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8-6-87

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

21 CFR PART 175

[DOCKET NO. 80F-0499]

INDIRECT FOOD ADDITIVES: ADHESIVES AND COMPONENTS OF  
COATINGS

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the food additive regulations to provide for the safe use of 1,2-bis(3,5-di-tert-butyl-4-hydroxyhydrocinnamoyl)hydrazine as a component of adhesives in articles intended for food-contact use. This action responds to a petition filed by Ciba-Geigy Corp.

DATES: Effective (insert date of publication in the FEDERAL REGISTER); objections by (insert date 30 days after date of publication in the FEDERAL REGISTER).

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

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FOR FURTHER INFORMATION CONTACT:

Julius Smith,  
Center for Food Safety and Applied Nutrition (HFF-335),  
Food and Drug Administration,  
200 C St. SW.,  
Washington, DC 20204,  
202-472-5690.

SUPPLEMENTARY INFORMATION: In a notice published in the FEDERAL REGISTER of January 16, 1981 (46 FR 3982), FDA announced that a petition (FAP OB3487) had been filed by Ciba-Geigy Corp., Ardsley, NY 10502 (the firm is now located at Three Skyline Dr., Hawthorne, NY 10532), proposing that § 175.105 Adhesives (21 CFR 175.105) be amended to provide for the safe use of 1,2-bis(3,5-di-tert-butyl-4-hydroxyhydrocinnamoyl)hydrazine as a component of adhesives in articles intended for food-contact use.

FDA, in its evaluation of the safety of this additive, reviewed the safety of both the additive and the starting materials used to manufacture the additive. Although, 1,2-bis(3,5-di-tert-butyl-4-hydroxyhydrocinnamoyl)hydrazine has not been found to cause cancer, it may contain minute amounts of an impurity, hydrazine, as a byproduct of its production. Hydrazine has been shown to cause cancer in test animals. Residual amounts of reactants and manufacturing aids, such as this chemical, are commonly found as contaminants in chemical products, including food additives.

FDA proposed to prohibit the use of hydrazine as a food additive in boiler water used to produce steam for food processing (21 CFR 173.310) in the FEDERAL REGISTER of June 12, 1979 (44 FR 33693). The agency's proposal was based upon information, using new analytical methods, that hydrazine was present at low levels (parts per billion) in steam condensate from boilers using hydrazine as a boiler water additive. The agency intends to take further action on the June 12, 1979, proposal at a future date.

FDA's evaluation of any risks created by the presence of hydrazine as an impurity in 1,2-bis(3,5-di-tert-butyl-4-hydroxyhydrocinnamoyl)hydrazine is based on different considerations than its evaluation of the safety of hydrazine as a food additive, however. Therefore, FDA concludes that it can proceed with this rulemaking independently of the latter evaluation.

#### I. DETERMINATION OF SAFETY

Under section 409(c)(3)(A) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 348(c)(3)(A)), the so-called "general safety clause" of the statute, 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. The concept of safety embodied in the Food Additives Amendment of 1958 is explained in the legislative history of the provision: "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 circumstances." H. Rept. 2284, 85th Cong., 2d Sess. 4 (1958). This definition of safety has been incorporated into FDA's food additive regulations (21 CFR 170.3(i)). The anticancer or Delaney clause of the Food Additives Amendment (section 409(c)(3)(A) of the act (21 U.S.C. 348(c)(3)(A))) provides further that no food additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal.

In the past, FDA has often refused to approve the use of an additive that contained or was suspected of containing even minor amounts of a carcinogenic chemical, even though the additive as a whole had not been shown to cause cancer. The agency now believes, however, that developments in scientific technology and experience with risk assessment procedures make it possible for FDA to establish the safety of additives that contain carcinogenic chemicals but that have not themselves been shown to cause cancer.

In the preamble to the final rule permanently listing D&C Green No. 6, published in the FEDERAL REGISTER of April 2, 1982 (47 FR 14138), FDA explained the basis for approving the use of a color additive that had not been shown to cause cancer, even though it contains a carcinogenic impurity. Since that decision, FDA has approved the use of other color additives and food additives on the same basis.

An additive that has not been shown to cause cancer, but that contains a carcinogenic impurity, may properly be evaluated under the general safety clause of the statute using risk assessment procedures to determine whether there is a reasonable certainty that no harm will result from the proposed use of the additive.

The agency's position is supported by Scott v. FDA, 728 F.2d 322 (6th Cir. 1984). That case involved a challenge to FDA's decision to approve the use of D&C Green No. 5, which contains a carcinogenic chemical but has itself not been shown to cause cancer. Relying heavily on the reasoning in the agency's decision to list this color additive, the United States Court of Appeals for the Sixth Circuit rejected the challenge to FDA's action and affirmed the listing regulation.

## II. SAFETY OF PETITIONED USE

FDA estimates that the petitioned use of 1,2-bis(3,5-di-tert-butyl-4-hydroxyhydrocinnamoyl)hydrazine will result in extremely low levels of exposure to this additive. FDA does not ordinarily consider chronic testing to be necessary to determine the safety of an additive whose use will result in such low exposure levels (Refs. 1 and 2), and the agency has not required such testing here. Because 1,2-bis(3,5-di-

tert-butyl-4-hydroxyhydrocinnamoyl)hydrazine has not been shown to cause cancer, the anticancer clause does not apply to it.

FDA has evaluated the safety of this additive under the general safety clause, considering all available data and using risk assessment procedures to estimate the upper bound limit of risk presented by the carcinogenic chemical that may be present as an impurity in the additive. Based on this evaluation, the agency has concluded that the additive is safe under the proposed conditions of use.

The risk assessment procedures that FDA used in this evaluation are similar to the methods that it has used to examine the risk associated with the presence of minor carcinogenic impurities in various other food and color additives that contain carcinogenic impurities (see, e.g., 49 FR 13018, 13019; April 2, 1984). This risk evaluation of the carcinogenic impurity hydrazine has two aspects:

(1) assessment of the worst case exposure to the impurity from the proposed use of the additive and (2) extrapolation of the risk observed in the animal bioassay to the conditions of probable exposure to humans.

#### A. Hydrazine

Based on the fraction of the daily diet that may be in contact with surfaces containing 1,2-bis(3,5-di-tert-butyl-4-hydroxyhydrocinnamoyl)hydrazine and on the level of hydrazine that may be present in the additive (Ref. 3), FDA

estimated the hypothetical worst case exposure to hydrazine from the use of this additive to be 20 nanograms per person per day. The agency used data in a carcinogenesis bioassay on hydrazine conducted by Toth et al. at the University of Nebraska College of Medicine (Ref. 4) to estimate the upper bound limit of lifetime human risk from exposure to this chemical stemming from the proposed use of 1,2-bis(3,5-di-tert-butyl-4-hydroxyhydrocinnamoyl)hydrazine. The results of the Toth bioassay on hydrazine demonstrated that the material was carcinogenic for male and female mice under the conditions of the study. The test material caused significantly increased incidences of lung tumors in male and female mice.

The Center for Food Safety and Applied Nutrition's Cancer Assessment Committee reviewed this bioassay and other relevant data available in the literature and concluded that the findings of carcinogenicity were supported by this information on hydrazine. The committee further concluded that the Toth bioassay provided the appropriate basis on which to calculate an estimate of the upper bound level of lifetime human risk from potential exposure to hydrazine stemming from the proposed use of 1,2-bis(3,5-di-tert-butyl-4-hydroxy-hydrocinnamoyl)hydrazine.

The agency used a quantitative risk assessment procedure (linear proportional model) to extrapolate from the dose used in the animal experiment to the very low doses

encountered under the proposed conditions of use. This procedure is not likely to underestimate the actual risk from very low doses and may, in fact, exaggerate it because the extrapolation models used are designed to estimate the maximum risk consistent with the data. For this reason, the estimate can be used with confidence to determine to a reasonable certainty whether any harm will result from the proposed conditions and levels of use of the food additive.

Based on a worst case exposure of 20 nanograms per person per day, FDA estimates that the upper bound limit of individual lifetime risk from potential exposure to hydrazine from the use of 1,2-bis(3,5-di-tert-butyl-4-hydroxyhydrocinnamoyl)hydrazine is  $7 \times 10^{-8}$  or less than 1 in 10 million. Because of numerous conservatisms in the exposure estimate, lifetime averaged individual exposure to hydrazine is expected to be substantially less than the estimated daily intake, and, therefore, the calculated upper bound limit of risk would be less. Thus, the agency concludes that there is a reasonable certainty of no harm from the exposure to the hydrazine that might result from the proposed use of 1,2-bis(3,5-di-tert-butyl-4-hydroxyhydrocinnamoyl)hydrazine.

#### B. Need for Specifications

The agency has also considered whether a specification is necessary to control the amount of the hydrazine impurity

in the food additive. The agency finds that a specification is not necessary for the following reasons: (1) because excess hydrazine is removed during the additive's manufacturing process, the agency would not expect this impurity to become a component of food at other than extremely small levels; and (2) the upper bound limit of lifetime risk from exposure to this impurity, even under worst case assumptions, is very low, less than 1 in 10 million.

### III. CONCLUSION ON SAFETY

FDA has evaluated the available toxicity data and the exposure calculation for the additive and has determined that the additive is safe for its proposed use.

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 (address above) by appointment with the information contact person listed above. As provided in 21 CFR 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.

The agency has carefully considered the potential environmental effects of this action and 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 may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday. Under FDA's regulations implementing the National Environmental Policy Act (21 CFR Part 25), an action of this type would require an abbreviated environmental assessment under 21 CFR 25.31a(b)(1).

#### 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. Carr, G. M., "Carcinogenicity Testing Programs" in "Food Safety: Where Are We?," Committee on Agriculture, Nutrition, and Forestry, United States Senate, July 1979, p. 59.

2. Kokoski, C. J., "Regulatory Food Additive Toxicology" presented at the "Second International Conference on Safety Evaluation and Regulation of Chemicals," October 24, 1983, Cambridge, MA.

3. Memorandum dated October 2, 1985, from Food Additive Chemistry Evaluation Branch to Indirect Additive Branch. "FAP 0B3487--Exposure to Hydrazine."

4. Toth, et al., "Hydrazine Methylhydrazine and Methylhydrazine Sulfate Carcinogenesis in Swiss Mice," International Journal of Cancer, 9:109, 1972.

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.

List of Subjects in 21 CFR Part 175

Adhesives, Food additives, Food packaging.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, Part 175 is amended as follows:

PART 175--INDIRECT FOOD ADDITIVES: ADHESIVES  
AND COMPONENTS OF COATINGS

1. The authority citation for 21 CFR Part 175 continues to read as follows:

AUTHORITY: Secs. 201(s), 409, 72 Stat. 1784-1788 as amended (21 U.S.C. 321(s), 348); 21 CFR 5.10 and 5.61.

2. Section 175.105 is amended in paragraph (c)(5) by alphabetically inserting a new item in the table to read as follows:

§ 175.105 Adhesives.

\* \* \* \* \*  
(c) \* \* \*  
(5) \* \* \*

Substances

Limitations

\* \* \* \* \*  
1,2-Bis(3,5-di-tert-butyl-4-hydroxyhydrocinnamoyl)hydrazine (CAS Reg. No. 32687-78-8).

\* \* \* \* \*  
For use at a level not to exceed 2 percent by weight of the adhesive.

\* \* \* \* \*

Dated: July 30, 1987  
JUL 30 1987

John M. Taylor

John M. Taylor  
Associate Commissioner  
for Regulatory Affairs

CERTIFIED TO BE A TRUE COPY OF THE ORIGINAL

John M. Taylor