MONSANTO COMPANY
St. Louis, Missouri

DEV. DEPT. CALL REPORT NO. 103-69

Food and Drug Administration
Washington, D. C.

Date of Call: November 25, 1969

FOR FDA
W. F. Randolph
A. Holz
Krishna Misera
Higenbothem

FOR MONSANTO
E. P. Benzing
W. H. Hunt
R. E. Keller
D. L. Taylor

cc: E. P. Benzing
D. R. Dill
A. J. Lauck
J. P. Petrovich
J. G. Bergomi
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M. V. Merchant
R. E. Keller
W. H. Hunt
George Ingle - Washington

df: FDA
Resins, Wet Strength

PURPOSE OF CALL: To review new RPC-1101 water extraction data prior to submitting a new petition.

ACTION:

1) Complete the RPC-1101 extraction study using the other food simulating solvents,

2) Characterize the chemistry of the water extraction residue,

3) Review completed data with FDA.

4) Initiate extraction studies with high pressure EVCl latices and review data with FDA.

SUMMARY: The new data, showing 20 to 90 times less RPC-1101 extracted by water than reported in our now withdrawn petition, puts us near the "non-extractable" range. FDA advised completion of the extraction study and chemical characterization of the water extract prior to our considering any 90-day feeding studies. We should then seek an advisory opinion from them. We learned two important points regarding extraction data on uncoated paper:

1) The FDA now defines the sample area extracted as only one side of the paper specimen even though it is thoroughly soaked -- this doubles our previously reported extractability figures;

2) The FDA no longer demands "extraction to equilibrium" data on uncoated paper -- 24 hour, 120° F. data is sufficient.

3) PB-702 is FDA approved for dry food contact under regulation 121.2571.

4) Guidance on which latex compositions to select for extraction studies has been obtained.

5) Extraction studies made on coatings on inert substrates will be acceptable.

DETAILS:

A week before the meeting we had sent Randolph the new data showing $1.1 \times 10^{-4}$ mg/in of RPC-1101 extracted by water from paperboard treated at 10 lb./ton and $4.3 \times 10^{-4}$ mg/in from a 20 lb./ton treated board. Reduction from the $90 \times 10^{-4}$ mg/in reported in the original petition resulted from several refinements in our papermaking and extraction techniques as detailed in the attached table. This table was not shown to the FDA because they did not question the validity of the new data.

Randolph began his commentary by pointing out that our extraction data in terms of mg/in$^2$ were low by a factor of two. We had been counting both sides of the paper sample as extracted area because a) the samples are entirely soaked through by the solvent; and b) the FDA at one time recommended counting both sides. Their current view is that food contacts only one side of a paperboard package or container but could extract material out of the entire thickness of the paperboard. Therefore where we had counted 100 in$^2$ from eight $2\frac{1}{2}$ inch squares, the FDA now counts only 50 in$^2$. This, of course, doubles our reported weight per unit area extraction data.

Randolph mentioned that we may be penalizing ourselves by using the "sandwich" extraction technique rather than the ASTM flat cell technique where the sample is backed by a metal plate. The sandwich method as we have been running it (screen/paper/screen/paper, etc.) allows extractives to diffuse out of both surfaces of the paper, whereas this is less likely in the cell method. A post-meeting review of the data in our petition shows that this may be so. The residue extracted (one-side basis) by the two methods from a waterleaf board by 120° F. water in 24 hours was:

a) Cell method (pg. B-40) = 0.14 mg/in$^2$

b) Sandwich method (pg. B-12) = 0.32 mg/in$^2$

We'll recheck this point on paperboard made by the improved procedures. This time we will follow exactly the sandwich method described in Section 121.2526 of the Federal Regulations which involves back-to-back paper samples: screen/paper/paper/screen/paper/paper, etc.

FDA says that our new extraction data puts RPC-1101 very near to the "non-extractable" classification, with water as solvent. Randolph offered that we definitely should not begin expensive 90-day feeding studies before first completing the extraction work and seeking an advisory opinion from FDA. After scaling up our extraction results by a factor of two, as discussed above, FDA calculates that an aqueous food could absorb 0.02 ppm of RPC-1101 from paperboard treated at 10 lb./ton and 0.09 ppm from paperboard treated at 20 lb./ton. To place these figures in perspective, consider the following:

a) The "FDA Guidelines" of 1966 say that 0.01 ppm of a substance added to food by migration is not considered a food additive.

b) The FDA is currently considering raising this to 0.05 ppm as a result of discussions with industry at a 1968 FDA sponsored conference.

c) According to Randolph, industry representatives are suggesting 0.5 ppm as being more realistic.

d) Dr. J. P. Frawley (chief toxicologist, Hercules) proposed at the 1968 conference that food packaging components contributing less than 0.1 ppm to the total diet of man be considered as nonmigratory.

Thus our extraction data is near to demonstrating "non-extractability" of RPC-1101, depending on how that term is defined. For this reason the FDA wants to see new extraction data with the other food simulating solvents and a chemical characterization of the water extract before offering an advisory opinion on whether we can justifiably petition for RPC-1101 on the basis on non-extractability.

Randolph said that the new extractions need be run only for 24 hours at 120° F in the case of uncoated paper. This represents a considerable easing on the "extraction to equilibrium" requirement stated in the Guidelines. The principal extraction data in our petition was at 120 hours. Another point made by Randolph and Holtz was that 8% ethanol would be a more realistic solvent to use than the 50% ethanol in the Guidelines. The other solvents will be 3% acetic acid and n-heptane.

To satisfy their request for more thorough chemical characterization of the water extract we will obtain 0.2 g of residue from untreated and 1% RPC-1101 treated paperboard by running 24-replicate extractions of each. This will provide enough material to determine C, H, N, Cl, infra-red spectra, average molecular weight, and vapor phase chromatograph. If the latter shows unique peaks in the extract from the treated board we may use the rapid scan mass spectrum technique to further characterize these peaks.

With regard to the September 23 FDA request for acute oral toxicity data on selected components of the amine raw material and for subacute (90-day) feeding studies on the RPC-1101, Randolph said that these requests no longer stand because they were based on the data available at that time. The new data will be judged on its own merits. Misera said that if the new data still showed the need for subacute feeding studies, the paper extract itself is what should be fed, not the resin solution. We agreed that this was proper however I pointed out that obtaining the large amounts of residue needed would be a nearly impossible task. Misera suggested that we could identify the residue chemically and then synthesize it. I feel that the possibility of doing this is quite remote. Hopefully the new data will render this problem irrelevant.

PIGMENT BINDER

PB-702 is covered for dry food contact under an existing regulation 121.2571 and no further work on our part is needed for such applications.

We explained that we would be interested in obtaining clearance for latexes with the following composition ranges: 60 - 95% vinylchloride, 5 - 40% ethylene, and 0 - 5% acrylamide with the acrylamide either intact or partially or completely hydrolyzed. We asked for guidance as to what compositions to use for the extraction studies. FDA personnel felt they had enough experience with ethylene and vinylchloride polymers to conclude that changing ratios of these monomers in the proposed range was not critical to toxicity. Of greater concern would be the acrylamide problem and what influence the hydrolysis step might have on amount and nature of extractants. The extraction study should be done on the polymer containing the highest level of acrylamide that we want to get approved and for hydrolyzed and unhydrolyzed polymer. Ethylene and vinylchloride contents at the level we are presently using will be satisfactory.

Polyacrylamide in the aqueous phase will be covered by the existing regulation in 121.2512 (no molecular weight limitation < 0.2% acrylamide monomer).

We indicated that we would like to obtain approval for pigment binder, prime coating and barrier coating applications. Randolph confirmed that for the barrier application extraction requirements would be more stringent and that if we could pass these, they could assume that we would be OK for less severe applications.

FDA agreed that if we would prepare our coatings on a non-paper substrate, e.g., glass or metal under the same conditions as paper coatings we could use them for extraction studies.

Holtz had reviewed the 1967 Monsanto internal extraction report by R. E. Keller. He suggested that our petition include validation of our analytical methods at the best achievable sensitivity levels. It should also include a more complete description of our process including the hydrolysis step. There was considerable discussion as to the best method to characterize extractable low molecular weight material. It was agreed that this would depend on the nature of the material. In some cases N analysis would be best in others Cl analysis and in still others a combination. The extraction data should be represented in tables showing the amounts of extract in $mg/in^2$. Sample calculations should be shown.

Holtz suggested that after we reorganize our data in this manner we contact them again for further comment.

E. P. Benzing

D. L. Taylor

/ds
Attachment

RSV 0008912

RPC-1101

FDA WATER EXTRACTIONS

NITROGEN DATA

| Procedures | 1968 Data in Petition 9B2371 | | Oct., 1969 | | Nov., 1969 | |
|---|---|---|---|---|---|---|
| Papermaking Water | Deionized | | Deionized | | Distilled | |
| Pressing | Wool Felt | | Wool Felt | | Blotters | |
| Curing, min. at 120° C. | 20 | | 10 | | 10 | |
| Extraction Water | Deion., Dist. | | Deion., Dist. | | Redist.,over acid | |
| Hours extracted at 120° F. | 120 | | 24 | | 24 | |
| Replicate Extractions | 1 or 2 | | 2 | | 6 | |
| Nitrogen Analysis | Combustion | | Kjeldahl | | Kjeldahl | |
| **Nitrogen, µg per Extract** | | **Net** | | **Net** | | **Net** |
| 0% Resin Added | 206 | | 99 | | 15.2 | |
| ½% Resin Added | - | | 97 | (-2) | 16.1 | (0.9) |
| 1% Resin Added | - | | 104 | ( 5) | 18.6 | (3.4) |
| 2% Resin Added | 278 | (72) | - | | | |
| Background from Water only | - | - | 73 | | 8.5 | |
| Background from Paper only (by diff.) | - | | 26 | | 6.7 | |
| 90% Confidence Limits | - | | ±30 | | ± 2.0 | |

Conversion Factor: ppm in food = (µg of N per extract)/80

FDA Consultation
11/20/69

## FDA QUESTIONS

1. What techniques have been used to detect and quantify polyacrylamide.

   (a) What techniques are recommended to analyze for molecular weights of polyacrylamide.

   (b) Will an average molecular weight of polyacrylamide be acceptable.

2. For the emulsion we can provide pH, solids, particle size-- is there any additional information needed? For the polyvinyl we can provide monomer content Tg, molecular weight -- is anything more needed?

3. Should we aim for an addition to the listing of substances under 121.2526 paragraphs (a) and (b) or for a separate section such as 121.2609 (vinyl chloride ethylene)which is not specific for paper.

4. Our polymer is listed under sections 121.2520 and 121.2571, covering adhesives and contact with any foods. Should this be cited in the petition?

5. Refer to section 121.2526, paragraph (b). This cites broad coverage to acrylic copolymers and gives a 5% limit to specific comonomers. Were these given some blanket approval or were extractions run for each of the numerous combinations.

6. If our polymer varies in acrylamide content from 5 to 1% must we run extractions for all products within this range or can we get coverage by studying only the 5% (acrylamide) product?

7. We have changed our process, i.e., gone to higher pressures -- does this necessarily mean we must rerun our extractions, our monomer ratios remain unchanged. Could we spot check the extractable polyacrylamide and submit our data in petition?

8. To eliminate the effects of high extractables from the blank or control substrate, may we apply coatings to glass or metal instead of paper or paperboard?

M. V. Merchant

/ds

Medical Department

E. P. Benzing
N. V. Merchant

December 3, 1969

Ethylene Vinyl Chloride Latex
PB 702

J. O. Bergomi

Y-69-126

The undiluted sample was classed as practically non-toxic when administered orally to mixed sex rats. The acute minimal lethal dose was greater than 15,800 mg/kg. There were no toxic signs. Macroscopic examination of the sacrificed animals revealed a normal viscera.

The undiluted sample was classed as practically non-toxic when applied to and retained for 24 hours on the clipped intact skin of mixed sex rabbits. The acute minimal lethal dose was greater than 7940 mg/kg. There were no toxic signs. Macroscopic examination of the sacrificed animals revealed a normal viscera.

The undiluted sample was found to be non-irritating when applied to andretained for 24 hours on the clipped intact skin of mixed sex rabbits. The score throughout was 0/8.

The undiluted sample was classed as a slight irritant when instilled into and retained for 24 hours in the conjunctival sac of the rabbit eye. At 1 hour of contact the score was 8/110; at 24 hours the score was 0/110; at which time the eye was flushed with water.

This preparation requires no special handling.

In case of skin contact wash off with soap and water for hygienic reasons.

In case of accidental eye contact flush out with water.

William N. Hunt, Ph.D.
Toxicologist

RSV 0008914