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LEGAL DEPARTMENT

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H. A. LIPS
ORGANIC CHEMICALS DEPARTMENT

FOOD ADDITIVE PETITION NO. 5B1747
"ZONYL" RP PAPER FLUORIDIZER

S. E. Krahler, H. Sherman and the undersigned met with Messrs. Blumenthal, McLaughlin, Orr and Detwiler of FDA on March 22, 1966, to determine whether there is a basis upon which the above Food Additive Petition may be approved.

Initially, we inquired of the FDA officials as to the reasons for not accepting the Petition for filing. They indicated that with respect to compounds with which they are not familiar, two-year feeding studies are the usual standard requirement. In the event ninety-day studies are utilized, they now look for a no-effect level of 1,000. The migration data which we had submitted indicated that approximately 1 ppm might migrate into the food and, therefore, FDA would require no effect at the 1,000 ppm level. The toxicity data at the 1,000 ppm level did show some enlargement of livers, although unaccompanied by histological changes. Such an enlargement is considered an "effect" by FDA since, with only the ninety-day studies, they are unwilling to speculate as to whether the effect would increase or decrease after feeding was continued for two years. They indicated that often at the end of ninety days the results look their worst, and that, if continued for two years, the apparently adverse results at ninety days might well appear without significance at the end of two years.

There thus was no basis upon which we could persuade FDA to accept 1 ppm in food on the basis of our ninety-day studies. Since additional toxicity studies would appear to be out of the question for reasons of time and money, we approached the problem on the basis

that undoubtedly actual migration would be significantly less than 1 ppm. We presented the revised calculations based on ZONYL RP treatment of 0.25% (OWP) and compared the average ppm extraction of ZONYL RP solids against such extractions based upon 0.50% (OWP) treatment. We basically told them we could live with a regulation limited to .5 ppm extraction. FDA indicated that this would be unsatisfactory.

However, FDA did indicate that .1 ppm probably would be acceptable based upon the toxicity data already submitted. They did not indicate exactly what number would be acceptable but at least we clearly know the limits: .5 ppm is not acceptable and .1 ppm would be acceptable.

Dr. McLaughlin advanced an interesting idea as to what actually is causing the toxic reaction in the compound. He recalled that diethylamine salt has been known to cause increased liver weight without histological change. Dr. Blumenthal confirmed this by reference to toxicity data developed by the Mellon Institute for Union Carbide. Thus it may be that the diethylamine salt rather than the perfluoroalkyl phosphate is the bad actor. If so, FDA would be more inclined to approve our petition since they have some familiarity with diethylamine salts and are reluctant to approve a petition involving perfluoroalkyl phosphates with which they are totally unfamiliar. Also, there is always the possibility that we could eliminate the diethylamine salt, thereby eliminating the toxicity problem. However, we did not indicate that this was a practical alternative since, even if the diethylamine salt were eliminated, we would still have to submit data on the perfluoroalkyl phosphate or else absolutely prove that the diethylamine salt was causing the toxicity.

Our task is now threefold. First, Technical Lab will have to determine the maximum level at which we can expect customers to apply ZONYL to the surface of paperboard. Obviously, this figure will have to be rather precise since we cannot afford to have a level of application any higher than is absolutely necessary for practical commercial use. Secondly, Jackson Lab will then

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have to conduct extraction tests based upon the level of application determined by Technical Lab. Probably two or three sets of extraction tests should be run on levels of application close to the figure determined by Technical Lab. These extraction tests need only be run on water and Wesson Oil. Third, we will need a write-up by Haskell as to any ideas they might have on the toxicity of the diethylamine salt.

The above information will then be prepared as a supplement to the original petition and we will no doubt take it down to FDA and review it with them. It is extremely difficult to speculate on the ppm figure which FDA will accept but probably it will not accept anything more than .3. This must be borne in mind in determining levels of application.

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