

UNITED STATES GOVERNMENT

Memorandum

TO : Petitions Control Branch

DATE: February 3, 1966

FROM : Drs. K. P. Misra & J. McLaughlin, Jr. *K. P. Misra & J. McLaughlin, Jr.*
Division of Toxicological Evaluation
Petitions Review Branch

SUBJECT: Amend regulation 121.2526 (Components of paper and paperboard in contact with aqueous and fatty foods) to include mono-, and bis-(1H, 1H, 2H, 2H-per fluoroalkyl)phosphates-diethanolamine salts as an optional component of paper and paperboard.

FOOD ADDITIVE PETITION NO. 5B-1747
(Final Evaluation)

E. I. DuPont de Nemours & Co.
Wilmington, Delaware
(AF 4-408)

(b) (4) paper fluoridizer is a complex mixture, the active portion is diethanolamine salt of a 1:1 mixture of mono-, and bis-(fluoroalkyl) phosphates. The alkyl groups could be from C₆ through C₁₆ normal carbon chain members. The predominant members among the alkyl groups are (Memo of Conference of January 19, 1966) C₆, C₈ and C₁₀ carbon chain members. The chemical will be used as an internal size (0.5% level) or as a component of coating (0.35%). It imparts water repellency or prevents wicking of oil and grease to paperboard.

The Division of Food Standards and Additives have suggested (FSA memo to PCB of April 21, 1965) a migration of less than 1 ppm to all foods. The migration to alcoholic beverages (Memo of Conference, January 19, 1966) will also be less than 1 ppm.

The petitioner has now submitted two 90-day sub-acute oral feeding data in response to our requirements (TE memo to PCB of April 28, 1965 and Memo of Conference of May 17, 1965). The dog study utilized 3 male and 3 female beagles per dose groups of 0, 100, 500 and 2500 ppm of Zonyl RP in the Purina dog chow. After 35 days on such a regimen, and in the absence of any visible signs of toxicity, the 500 and 2500 ppm levels were increased to 1000 and 5000 ppm levels respectively for the remainder portion of 13-week experiment. The criterias of evaluation were:

1. Physical examination (heart sounds, pulse rate, eyes, and reflexes)
2. General appearance and behavior
3. Survival, gain in body weight, food intake and compound intake
4. Hematology (hemoglobin content, hematocrit, red blood cell counts, white blood cell counts and differentials, sediment rate)
5. Blood chemistry (glucose, protein, albumin, urea nitrogen, and albumin/globulin ratios), and liver function (cholesterol, SGOT,



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134

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February 3, 1966

SGPT, alkaline phosphatase and serum electrophoretic protein pattern) tests

6. Urinalysis (bilirubin content, occult blood, albumin, glucose, pH, specific gravity, sediments and microscopic examination)
7. Pathology (gross, organ weights in relation to body weights and microscopic).

The liver function tests suggested a dose related effect at 2500-5000 ppm level intake. The organ weight data showed effects (liver weight) at 500-1000, and 2500-5000 ppm levels. Microscopic (pathology) examination confirmed effect at 2500-5000 ppm level. This was described as slight hypertrophy of the centrilobular parenchymal cells. The "no effect" level is less than 1000 ppm, and in the present context 100 ppm as the "500 ppm" level was changed to 1000 ppm at the end of six weeks of experiment.

A similar situation confronts with the rat experiment. Here 20 male and 20 female Charles River rats per group were given 0, 100, 500 and 2500 ppm of (b) (4) in the Purina rat chow. The initial rat body weights were between 47-64 gm. After 35 days, the 500 and 2500 ppm levels, in the absence of any visible toxicity syndromes, were increased to 1000 and 5000 ppm levels, respectively. With essentially the same criteria of evaluations, as in the above dog experiment, we find an effect on liver and kidney weights at the 1000 and 5000 ppm levels. The gross and microscopic pathology also suggested dose related effects. At the 5000 ppm level there was indication of an "anemia-type effect" in rats, at the terminal phase of experiment. The "no effect" level from this study is also less than 1000 ppm, and could be possibly greater than 100 ppm. We can only set 100 ppm as "no effect" level for calculation purposes.

EVALUATION:

The two above mentioned 90 day sub-acute oral feeding studies in rat and dog lead us to set a "no effect" level of 100 ppm in their diets. With a 1000-fold margin of safety factor, the maximum safe level for (b) (4) is 0.1 ppm. Therefore, this data is not adequate to support a migration of 1 ppm of (b) (4) to all types of foods.

CONCLUSION:

The petition is not acceptable for filing. We need a more realistic estimate of the extent of migration of (b) (4). The two 90-day sub-acute oral feeding data with rat and dog has a draw back that we can set 100 ppm as the "no effect level" for this compound in the diets of rat and dog. This could permit a migration of 0.1 ppm of (b) (4) to food.

INIT: HBlumenthal
cc: FSA, TE, FAP No. 5B-1747
KPM:ira & JMcLaughlin:mmt 2/3/66

Handwritten: Hangman's comment
Handwritten: 1/27/66

134

135

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UNITED STATES GOVERNMENT

MEMO

Memorandum

TO : Dr. O. G. Fitzhugh


DATE: February 24, 1966

FROM : E. C. Hagan

SUBJECT: (b) (4) FAP 5B-1747

From what I have been able to learn it would be difficult to pin down the extent of use of (b) (4)

Food Packaging comments seem valid.


Ernest C. Hagan

RD/ECHagan:sah
2/24/66

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133

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