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November 10, 1969

Mr. Robert M. Miller
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Dear Bob:

Following up on our letter of last week, I thought you and all of the members of our Food, Drug and Cosmetic Packaging Materials Committee might be interested in seeing the coverage given the release of the NAS-NRC "Toxicological Insignificance" report by Lou Rothschild, editor of Food Chemical News. Thus, as we have done in the past, I have obtained Lou's permission to reproduce pages 14 through 17 of this week's issue, and am enclosing reproductions of the same herewith.

I realize, of course, that many of our Committee members receive Lou's excellent trade paper but I know that some do not. In any case, sending you this material should help to provide everyone with a further insight into what is happening as regards the anticipated proposal to revise Section 121.2500 of the Food Additive Regulations.

While writing to bring this information to your attention, let me also take this opportunity to mention that I have noticed a new series of articles on food additives being run in The New York Times as an aftermath of "Cyclamania." The first in this series, written by a Miss Sandra Blakeslee, began on the first page of yesterday's "Times." I was particularly interested in Miss Blakeslee's observations about "accidental or unintentional food additives."

Interestingly the [illegible]
'As many experts have [illegible]
been done to limit and [illegible]
of unintentional additives [illegible] that has
been done to control [illegible] of un-
tentional additives.' [illegible] whether
this really amounts to [illegible] and or
not, but I commend the [illegible] the acute
observation. It may [illegible] many
of our Committee members [illegible] the
Times' series, as we [illegible]

We shall do [illegible] informing you about these matters. If you have any questions in the meantime, please do not hesitate to let us know.

Cordially yours,

[signature]

cc SPI Food, Drug and Cosmetic Packaging
Materials Committee

FDA noted it conducted during 1969 three studies "to determine the residues of sulfa drugs in animal tissues resulting from feeding studies conducted according to authorized use of such drugs." The agency explained that "the results of this study will provide assurance for BVM in reaching a decision as to the safety of the continued use of these three registered sulfa drugs."

Under study were: (1) sulfaquinoxaline residues in chicken tissues; (2) sulfathiazole residues in swine tissues; and (3) sulfamerazine residues in calf tissues.

Among FDA's objectives for the fiscal year 1969-1974 period is the development of "new and better methods for detecting residues of antibiotic and non-antibiotic drugs in meat and milk for 40 drugs for which tolerance levels have not yet been established," the report disclosed.

During 1969, FDA said, 12 analytical methods were validated, 8 of them for drug residues in animal tissues and 4 for drug residues in animal feeds. "The results of the validation studies provide BVM with the necessary information in order to determine the safety of proposed uses of such drugs," FDA said.

Methods were validated for residues in animal tissues of: (1) ronidazole; (2) zearalanol; (3) rofenaid; (4) chlormadinone acetate; (5) maretin; (6) medrol; (7) 1-tetramisole; and (8) decoquinoate. Methods were validated for residues in feeds of: (1) ronidazole; (2) chlormadinone acetate; (3) cyzine; and (4) dimetridazole.

FDA also said that during fiscal year 1969 it conducted a study designed to develop a method for determination of the gramicidin and tyrocidin components of tyrothricin in milk. The study showed that such a method is "feasible," the agency said.

NAS-NRC TOXICOLOGICAL INSIGNIFICANCE REPORT FINALLY PUBLISHED

The National Academy of Sciences-National Research Council's Food Protection Committee has officially released its task force report on "Guidelines for Estimating Toxicologically Insignificant Levels of Chemicals in Food," as expected (See FOOD CHEMICAL NEWS, Sept. 29, Page 2).

The report was held up five months after it was informally transmitted to the Food and Drug Administration and was reported in FCOD CHEMICAL NEWS (See FOOD CHEMICAL NEWS, Feb. 3, Page 29). Despite the long delay in publication of the 8-page pamphlet, only editorial changes were made in the report. There were no substantive changes.

Net effect of the NAS-NRC delay was to officially release the report at the wrong time - - politically, that is. With the current furor over food additives, and especially those exempted from clearance procedures, the official exclusion of indirect additives from clearance procedures at this time could subject both FDA and industry to widespread criticism.

The task force report, and any adoption of the principle of "toxicological insignificance" by FDA, is scientifically acceptable, at any time. Politically, however, it might be unpalatable right now.

FDA May Propose Regulations for Indirect Additives

Despite the political realities, FDA may forge ahead with its proposal to exclude toxicologically insignificant indirect additives from clearance procedures. The agency earlier distributed a "discussion draft" of its proposal (See FOOD CHEMICAL NEWS, May 12, Page 3), and has received industry comments on it (See FOOD CHEMICAL NEWS, Sept. 15, Page 3). The agency was waiting only for formal publication of the NAS-NRC task force report.

Armed with the report, the agency is now seeking final comments from FDA-ers on the proposal - - in the light of the task force report and industry comments. Next step will be publication of a proposal in the Federal Register - - unless politically sensitive officials in FDA's parent Health, Education and Welfare Department decide to sit tight until the current food additive hysteria blows over.

Of long-range significance is the NAS-NRC acceptance of the principle of "toxicological insignificance," with FDA acceptance of the idea apparently imminent. Whereas the primary practical impact may be in the field of indirect additives, there eventually could be a similar change in attitude towards many direct food additives used at low levels.

On the one hand, the current furor over the "generally recognized as safe" list of additives excluded from clearance procedures may make it difficult to implement the "toxicological insignificance" principle at this time. On the other hand, however, problems of the status of some substances now considered GRAS could ultimately be resolved by a finding that they are "toxicologically insignificant."

Copies of "Guidelines for Estimating Toxicologically Insignificant Levels of Chemicals in Food" are available from NAS-NRC.

The report excludes from consideration for toxicological insignificance certain impurities or contaminants of natural origin such as aflatoxin, certain essential nutrients and hormones, certain heavy metals and their compounds, and certain organic compounds employed for their biological activity. The FDA discussion paper had similar exclusions.

The task force recommended that a chemical be considered toxicologically insignificant if it has been in commercial production for five years or more, "without evidence of toxicological hazard incident to its production or use," if it is used at a level that provides no more than 0.1 p.p.m. to the diet.

Substances used above 0.1 p.p.m. of the diet but at 1.0 p.p.m. or less would be considered toxicologically insignificant if they are of known structure and purity, they are structurally simple, they are readily handled through known m tabolic pathways, and they are members of closely related groups of substances that are low in toxicity.

The report also discussed new substances where studies establish safe levels of at least two analogous substances, where the acute or subacute toxicity of the new substance and the analogous substances is of the same nature and degree. If the safe levels for all structurally analogous substances are "essentially identical," the report said, 1/10 of the estimated safe level can be considered toxicologically insignificant. If there is appreciable difference among the safe levels of analogous substances, the insignificant level would be 1/20 of the estimated safe level.

In contrast to the NAS-NRC recommendation on toxicological insignificance based upon the amount of a substance in the total diet, FDA in its draft paper proposed that a substance be considered toxicologically insignificant if it can be present at not more than 0.05 p.p.m. in contacted food.

Although industry would prefer the NAS-NRC approach, involving amounts in the total diet, it is apparent that it would go along with FDA's approach basing toxicological insignificance on amounts in contacted foods. However, industry spokesmen have urged a maximum amount of 0.5 p.p.m. rather than 0.05 p.p.m., and there have been indications that FDA may raise the 0.05 p.p.m. figure.

FDA is not expected to go along with an industry proposal, first propounded by Hercules' Dr. John Frawley, exempting from clearance procedures substances used at less than 0.2% by weight of packaging material.

Another recommendation in the NAS-NRC report dealt with pesticide degradation products. The report said, "If the safe level of the pesticide is 1 p.p.m. or above, it appears to be a safe working guideline that dietary levels of degradable products below 0.1 p.p.m. are insignificant and undeserving of laboratory investigation."

A portion of the FDA draft proposal which is non-controversial would exclude from clearance procedures broad categories of substances which are not technically "food additives." These substances, although many are now cleared under Food Additive Orders, do not actually get into food.

The Task Force included in its report a mildly-worded criticism of the Delaney Clause of the Food Additive Law. Noting that the Delaney Clause bans use of a substance "if a level in the feeding test that permits survival of at least some of the animals for the duration of the test is found to produce cancer," the report said:

> "An observation of any such serious condition makes it prudent to consider the nature of the dose-response relationship and the physiologic, metabolic, or pathologic processes involved to insure against the possibility that the same effect might occur in man."

In the wake of the banning of cyclamates as a food ingredient, there has been increased discussion about the possible revocation of the Delaney Clause. However, it is apparent that repeal or even amendment of the provision will

be politically difficult, until some common, needed food ingredients are shown to be carcinogenic in animal tests. (See story, Page 3).

Under discussion outside of government circles is the possibility of amending the Delaney Clause to bar substances found to be carcinogenic to laboratory animals only if the tests are deemed by FDA to be applicable to human exposure.

NCA OPPOSES ASCORBIC ACID QUANTITY LABELING FOR PEACHES

The National Canners Association, which proposed an amendment to the food standard for Canned Peaches to permit use of ascorbic acid and erythorbic acid, wrote to the Food and Drug Administration recently to oppose a suggestion that labels declare the minimum amount of ascorbic acid.

In a comment on the proposed amendment, University of California's (Berkeley) Dr. George M. Briggs urged that the minimum quantity be declared (See FOOD CHEMICAL NEWS, Oct. 13, Page 23). NCA said in its letter that "the declaration of ascorbic acid as vitamin C would only serve to mislead the consumer into believing that canned peaches might be intended as a proper source of vitamin C in her diet."

The Association said that the addition of nutrients to standardized foods for fortification "is subject to a number of criteria relating to the suitability of adding the particular nutrient to the food under consideration." NCA said its proposal "makes no showing that these criteria are met with respect to the addition of ascorbic acid to canned peaches and NCA has no intention of demonstrating, or ability to demonstrate, that the proposed addition would meet these criteria." The Association explained:

> "While Professor Briggs is entirely correct that ascorbic acid has recognized nutritive values as vitamin C in addition to its color fixative properties, his comment misses the mark. As proposed by NCA the only purpose of the additive ascorbic acid is as a color fixative. While this additive may have the incidental effect of providing some vitamin C fortification for this product, this is not its intent. Hence, the quantity added will vary according to the technical requirements of the preservation of color and may well vary so much that no meaningful or consistent statement could be made of its incidental attributes."

IMITATION MILK OPTIONAL INGREDIENT REVISION ASKED

Central Soya last week asked the Food and Drug Administration to revise the provision of the proposed food standard for Imitation Milk which covers optional ingredients.

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November 6, 1969

Mr. Robert M. Miller
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Dear Bob:

As you are aware, for quite some time now we have been awaiting word that the Food Protection Committee - Food and Nutrition Board of the National Academy of Sciences - National Research Council has finally published the Food Protection Committee's report entitled 'Guidelines for Estimating Toxicologically Insignificant Levels of Chemicals in Food.' Indeed, for the past several weeks, we have been informed by the Food and Drug Administration that it, too, was awaiting receipt of the formal document and would be delaying action on the proposal to amend Section 121.2500 of the Food Additive Regulations until this report was official.

We are pleased to inform you that this report has now been printed, copies have been sent to FDA, and we have been able to obtain a very small supply. At our request, Mr. Paul Johnson of the National Academy of Sciences is preparing an additional 150 copies so that we can transmit one to each member of the SPI Food, Drug and Cosmetic Packaging Materials Committee. The reproduction effort by Mr. Johnson is underway so we should have the copies for everyone within the next week or so. In the meantime, one copy is enclosed herewith for your information.

Now that the "Guidelines" are in every sense 'official," we believe that the FDA Staff will complete its work on the draft revisions of Section 121.2500 and publish the same as a "Notice of Proposed Rule Making" in a forthcoming issue of the Federal Register. Exactly when this will happen is difficult to predict, especially in light of the Agency's present preoccupation with the aftermath of its Cyclamates announcement. 'Cyclamania" is the order of the day at the Food and Drug Administration now so the publication of any proposal to relax food additive control to any degree is apt to be delayed for a more favorable time.

From all we have been able to gather at this point, we doubt that FDA will publish anything more favorable than the proposal previously submitted to us and considered in such depth by the Inter-Industry Committee. In other words, we are not too optimistic about the possibility of the Agency's raising the .05 ppm extraction criterion. In any case, there is little we can do other than to wait for the publication of the anticipated "Notice of Proposed Rule Making." In keeping with some of our previous discussions, I continue to feel that the next meeting of our Committee should be delayed until the "Notice of Proposed Rule Making" is published.

As soon as we have the additional copies of the Food Protection Committee's report, we shall be writing to you and the other members of the Committee again to transmit the same. At that time, I will also try to give you any further word we may have received

concerning action on the over-all incidental additives problem. If you have any questions before then, please do not hesitate to let me know.

Cordially yours,

Jerome W. Hickman

cc SPI Food, Drug and Cosmetic Packaging
Materials Committee