

II. Safety of Petitioned Use of the Additive

FDA estimates that the petitioned use of the additive, *N,N*-bis (2-hydroxyethyl) alkyl (C₁₃-C₁₅) amine, will result in exposure to no greater than 23 parts per billion (ppb) of the additive in the daily diet (3 kilograms (kg)) or an estimated daily intake of 69 micrograms per person per day ($\mu\text{g/p/d}$) (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 this 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 1,4-dioxane and ethylene oxide, the carcinogenic chemicals that may be present as impurities in the additive. This risk evaluation of 1,4-dioxane and ethylene oxide has two aspects: (1) Assessment of exposure to the impurities from the petitioned use of the additive, and (2) extrapolation of the risk observed in the animal bioassays to the conditions of exposure to humans.

A. 1,4-Dioxane

FDA has estimated the exposure to 1,4-dioxane from the petitioned use of the additive as an antistatic agent in polypropylene homo- and copolymers intended for contact with food to be no more than 0.09 ppb in the daily diet (3 kg), or 0.28 $\mu\text{g/p/d}$ (Ref. 1). The agency used data from a carcinogenesis bioassay on 1,4-dioxane, conducted by the National Cancer Institute (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 results of the bioassay on 1,4-dioxane demonstrated that the material was carcinogenic for female rats under the conditions of the study. The authors

reported that the test material caused significantly increased incidence of squamous cell carcinomas and hepatocellular tumors in female rats.

Based on the agency's estimate that exposure to 1,4-dioxane will not exceed 0.28 $\mu\text{g/p/d}$, FDA estimates that the upper-bound limit of lifetime human risk from the petitioned use of the subject additive is 9.8×10^{-9} , or 9.8 in one 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 a reasonable certainty that no harm from exposure to 1,4-dioxane would result from the petitioned use of the additive.

B. Ethylene Oxide

FDA has estimated the exposure to ethylene oxide from the petitioned use of the additive as an antistatic agent in polypropylene homo- and copolymers intended for contact with food to be no more than 2 parts per trillion in the daily diet (3 kg) or 6 nanograms (ng)/p/d (Ref. 1). The agency used data from a carcinogenesis bioassay on ethylene oxide, conducted for the Institute of Hygiene, University of Mainz, Germany (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 results of the bioassay on ethylene oxide demonstrated that the material was carcinogenic for female rats under the conditions of the study. 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 6 ng/p/d, FDA estimates that the upper-bound limit of lifetime human risk from the petitioned use of the subject additive is 1.1×10^{-8} , or 1.1 in 100 million (Ref. 4). Because of the numerous conservative assumptions used in calculating the exposure estimate, 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 the exposure to ethylene oxide would result from the petitioned use of the additive.

C. Need for Specifications

The agency has also considered whether specifications are necessary to control the amounts of 1,4-dioxane and ethylene oxide present as impurities in the additive. The agency finds that specifications are not necessary for the following reasons: (1) Because of the low levels at which 1,4-dioxane and ethylene oxide may be expected to remain as impurities following production of the additive, the agency would not expect these impurities to become components of food at other than extremely small levels; and (2) the upper-bound limits of lifetime human risk from exposure to 1,4-dioxane and ethylene oxide, are very low, 9.8 in a billion and 1.1 in 100 million, respectively.

III. Conclusion

FDA has evaluated data in the petition and other relevant material. Based on this information, the agency concludes that the proposed use of the additive in food-contact articles is safe, that the additive will achieve its intended technical effect, and therefore, that the regulations in § 178.3130 should be amended as set forth below in this document.

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.

IV. Environmental Impact

The agency has previously considered the environmental effects of this rule as announced

been received that would affect the agency's previous determination that there is no significant impact on the human environment and that an environmental impact statement is not required.

V. Paperwork Reduction Act of 1995

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

VI. Objections

Any person who will be adversely affected by this regulation may at any time on or before *(insert date 30 days after date of publication in the **Federal Register**)*, file with the Dockets Management Branch (address above) written objections thereto. 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 shall be submitted and shall 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.

VII. 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 8B4602 (MATS #976 M2.1): ICI Surfactants; Submission of 4/7/99. *N,N*-Bis(2-Hydroxyethyl) Alkyl (C₁₃-C₁₅) Amine as an Antistatic Agent in Polypropylene Used in Contact With Fatty Foods Hot Filled or Pasteurized Above 66 °C,” dated May 28, 1999.

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

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

4. Memorandum from the Division of Petition Control (HFS-215) to Executive Secretary, Quantitative Risk Assessment Committee (HFS-308) entitled “Estimate of the Upper bound Lifetime Risk From Residual 1,4-Dioxane (DO) and Ethylene Oxide (EO) in *N,N*-bis (2-Hydroxyethyl) Alkyl (C₁₃-C₁₅) Amine Intended for Use as an Antistatic Agent in Polypropylene Homo- and Copolymers Contacting Food: FAP 8B4602,” dated June 8, 1999.

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

List of Subjects in 21 CFR Part 178

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 178 is amended as follows:

PART 178—INDIRECT FOOD ADDITIVES: ADJUVANTS, PRODUCTION AIDS, AND SANITIZERS

1. The authority citation for 21 CFR part 178 continues to read as follows:

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

2. Section 178.3130 is amended in the table in paragraph (b) by revising the entry for *N,N*-bis (2-hydroxyethyl) alkyl (C₁₃-C₁₅) amine under the heading “Limitations” to read as follows:

§ 178.3130 Antistatic and/or antifogging agents in food-packaging materials.

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(b) * * *



