

DEPARTMENT OF HEALTH AND HUMAN SERVICES

OMB

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Food and Drug Administration

21 CFR Part 176

[Docket No. 99F-1423]

Indirect Food Additives: Paper and Paperboard Components

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 safe use of 4,5-dichloro-1,2-dithiol-3-one (also known as 4,5-dichloro-3H-1,2-dithiol-3-one) as a slimicide in the manufacture of food-contact paper and paperboard. This action is in response to a petition filed by Yoshitomi Fine Chemicals, Ltd.

DATES: The regulation 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: Mark A. Hepp, Center for Food Safety and Applied Nutrition (HFS-215), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-41 S-3098.

SUPPLEMENTARY INFORMATION: In a notice published in the **Federal Register** of May 27, 1999 (64 FR 28825), FDA announced that a food additive petition (FAP 9B4654) had been filed by Yoshitomi Fine Chemicals, Ltd., c/o SRS International Corp., suite 1000, 1625 K St. NW., Washington, DC 20006-1604. The petition proposed to amend the food additive regulations in

§ 176.300 *Slimicides* (21 CFR 176.300) to provide for the safe use of 4,5-dichloro-1,2-dithiol-3-one as a slimicide in the manufacture of food-contact paper and paperboard.

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 1,2-dichloroethane and tetrachloroethylene, carcinogenic impurities resulting from the manufacture of the additive. Residual amounts of reactants and manufacturing aids, such as 1,2-dichloroethane and tetrachloroethylene, 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(~)(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, 4,5-dichloro-1,2-dithiol-3-one, will result in exposure to no greater than 0.8 part per billion of the additive in the daily diet (3 kilogram (kg)) or an estimated daily intake of 2.4 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 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 1,2-dichloroethane and tetrachloroethylene, the carcinogenic chemicals that may be present as impurities in the additive. This risk evaluation of 1,2-dichloroethane and tetrachloroethylene 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 bioassays to the conditions of exposure to humans.

A. *1,2-Dichloroethane*

FDA has estimated the exposure to 1,2-dichloroethane from the petitioned use of the additive as a slimicide in the manufacture of food-contact paper and paperboard to be no more than 24 parts per trillion (ppt) in the daily diet (3 kg), or 72 nanograms(ng)/p/d (Ref. 4). The agency used data from a carcinogenesis bioassay on 1,2-dichloroethane, 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 authors reported that the test material caused significantly increased incidence of squamous cell carcinomas of the forestomach and hemangiosarcomas of the circulatory system in male rats and adenocarcinomas of the mammary gland in female rats.

Based on the agency's estimate that exposure to 1,2-dichloroethane will not exceed 72 ng/p/d, FDA estimates that the upper-bound limit of lifetime human cancer risk from the petitioned use of the subject additive is 1.3×10^{-8} , or 1.3 in 100 million (Ref. 4). Because of the numerous conservative assumptions used in calculating the exposure estimate, the actual lifetime-averaged individual exposure to 1,2-dichloroethane 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 **1,2-dichloroethane** would result from the petitioned use of the additive.

B. Tetrachloroethylene

FDA has estimated the exposure to tetrachloroethylene from the petitioned use of the additive as a slimicide in the manufacture of food-contact paper and paperboard to be no more than 2.4 ppt in the daily diet (3 kg), or 7.2 ng/p/d (Ref. 4). The agency used data from a carcinogenesis bioassay on tetrachloroethylene, conducted by the National Toxicology Program (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 caused significantly increased incidence of hepatocellular adenomas and carcinomas in male mice and hepatocellular carcinomas in female mice.

Based on the agency's estimate that exposure to tetrachloroethylene will not exceed 7.2 ng/p/d, FDA estimates that the upper-bound limit of lifetime human risk from the petitioned use of the subject additive is 3.6×10^{-10} , or 3.6 in 10 billion (Ref. 4). Because of the numerous conservative assumptions used in calculating the exposure estimate, the actual lifetime-averaged individual exposure to tetrachloroethylene 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 tetrachloroethylene would result from the petitioned use of the additive.

C. Need for Specifications

The agency also has considered whether specifications are necessary to control the amount of 1,2-dichloroethane and tetrachloroethylene as impurities in the additive. The agency finds that specifications are not necessary for the following reasons: (1) Because of the low level at which 1,2-dichloroethane and tetrachloroethylene 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 small levels; and (2) the upper-bound limits of lifetime risk from exposure to 1,2-dichloroethane, and tetrachloroethylene are very low, less than 1.3 in 100 million, and 3.6 in 10 billion, respectively.

III. Conclusion

FDA has evaluated the data in the petition and other relevant material. Based on this information, the agency concludes that the proposed use of the additive is safe, that the additive will achieve its intended technical effect, and therefore, that the regulations in § 176.300 should be amended as set forth below.

The additive, 4,5-dichloro-1,2-dithiol-3-one, intended for use as a slimicide in the manufacture of food-contact paper and paperboard, is regulated under section 409 of the act (21 U.S.C. 348) as a food additive and not as a pesticide chemical under section 408 of the act (21 U.S.C. 346a). However, this intended use of 4,5-dichloro-1,2-dithiol-3-one may nevertheless be subject to regulation as a pesticide under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). Therefore, manufacturers intending to use 4,5-dichloro-1,2-dithiol-3-one as a slimicide in the manufacture of food-contact paper and paperboard should contact the Environmental Protection Agency to determine whether this use requires a pesticide registration under FIFRA.

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 in the notice of filing for FAP 9B4654 (44 FR 28825). No new information or comments have 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 collection 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 and Environmental Review Team, FDA, to the Division of Petition Control, FDA, "FAP 9B4654 (MATS # 1039)—SRS International Corp. (on behalf of Yoshitomi Fine Chemicals, Ltd.). 4,5-Dichloro-3H-1,2-Dithiol-3-One (RYH-86) as a Slimicide in the Manufacture of Paper and Paperboard. Division of Petition Control (DPC) E-Mail Request of 9-14-99," October 12, 1999.
2. Kokoski, C. J., "Regulatory Food Additive Toxicology," ***Chemical Safety Regulation and Compliance***, edited by F. Hornburger, and J. K. Marquis, published by S. Karger, New York, NY, pp. 24-33, 1985.
3. "Bioassay of 1,2-Dichloroethane for Possible Carcinogenicity," National Cancer Institute, NCI-CG-TR-551978.
4. Memorandum from the Indirect Additives Branch, FDA, to the Executive Secretary, Quantitative Risk Assessment Committee, FDA, "Third Estimation of the Upper-Bound Lifetime Risk From 1,2-Dichloroethane (DCE) and Tetrachloroethylene (TCE) in 4,5-Dichloro-1,2-Dithiol-3-One for FAP 8B4654," October 13, 1999.
5. "Toxicology and Carcinogenesis Studies of Tetrachloroethylene (Perchloroethylene) in F344/N Rats and B6C3F₁ Mice (Inhalation Studies)," ***National Toxicology Program Technical Report Series No. 311***, 1986.

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:

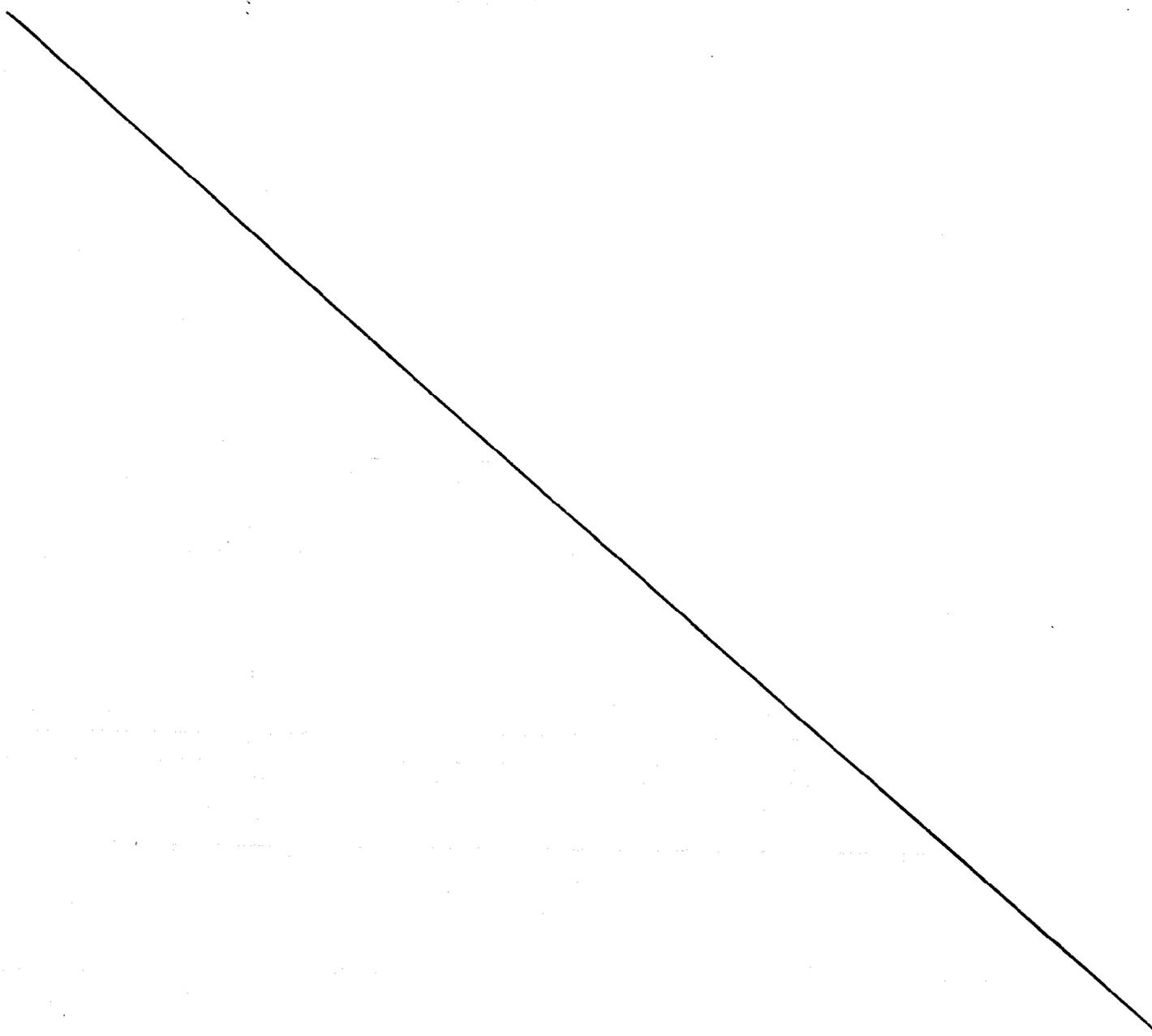
Authority: 21 U.S.C. 321, 342, 346, 348, 379e.

2. Section 176.300 is amended in the table *in* paragraph (c) by alphabetically adding an entry under the headings “Lists of substances” and “Limitations” to read as follows:

§ 176.300 Slimicides.

* * * * *

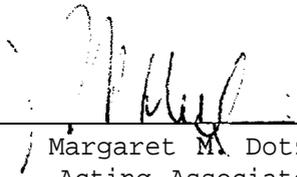
(c) * * *



List of substances	Limitations
* . * 4,5-dichloro-1, 2-dithiol-3-one (CAS Reg. No. 1192-52-5). * * *	* . * For use only at levels not to exceed 10 milligrams per kilogram in the pulp slurry. * * *

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Dated: 12-7-99
December 7, 1999



Margaret M. Dotzel
Acting Associate Commissioner for Policy

[FR Doc. 99-???? Filed ??-??-99; 8:45 am]

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