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See note
4-14-78
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To: All Members of:

SPI-VCM/PVC Mailing List (Letter No. 38)
Plastic Bottle Institute
Plastic Beverage Container Group
AN Safety Group
PET Safety Group
Food, Drug and Cosmetic Packaging
Materials Committee
PVC Safety Group

Letter Highlights

(1) FDA has made available an assessment of the risk of liver cancer from aflatoxin contamination of corn and peanut products. Copies are enclosed because of its relevance to estimating the risk associated with other substances such as components of packaging materials.

(2) The risk assessment techniques applied by FDA with regard to aflatoxin are far less conservative than the risk assessments that have been submitted to FDA for food packaging materials.

(3) Data from Professor Maltoni's ingestion studies of acrylonitrile and vinyl chloride have become available and are discussed. Copies of the final acrylonitrile report and excerpts of the vinyl chloride interim report are enclosed.

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(4) "Back-of-the-envelope" type risk calculations indicate that the latest toxicological data will confirm that maximum projected migration of acrylonitrile and vinyl chloride from food packaging materials are well below an "acceptable tolerance level," even if much more stringent criteria than those used in the aflatoxin document are employed. A conservative tolerance level of 16 ppb for products like acrylonitrile copolymer beverage containers and 52-104 ppb for polyvinyl chloride food packaging are estimated.

Ladies and Gentlemen:

As reported in our letter of February 28, 1978, Sherwin Gardner, Deputy Commissioner of Food and Drugs, has informally requested that risk assessments be performed for plastics packaging using the approach being developed by the Food and Drug Administration (FDA) with regard to aflatoxin and lead contamination. Accordingly we are sure you will be interested in reading FDA's newly released "Assessment of Estimated Risk Resulting from Aflatoxins in Consumer Peanut Products and Other Food Commodities," dated January 19, 1978, a copy of which we are enclosing. Notice of the availability of this risk assessment appeared in the Federal Register on March 3, 1978. FDA's risk assessment for lead migration has not been published yet.

We have recently obtained and are enclosing copies of additional information regarding the acrylonitrile and vinyl chloride studies of Professor Maltoni, Director of the Institute of Oncology in Bologna, Italy. These new data are crucial because risk extrapolations can most effectively be performed only when complete data are available.

Aflatoxin Risk Assessment

By comparison to other risk extrapolations that have been submitted to FDA for food packaging materials (PVC and AN copolymers), the FDA assessment of the cancer

risk posed by aflatoxin could be termed recklessly non-conservative. Indeed, it is hard to compare the FDA assessment of the risk presented by aflatoxin to existing calculations of risk for acrylonitrile or vinyl chloride since FDA's methodology with regard to aflatoxin departs drastically from previously accepted norms with respect to both the mathematical model employed and in the handling of the data.

FDA's risk assessment for aflatoxin concerns itself solely with aflatoxin contamination of corn and peanut products since, according to FDA, these are the only products where such contamination is generally at a detectable level. FDA justifies ignoring the levels of aflatoxin in other food products on the grounds that considering them would not significantly alter the conclusions of the report. We are at a loss to understand why the level of aflatoxin contamination in other foods known to contain aflatoxin is not assumed to be at a level just below the sensitivity of analytical detection methods, an assumption FDA routinely applies to other products.

Another interesting aspect of the risk assessment for aflatoxin is FDA's method of estimating dietary consumption. Although the 90th percentile of consumption is considered, nowhere in the document is there any reference to a gluttonous consumer of peanut or corn products who might make corn or peanuts the major portion or sole constituent of his diet, as was insisted upon by the Government in dealing with carbonated beverages in the hearing on acrylonitrile copolymer beverage containers; nor is any discussion devoted to the risk to a child who eats only peanut butter and jelly sandwiches. From a statistical standpoint, it is, of course, proper to ignore such transient or aberrant dietary practices since they have little significance when assessing the average risk to the entire population over a full life span. It appears that the Commissioner now concurs with this position although he chose to decide otherwise when dealing with beverage containers.

A very significant non-conservatism in FDA's risk assessment concerns the level of confidence associated with its Mantel-Bryan risk extrapolation. In all previous Mantel-Bryan extrapolations on acrylonitrile and vinyl chloride, the toxicological data was conservatively handled (i.e., given a "worst case" interpretation) in a manner that yielded

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a 99% confidence factor for the result. This 99% confidence factor is part of the modified Mantel-Bryan procedure and was adopted by FDA in its Sensitivity of Method Regulation on Carcinogenic Animal Drug Residues. We have not been able to verify independently the confidence limit used in FDA's aflatoxin risk extrapolation, but the discussion on page 11 and the accompanying Table V suggest to us that no such conservative treatment of the toxicological data was applied before performing the Mantel-Bryan extrapolation.

The above comments barely begin to cover the inconsistencies between FDA's risk assessment for aflatoxin and the ultraconservative, by comparison, risk assessments that have been submitted to FDA for residual monomers that unavoidably contaminate plastics packaging materials. Candidly, our general impression is that FDA made unsupported assumptions and distorted the numerical presentations in the aflatoxin document to support the conclusion it wanted to reach.

We considered preparing SPI comments on FDA's aflatoxin risk assessment, but have concluded that such comments would be more appropriate on the risk assessment for lead migration which is being prepared by FDA and should be available shortly. Inasmuch as FDA provided only a brief period for comment with respect to aflatoxin, and suspecting that an equally brief time will be allowed vis-a-vis any lead document, it may not be possible for us to go through normal full-scale clearance procedures with respect to comments on the risk assessment for lead. Nonetheless, we shall proceed on the basis that comments on the lead assessment will be desirable and will endeavor to get draft comments to a cross-section of SPI members for clearance prior to filing.

Risk Assessments for Plastics Monomers

A major criticism of risk extrapolations for both acrylonitrile and vinyl chloride have concerned the fact that they were based on the results of incomplete feeding data in one case and on inhalation data in the other. Professor Maltoni has now completed his ingestion studies of acrylonitrile and vinyl chloride. A final report on the

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acrylonitrile study has been published and we are enclosing a copy for your information. Professor Maltoni concludes that at a level of 5mg/kg administered three times per week, acrylonitrile exhibited a "borderline" oncogenic effect. We are hopeful, but not optimistic, that a final report on vinyl chloride will be forthcoming shortly.

In the meantime, through the very gracious cooperation of one of our members, a monograph presenting (in French) the papers and the ensuing discussions delivered at a Colloquium held in Paris on March 2, 1976, has now become available. Professor Maltoni presented a comprehensive review of his work to that date on vinyl chloride carcinogenicity and a full copy of his paper has been provided to the Food and Drug Administration (FDA). Because of the length of the paper, we cannot distribute it to all of you receiving this letter but we are enclosing copies of pages 25 and 26 of the monograph which report the results of the gavage (stomach tube) feeding experiments to that date.

The conclusions Professor Maltoni drew from the almost completed feeding test (page 26) can be translated roughly as follows:

(1) At 50 and 16.65 mg/kg VCM produces angiosarcomas of the liver and nephroblastomas; these two tumors are the most characteristic produced by the monomer.

(2) At 3.3 mg/kg the two angiosarcomas which have been observed were not located in the liver. (One appeared in the lung, the other near the kidneys.)

(3) There is a clear relationship between dose of monomer and tumor response with a sharp drop-off between 16.65 and 3.33 mg/kg.

Professor Maltoni further stated that in his experiments the 3.33 mg/kg dosage appeared to have a "border line" carcinogenic effect. He then reported that in another experiment in which animals were treated with 1 mg/kg, 0.3 mg/kg and 0.03 mg/kg, no tumors had been observed after 57 weeks into the test.

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In our last letter to the SPI-VCM/PVC Mailing List (Letter No. 37), we discussed the need for completed toxicology studies to provide a sound basis for a risk assessment. Using the FDA risk assessment for aflatoxin as a model, the results of completed long-term feeding studies for acrylonitrile and the most recent vinyl chloride data, we are now in a better position to calculate the risk associated with residual monomers that contaminate food packaging on a basis comparable to that used by FDA. As crude examples (the following should be considered to be merely illustrative and not definitive since it is based on the still incomplete Maltoni data for vinyl chloride and rule-of-thumb calculations) of how a Mantel-Bryan risk evaluation might work, Dr. Dixler has estimated the dietary concentrations for vinyl chloride and acrylonitrile that assure a risk to humans of no more than one in one hundred million (10^{-8}). You may recall that FDA used a risk level of 10^{-6} in its Regulation on Carcinogenic Animal Drug Residues. Because of conservatism in the procedure, however, FDA has stated that the risk presented by its sensitivity of method approach is no more than 10^{-8} .

Vinyl Chloride

Assume that the final Maltoni data for vinyl chloride indeed demonstrates that 3.33 mg/kg administered between four and five days a week is a "no effect" level. Since the vinyl chloride was administered only four to five days a week, we shall assume that the daily dose was 4.5/7ths of 3.33 mg/kg or 2.14 mg/kg. Applying the usual Mantel-Bryan "worst case" assumptions, it can be roughly estimated that, at a 99% confidence level, 2.14 mg/kg would "produce" 4.5 cancers in 100 (4.5%). The Mantel-Bryan "safe" dose at a risk of one in one hundred million is approximately 1/8300 of the dose that causes a 4.5% incidence of cancer. Therefore, a dietary intake of 2.14 divided by 8300 or 0.00026 mg/kg could be deemed "safe" as a total dietary exposure.

Depending upon the assumptions used to convert mg/kg of body weight in the rat to parts per million (ppm) in the total diet in man, 0.00026 mg/kg is equivalent

to 5.2-10.4 parts per billion (ppb) as the safe total dietary exposure for man. Since one can very conservatively assume that PVC could not package more than 10% of the diet, an actual migration level of ten times the safe exposure level could be set as a "tolerance." This tolerance (not more than 52-104 ppb migrating to food) assures that the risk of cancer could not exceed one in one hundred million. In this light, it would certainly seem reasonable to us that a finding of "non-detectable" with an analytical method sensitive to 2 ppb should be deemed to assure virtually absolute safety.

Acrylonitrile

A similar exercise for acrylonitrile, assuming that 5 mg/kg administered thrice weekly is a "no effect" level, also gives an approximate safe total dietary exposure for rats of 0.00026 mg/kg. For a 60 kg (132 lb) person, this is equivalent to a daily intake of 0.0156 mg, as posing a risk no higher than one in one hundred million. Based on the 90th percentile for carbonated beverage consumption (1 liter/day) and assuming all such consumption were from acrylonitrile copolymer packaging, the acceptable migration tolerance would be 16 ppb. If we make the more reasonable assumption that no more than 50% of the carbonated beverage consumption were packaged in AN copolymer containers, a tolerance of 31 ppb would assure virtually absolute safety. Here again, the present analytical sensitivity of 10 ppb is sufficient to reduce any risk from AN to below any meaningful level.

We are sure you will recognize that the foregoing exercises in arithmetic are provided merely to show how important completed toxicology studies are in order to provide a firm basis for risk assessments. In addition to animal studies, FDA would also consider such epidemiological data as can be presented, as well as other methods than the Mantel-Bryan procedure for extrapolating from observed risks at high exposure levels to estimated risks at infinitesimal exposure levels, as was done for aflatoxin.

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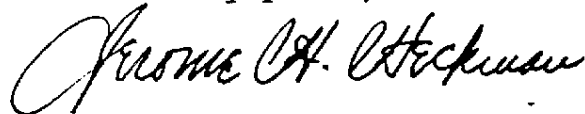
The risk that society might accept for a food packaging material may well be less than the risk considered acceptable for aflatoxin in food. Be that as it may, justice would seem to require that the relevant risk assessments be carried out in a consistent fashion or one is left trying to compare apples to oranges. Even with the biased comparison, the conservative risk assessments that have been done for acrylonitrile and vinyl chloride predict a risk orders of magnitude lower than that accepted by FDA for aflatoxin. It appears that if the acrylonitrile and vinyl chloride data were treated in a manner consistent with the FDA risk assessment for aflatoxin, the estimated risk associated with such food packaging would have to be deemed unworthy of any concern.

There must be a finite level of risk that can be accepted for food packaging since it clearly has social utility. Even such staunch defenders of the public health as Senator Edward Kennedy (D.-Mass.), have now publicly recognized that absolute safety is unattainable. A copy of a speech given by Senator Kennedy at an FDA/EPA Symposium on risk-benefit which appeared in the Congressional Record is enclosed.

It appears, therefore, that recent data concerning the toxicology of acrylonitrile and migration potential (or lack thereof) for vinyl chloride, as well as public and legislative opinion are beginning to realign in a way that may yet make it possible for FDA to acknowledge the existence of a slight risk with respect to packaging materials in general, and that the risk from assumed acrylonitrile or vinyl chloride (and ultimately for any other residual monomer that becomes a concern) migration is trivial and not worthy of regulatory attention.

We shall, as usual, keep you up-to-date regarding the various regulatory activities relating to vinyl chloride polyvinyl chloride and acrylonitrile. In the meantime, those of you who require a complete copy of Professor Maltoni's paper are requested to contact us so we can make special arrangements with you to make it available.

Cordially yours,



Enclosures

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