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COMMERCIAL DEVELOPMENT CALL REPORT NO. 70-76

FOOD & DRUG ADMINISTRATION
WASHINGTON, D.C.

Date of Call: August 12, 1970

For FDA: Dr. H. Blumenthal, Chief, Petitions Review Branch
Dr. Higgenbotham, Div. of Chemistry
Dr. A. Holtz, Div. of Chemistry
Dr. J. McLaughlin, Div. of Toxicology
Dr. K. Mizra, Div. of Toxicology
Dr. W. Schaeffer
Dr. S. Shibco, Div. of Toxicology

For Monsanto: W. H. Hunt
J. P. Mieure
P. R. Graham

Objectives:

1. Santicizer 409 -- Answer questions and supply data requested in FDA's reply to our petition.
2. Santicizer 160 -- Final review of total extraction data and negotiation of revised petition wording.
3. Aroclor 5460 -- Re-establishment of dialogue with FDA on Aroclor 5460 and determine necessary steps required to get approval in adhesives.

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4. Santicizer 97A (C₇₋₉ Adipate) -- FDA opinion on the amount of data necessary to get FDA approval.
5. XL-8000 Lubricant -- Review of extraction data and determine if approval is possible without toxicological studies.

Summary of Results:

1. The FDA study of our Santicizer 409 petition resulted in a request for additional methodology information and indicated that the extraction data did not support the broad coverage we were seeking. They suggested we revise the proposed regulation limiting coverage to film thicknesses of 4 mils and below for packaging aqueous, and possibly fatty foods, where the migration level would not exceed 50-100 ppm.
2. The following general type of wording for the revised regulation for Santicizer 160 appeared to be acceptable to both Chemistry and Toxicology sections of the FDA: "when used in combination with di-2-ethylhexyl adipate in meat wrap film, provided that the film thickness does not exceed 0.003 in. and the extraction does not exceed 0.5 mg/in.² from aqueous solvents and 60 mg/in.² from heptane." This would allow as high as 18.8% (as phthalic acid) S-160 in the film.
3. The important items necessary for re-submission of the Aroclor 5460 petition are the control of the PCB content and the inclusion of acceptable methods for the product per se and contaminants. The FDA agreed that the quickest way to get approval is to restrict the petition to adhesives.
4. The FDA indicated good probability that we can get approval for Santicizer 97A (C₇₋₉ Adipate) if we can show no essential differences in extraction and toxicological effects between S-97A and DOA. A comparative 3-month, two species feeding study is advised.

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5. Our results showing no extraction of XL-8000 Lubricant from aqueous solvents and heptane would probably be sufficient for regulation in the release agent section provided we can validate the accuracy of our method and we specify the maximum level in PVC.

Details:

1. Santicizer 409. The FDA reaction to our recent S-409 petition consisted of several questions, most of which asked for analytical methods in greater detail and the inclusion of validation results. One question did relate to the sufficiency of our extraction data. Holtz indicated that we had not been specific about what type of end-use we are planning for this product. He found it difficult to arrive at a specific set of migration limits depending upon S-409 concentration, temperature, film thickness and environment-type. The reason for this, of course, is our uncertainty as to where the market will be for S-409. This uncertainty necessitated a broad extraction study with very little end-use specificity. Our extraction data appear to the FDA to be sufficient to write a regulation in 121.2511 limiting its use to compositions for packaging and handling of food provided that:

- the film thickness is 4 mils or less
- the temperature of storage is below 120° F.
- the amount of S-409 extracted is less than 50-100 ppm (0.5 - 1.0 mg/in.²) from aqueous and fatty food simulants (H₂O, Acetic Acid and Heptane).

Of extreme interest, was Holtz' opinion that S-409 is already regulated in 121.2514 (Polymeric Coatings), 121.2526 (Paper Coatings) and 121.2550 (Closures with sealing gaskets for Food Containers) because these sections cover polyester resins prepared from 1,3-butylene glycol; adipic acid; and fatty acids. Rohm

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and Haas has assumed this to be the case for some time and have published this opinion in their literature on polymeric plasticizers. On February 10, 1970 we wrote to the FDA Regulatory Branch asking for an opinion relating to S-409 coverage in these sections. We have received no answer as yet. When asked about this letter, Holtz said he had received it only a few days ago. He suggested we direct the question to Walter Schaeffer who would promptly give an official FDA opinion in the form of a letter.

Action:

1. PRG -- Prepare letter to Walter Schaeffer asking for opinion on S-409 inclusion in 121.2514 and the dependent 121.2526 and 121.2550.
 2. JPM -- Obtain two additional heptane extraction data points on S-409 to achieve equilibrium.
 3. PRG -- Prepare revised petition on S-409 including reworded regulation based on FDA suggestions of realistic limitations. This can be in the form of a letter to Walter Schaeffer.
2. Santicizer 160. It was the general opinion of both the Chemistry and Toxicology sections that we have sufficient data to revise the present S-160 regulation to cover meat wrap film containing realistic combinations of S-160 with DOA. Holtz was able to arrive at this set of conditions -- film thickness under 3 mils and S-160 concentrations up to 18.8% (calculated as phthalic acid) of the total composition. These conditions would result in H₂O migration of 5 ppm (0.5 mg/in.²) and heptane extraction of >60 ppm (6 mg/in.²) which would be acceptable to the Toxicology section. The higher tolerance

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for the fatty food simulant was based on the FDA standard estimation that fatty foods amount to ca. 10% of man's total diet. This reduces the level to 0.6 mg/in.².

Action:

PRG -- Revise proposed regulation to include acceptable limitations.

3. Aroclor 5460. The most important limitation in the use of Aroclor 5460 in adhesives is the PCB content. Although no upper limit for PCB content was suggested by FDA, they asked that the petition include the minimum expected levels and a validated method for detection and measurement of PCB. Blumenthal expressed the opinion that we could get some coverage for hot melt adhesives perhaps in various stages. He indicated that these would probably be no problem in such uses as cereal boxes where it is unlikely that the adhesive joint will contact food for extended periods. He also indicated that they would be more critical of its use in ice cream carton adhesives if the amount of PCB or other contaminants were felt to be above safe levels. Blumenthal agreed that the fastest way to get approval is to limit the first regulation to the specific applications corresponding to the largest markets for A-5460 and those uses where our extraction and safety data are sufficient.

Action:

JPM -- Complete analytical work. Write up Method for Assay and PCB content of A-5460.

PRG -- Revise old petition as indicated above and file when ready.

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4. Santicizer 97A (C₇₋₉ Adipate). Since the structure of S-97A is significantly different from DOA, it could not be assumed that its toxicological affect and migration rates would be the same. The FDA suggested we not petition for S-97A coverage based on simularity without some safety data. They suggested that we compare a 90 day rat and dog study of S-97A to DOA. If the results are essentially the same, they would extrapolate the ninety-day results and compare to their existing two-year study on DOA.

The identification of the C₇₋₉ alcohol given to the FDA is attached. If the expected alcohol varies significantly, it is recommended that the feeding studies be run on the realistic model.

Action:

LOR -- Determine proper Model. Justify the expenditure of funds (ca. \$25,000) for 90 day study.

PRG/WHH/JPM -- Plan safety and extraction data requirements and initiate studies.

5. XL-8000 Lubricant. The first reaction by the FDA to our proposal to petition for FDA approval for XL-8000 without feeding studies was positive. Our extraction data have shown no loss of XL-8000 to heptane or water within the limitation of our IR analytical method.

It was also suggested that we could possibly obtain a letter of agreement from the FDA indicating approval providing the extraction data are acceptable and the method can be validated.

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Action:

PRG -- Prepare letter containing extraction results,
accuracy of the IR method and a write-up of
method to the FDA requesting an official
opinion.

P. R. Graham

Attachment

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COMPOSITION OF SANTICIZER 97A (FOR FDA)

Adipic acid ester with less than 0.25% residual alcohol.

Alcohol moieties as follows:

45% C₇ alcohol consisting of:

$$\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{OH} \quad 72\%$$

n-heptanol

$$\text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\underset{\text{CH}_3}{\text{CH}}-\text{CH}_2\text{OH} \quad 20\%$$

2-methyl hexanol 8%

$$\begin{array}{c} \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}-\text{CH}_2\text{OH} \\ | \\ \text{C}_2\text{H}_5 \\ \text{2-ethyl pentanol} \end{array}$$

55% C₉ alcohol consisting of:

$$\text{CH}_3\text{--CH}_2\text{--CH}_2\text{--CH}_2\text{--CH}_2\text{--CH}_2\text{--CH}_2\text{--CH}_2\text{CH}_2\text{OH} \quad 72\%$$

n-nonanol

$$\text{CH}_3\text{--CH}_2\text{--CH}_2\text{--CH}_2\text{--CH}_2\text{--CH}_2\underset{\text{CH}_3}{\text{CH}}\text{--CH}_2\text{OH} \quad 17\%$$

2-methyl octanol

$$\text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\underset{\text{C}_2\text{H}_5}{\text{CH}}-\text{CH}_2\text{OH} \quad 7\%$$

2-ethyl heptanol

$$\begin{array}{c} \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}-\text{CH}_2\text{OH} \\ | \\ \text{C}_3\text{H}_7 \end{array} \quad 4\%$$

2-propyl hexanol

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