DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date: March 15, 1994

From: ADDITIVES EVALUATION BRANCH #1 (HFS-226)

Subject: The Safe Use of Perfluoroalkyl Substituted Phosphate Ester Acids, Ammonium Salts Formed by the Reaction of 2,2-bis[(r,W-perfluoro C_{4-20} alkylthio) methyl]-1,3-propane diol, Polyphosphoric Acid and Ammonium Hydroxide as an Oil and Water Repellent for Paper and Paperboard
Re: Assessment of Lodyne P-208E Genetic Toxicity Studies memo dated 1/27/94

To: INDIRECT ADDITIVES BRANCH (HFS-216)
ATTENTION: R. White

THROUGH: KIRK BIDDLE, PH.D. [redacted]
CHIEF, ADDITIVES EVALUATION BRANCH #1 (HFS-226)

FAP 3B4353

CIBA-GEIGY CORPORATION
SEVEN SKYLINE DRIVE
HAWTHORNE, NEW YORK 10532

This is a continuation of our previous memos (Chen of 9/7/93 and 11/5/93) in reference to the subject petition proposing that 21 CFR 176.170 (a)(5) of the food additive regulations be amended with respect to the safe use of perfluoroalkyl substituted phosphate ester acids, ammonium salts formed by the reaction of 2,2-bis[(r,W-perfluoro C_{4-20} alkylthio) methyl]-1,3-propane diol, polyphosphoric acid and ammonium hydroxide, as an oil and water repellent for paper and paperboard under the conditions of use A through H as defined in Table 2 of 176.170 (c). The paper and paperboard will be in contact with aqueous and fatty foods, and the trade name of the subject additive is (b)(4) [redacted]

Genetic Toxicity Studies and the Exposure Estimate of the Additive

The two genetic toxicity studies, the AMES test and the in vitro chromosome aberration assay on (b)(4) [redacted] has been reviewed by Dr. E. Matthews (HFS-226). The conclusion of his evaluation is that (b)(4) [redacted] was non-mutagenic to Salmonella typhimurium cells but the in vitro chromosome aberration assay in Chinese Hamster V79 cells was inadequate to address the potential clastogenicity of (b)(4) [redacted] in V79 cells. We had discussed Dr. Matthews's evaluation in a separate memo (Chen of 3/15/94).

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The dietary exposure to the subject additive was calculated by the Chemistry Review Branch (CRB HFS-247, Carberry memo

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9/28/93). According to the CRB, the migration data for the subject additive can only support the condition of use H (Frozen or refrigerated storage: Ready-prepared foods intended to be reheated in container at time of use) as defined on Table 2 of 176.170 (c). We had addressed this issue in a previous memo (Chen of 11/5/93). The dietary concentration (DC) of the subject additive is 0.008 ppm and the estimated daily intake (EDI) is 24 ug/p/d which is in the "virtually nil" exposure range (<0.05 ppm or <0.15 mg/person/day). The impurities included perfluoroalkyl disulfide, ammonium salt of phosphoric acid, ammonium salt of 2,2-bis[(r,W-perfluoro C_{4-20} alkylthio) methyl]-1,3-propane diol and tri-[2,2-bis[(r,W-perfluoro C_{4-20} alkylthio) methyl]-3-hydroxy propyl phosphate (by-product). Since the subject additive is in the "virtually nil" exposure range, the exposure to the impurities will be at least 100 fold less that of exposure to the additive itself, so the amount of the exposure to impurities would be negligible (conversation with CRB HFS-247, Carberry of 3/9/94).

Summary

The estimated daily intake (EDI) of the subject additive is in the "virtually nil" exposure range and the toxicology data included the LD_{50} in rats (greater than 5.0 g/kg BW) and a genotoxicity study (non-mutagenic to Salmonella typhimurium cells). Under the condition of use H (Frozen or refrigerated storage: Ready-prepared foods intended to be reheated in container at time of use) as defined in Table 2 of 176.170 (c), the "virtually nil" dietary exposure to the subject additive and the existing toxicology data can support its safety and the petition is suitable for regulation. However, if the petitioner decides to expand the usage of (b) (4) depending on the exposure estimate, additional feeding and/or genotoxicity studies may be needed.

[redacted]

Isabel S. Chen, Ph.D

cc:
HFS-200, HFS-225, HFS-226 (Biddle), HFS-227 (Edwards)
HFS-216, HFS-247, HFS-226:ISChen:254-3919:Doc:I3B4353.2

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From: Isabel S. Chen, Ph.D.
ADDITIVES EVALUATION BRANCH #1 (HFS-226)

Subject: Assessment of Lodyne P-208E Genetic Toxicity Studies

To: INDIRECT ADDITIVES BRANCH (HFS-216)
ATTENTION: R. White

THROUGH: KIRK BIDDLE, PH.D. [redacted]
CHIEF, ADDITIVES EVALUATION BRANCH #1 (HFS-226)

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The evaluation of two genetic studies, the AMES test and the in vitro chromosome aberration assay on (b) (4) has been completed by Dr. E. Matthews who concluded that (b) (4) was non-mutagenic to Salmonella typhimurium cells in AMES test but the in vitro chromosome aberration assay in Chinese Hamster V79 cells was inadequate to address the potential clastogenicity of (b) (4) in V79 cells. In the chromosome aberration assay, (b) (4) induced a weak response at the 72 ug/ml treatment dose but this activity was not repeatable in the second experiment and there was no clear dose-related increase in cytotoxicity over the range of the test doses of 24 to 240 ug/ml (see Matthews memo of 1/27/94).

Under the current submission, (b) (4) can be used only under condition of use H (Frozen or refrigerated storage: Ready-prepared foods intended to be reheated in container at time of use) as an oil and water repellent for paper and paperboard, as defined on Table 2 of 21 CFR 176.170 (c). The estimated daily intake (EDI) is 24 ug/p/d (CRB HFS-247, Carberry memo of 9/28/93), thus, the dietary exposure to the subject additive is in the "virtually nil" exposure range. Under the specific condition of use, the dietary exposure to the subject additive is very small, no additional genotoxicity study is required. However, if the petitioner decides to expand the usage of (b) (4) depending on the exposure estimate, additional genotoxicity study may be needed.

[redacted]
Isabel S. Chen, Ph.D.

cc: HFS-200, HFS-225, HFS-226 (Biddle), HFS-227 (Edwards)
HFS-216, HFS-226:ISChen:254-3919:Doc:I2B4353.EM

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