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PART V

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

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INDIRECT ADDITIVES: POLYMERS

Acrylonitrile Copolymers Used to Fabricate Beverage Containers; Final Decision

Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

[Docket No. 76N-0070]

PART 177—INDIRECT ADDITIVES: POLYMERS

Acrylonitrile Copolymers Used To Fabricate Beverage Containers; Final Decision

AGENCY: Food and Drug Administration (FDA).

ACTION: Final Decision Following A Formal Evidentiary Public Hearing, Findings Of Fact, Conclusions Of Law and Final Order.

SUMMARY: The Commissioner is publishing his final decision following a formal evidentiary public hearing in a rulemaking proceeding concerning acrylonitrile copolymers used to fabricate beverage containers. He has determined that acrylonitrile copolymers used to fabricate beverage containers are food additives and that they have not been shown to be safe. He affirms the Initial Decision of the Administrative Law Judge with the modifications and supplementation stated below. The food additive regulations at issue (21 CFR 177.1020, 177.1030, 177.1040, 177.1050, and 177.1480) are amended to eliminate use of acrylonitrile copolymers to fabricate beverage containers.

EFFECTIVE DATE: The effective date of the final decision is September 19, 1977. The final order amending the regulations is effective December 22, 1977.

ADDRESS: The transcript of the hearing, evidence submitted and all other documents cited in this decision may be seen in the Office of the Hearing Clerk (HFC–20), Rm. 4–65, 5600 Fishers Lane, Rockville, Md. 20857, between the hours of 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT:

Ted Herman, Compliance Regulations Policy Staff (HFC–10), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857, (303–443–3480).

SUPPLEMENTARY INFORMATION: The purpose of this rulemaking proceeding is to decide whether acrylonitrile copolymers used to fabricate beverage containers are food additives within the meaning of section 201(s) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 301 *et seq.*, *321(s)*, and whether they have been shown to be safe under section 409 of the Act, 21 U.S.C. 348.

I. History

Acrylonitrile copolymers have been permitted to be used in beverage containers under the following food additive regulations: 21 CFR 177.1020, 177.1030, 177.1040, 177.1050, and 177.1480. In the Federal Register of June 14, 1976 (41 FR 23940), the Commissioner issued an interim regulation (21 CFR 180.22, formerly 21 CFR 121.4010), requiring additional testing to be undertaken to determine whether acrylonitrile is safe for use in beverage containers and for other food contact uses. The Natural Resources Defense Council (NRDC) objected to the interim regulation, and requested a stay of the regulations and hearing on whether acrylonitrile could continue to be safely used. When the tests undertaken pursuant to the interim regulation showed positive results, the Commissioner issued an order, published in the Federal Register of March 11, 1977 (42 FR 13546), which stayed the regulations to the extent they permitted acrylonitrile copolymers to be used in beverage containers pending completion and evaluation of the studies required by the interim regulation. The Commissioner issued the stay on the basis of the objections filed earlier by NRDC. The Monsanto Co., a manufacturer of acrylonitrile bottles, sought judicial review of the stay before the United States Court of Appeals for the District of Columbia. *Monsanto Co. v. Gardner*, C.A. No. 77–1245 (D.C. Cir., 1977).

The Court found that the Commissioner could not stay the regulations on the basis of the objections filed by NRDC because of the passage of time. The Court held that the Commissioner, at least in substantial part, had acted on his own initiative pursuant to sections 409 (d) and (h) of the Act, 21 U.S.C. 348 (d) and (h). The Court ordered a prompt hearing on the Monsanto objections, and set a date, later extended to September 19, 1977, for issuance of a final decision. This proceeding has been held, and this decision is being issued, pursuant to the Court's order.

The Commissioner issued a notice of hearing in this matter and waived certain procedures in the Federal Register of April 1, 1977 (42 FR 17529). The participants in the hearing were the Bureau of Foods of the Food and Drug Administration (Bureau), Natural Resources Defense Council (NRDC) and, for the manufacturers of acrylonitrile bottles, the Monsanto Co. (Monsanto), Borg-Warner Corp. (Borg-Warner), and Vistron Corp. (Vistron). Following a formal evidentiary public hearing, the Administrative Law Judge issued an Initial Decision on August 4, 1977, finding acrylonitrile copolymers used to fabricate beverage containers to be food additives which had not been shown to be safe.[1] The manufacturers excepted to the Initial Decision and appealed it to the Commissioner. In their replies, the Bureau and NRDC requested the Commissioner to affirm the Initial Decision with clarifications or additional findings.

In reviewing the Initial Decision, the Commissioner has all the powers he would have in making the initial decision (21 CFR 12.130). The Initial Decision and the Final Decision must be based upon "a fair evaluation of the entire record," pursuant to section 409(f) of the Act, 21 U.S.C. 348(f), and must also meet the requirements of 21 CFR 12.120 and 12.130. After reviewing the record carefully, the Commissioner affirms the Initial Decision with the modifications and supplementation stated below.

II. Food Additive Status

A food additive is defined by section 201(s) of the Act, 21 U.S.C. 321(s) to be:

> • • • any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component • • • of any food (including any substance intended for use in • • • packing • • • or holding food), if such substance is not generally recognized, among *experts qualified by scientific training and experience to evaluate its safety*, as having been adequately shown through scientific procedures • • • *to be safe under the conditions* of its intended use • • •.

Acrylonitrile bottles are composed of single molecules (monomer) of acrylonitrile (AN) and other substances formed into a polymeric chain (copolymer) that constitutes the bottle wall. At issue here is whether acrylonitrile copolymers used to fabricate beverage bottles are food additives within the meaning of section 201(s) of the Act, 21 U.S.C. 321(s), because of the migration of residual acrylonitrile monomer (RAN) from the bottle wall into the contents of the bottles at levels that are not generally recognized as safe.

The Bureau of Foods has the burden of proof in this proceeding on the food additive status of acrylonitrile copolymer beverage bottles. To meet this burden, the Bureau must show that (1) the intended use of acrylonitrile beverage bottles results, or may reasonably be expected to result, in acrylonitrile monomer becoming a component of food, and (2) acrylonitrile is not generally recognized as safe under its intended conditions of use.

A. Initial Decision

The Administrative Law Judge found that acrylonitrile had been shown to become a component of food and not to be generally recognized as safe. (ID at 35–36.) He based his conclusion that acrylonitrile becomes a food component on the direct observation of acrylonitrile migration in three studies using laboratory detection methods. The studies were conducted with beverage bottles frabricated from acrylonitrile copolymer and stored for 6–7 months at room temperature. (ID at 12–14.) These storage conditions were regarded by the Administrative Law Judge as "normal usage conditions" for beverage bottles and

[1] The following abbreviations have been used in citing material in the record: Initial Decision: ID; Transcript: Tr.; Brief of a Participant to the Administrative Law Judge: Brief; Appeal from and/or Exceptions to Initial Decision: App.; Reply of a Participant to Appeal from and/or Exceptions to Initial Decision: Reply. The exhibits submitted to the record, including written direct testimony, are referred to by the symbol for the participant and number assigned to them upon filing by the Hearing Clerk. The following symbols were used by the Hearing Clerk to refer to the exhibits by the participants: Monsanto: M; Borg-Warner: BW; Vistron: V; Bureau: G; and NRDC: NRDC. Thus, the first exhibit submitted by Monsanto would be referred to as M–1.

"well within the parameters of intended use." (ID at 11 and 35.) The Administrative Law Judge also concluded that the direct observation data is "strengthened by other positive results which employ different conditions and models which predict migration under various circumstances," (ID at 35) and that it "justifies the use of other avenues for quantification of these observed levels to be considered, such as models predicting the quantity of migration, and analyses of tests under more severe conditions." (ID at 11.) Because direct observation of acrylonitrile migration was made under storage conditions "within the parameters of the intended conditions of use," the Administrative Law Judge found it unnecessary to resolve whether the manufacturers were correct that "testing for migration should be conducted under conditions simulating the intended conditions of use" or whether the Bureau was correct that the "details of time and temperature conditions" are "relevant only to safety questions." (ID at 9.)

B. EXCEPTIONS

The manufacturing parties have excepted on several grounds to the conclusion that acrylonitrile is a food additive. They stress that the Administrative Law Judge's findings were based upon the direct observation of migration from Monsanto's "old" bottles but that no similar direct observation of migration was made from either the "new" Monsanto bottle or the bottles of the other manufacturers. In order to provide an overview of the issues raised, the Commissioner has listed below the principal contentions of the manufacturing parties. The Commissioner will discuss each contention in more detail and respond individually to them, as well as to related minor exceptions, in the following section of this Decision. A summary of the principal exceptions follows.

(1) Monsanto contends that "if no migration of AN can be detected from the new bottle by the most sensitive validated analytical techniques presently available . . . after suitably exaggerated extraction, then it is not a food additive." (Monsanto App. at 18–19.) Borg-Warner's position is similar. (Borg-Warner App. at 9, footnote.)

(2) Monsanto maintains that the observation of migration from the "old" bottles is "irrelevant" with respect to the "new" bottles, and that it would be a "specious line of reasoning" to conclude that "if [acrylonitrile] migrates from the 'old' bottle, it can be said to migrate from all bottles." (Monsanto App. at 16–17.) Borg-Warner maintains that the Administrative Law Judge's findings are irrelevant to its bottles in the absence of a finding of actual migration from the actual Borg-Warner product. (Borg-Warner App. at 10–11.)

(3) The manufacturers maintain that the Bureau failed to show that acrylonitrile is not generally recognized as safe (GRAS) under its intended conditions of use. This exception is related primarily to their contention, stated below, that acrylonitrile is "toxicologically insignificant," but Monsanto argues also that the Administrative Law Judge's finding that scientific opinion is balanced establishes that the Bureau did not meet its burden of proof of showing that acrylonitrile is not GRAS. (Monsanto App. at 23–27.)

(4) All the manufacturers argue that if any acrylonitrile migrates into their current bottles, the amount is so small in amount as to be "toxicologically insignificant" and not "worthy of government concern." They believe the Bureau has the burden to show that any amount that may migrate is toxicologically significant, and they object to the Initial Decision for failing to impose this burden on the Bureau. (Monsanto App. at 3–5, 23–25; Borg-Warner App. 2–6; Vistron App. at 3.)

(5) Lastly, the manufacturers believe that a finding that acrylonitrile is a food additive would be inconsistent with FDA's actions on other substances. (Monsanto App. at 9–10, 27; Vistron App. at 3–11.)

C. COMMISSIONER'S RESPONSE TO EXCEPTIONS

1. *Food Additive Status of Undetectable Substances.* Monsanto objects to the Initial Decision because it finds acrylonitrile copolymer beverage containers to be food additives even though there is no detectable migration of acrylonitrile from Monsanto's currently producible bottle. (Monsanto App. at 3.) Monsanto maintains that the Bureau must show that acrylonitrile is a food additive under "the actual conditions of use" and that this requires a showing of detectable migration from the new bottle (Monsanto App. at 2, 18–23). If no migration of acrylonitrile can be detected from the new bottle by the most sensitive method available, Monsanto would argue, it cannot be considered a food additive. The most sensitive method currently available is one developed by Monsanto, able to detect substances at concentrations of 10 parts per billion (ppb) or above. (Monsanto App. at 18.) According to Monsanto, the matter of "whether or how much AN might be present below the limits of actual detection is conjecture, not evidence, and cannot be of decisional significance." (Monsanto App. at 19.) Borg-Warner's position is similar. (Borg-Warner App. at 9, footnote.)

The Commissioner rejects the contention that a substance is immune from regulation as a food additive simply because no migration can be detected by the most sensitive analytical method available. This contention is inconsistent with the statutory language and the Congressional purpose in enacting the food additive provisions of the Act. Under the food additive definition in section 201(s) of the Act, 21 U.S.C. 321(s), a substance can be considered a food component if its "intended use" either "results" or "may reasonably be expected" to result in its becoming a component of food. Contrary to the assertions of the manufacturing parties, the statutory language does not require that the amount of the migrating substance be analytically detectable or quantifiable or exceed some minimum threshold level before the substance can be considered a component of food. The statute requires only that, at a minimum, there be evidence establishing a reasonable expectation that some migration will occur. Congress adopted this approach in order to effectuate the "overriding congressional intent" underlying the Food Additives Amendment of 1958, which was "to exclude from food, the addition of harmful or unsafe substances." (ID at 6.) The Administrative Law Judge was correct in stating that:

> It is entirely contrary to any "rule of reason" approach to statutory construction to conclude that Congress intended to disregard the overriding intent merely because a substance migrates to food only in minute quantities * * * regardless of the possible harmful effects of consuming such minute quantities. (ID at 8.)

The Commissioner agrees also with the Administrative Law Judge's statement of the reason for not requiring that migration be either detectable or quantifiable:

> The manufacturers assert that the statutory requirement of a showing of migration necessitates a quantitative determination. Such an argument, taken to its logical extreme, would mean that a chemical which was undetectable by current methods, but whose unseen migration caused toxic effects in man, would be exempted from the requirements of the statute. The "reasonably expected" wording of the statute is clearly not meant to preclude regulation in such a situation. The overriding intent of the legislature to protect the health of the American public cannot reasonably be disregarded simply because the methods of detection are unable to quantify the precise level of migration. (ID at 13–14.)

Thus, as the Administrative Law Judge recognized, it would defeat the purpose of the Food Additives Amendment to require actual detection or quantification of a migrating substance before it could be considered a component of food. It is enough to show a "reasonable expectation" of migration.

2. *Reasonable Expectation of Migration; Relevance of Extraction Data.* The manufacturing parties contend that the direct observation of acrylonitrile migration in the "old" Monsanto bottles is "irrelevant" to the question of whether acrylonitrile migrates or may reasonably be expected to migrate from the "new" Monsanto bottle or the bottles made by the other manufacturers. The Commissioner disagrees and discusses below the reasonableness of expecting migration from each of the manufacturers' bottles.

a. *Monsanto Bottle.* According to Monsanto, its "old" bottles were manufactured between May 1975 and February 1977 and contained an average of 15.2 parts per million (ppm) of residual acrylonitrile monomer and a maximum of 39 ppm (Monsanto App. at 2, 16). The Initial Decision cites tests that directly observed migration from the "old" Monsanto bottle (ID at 12–13). The residual monomer level in the walls of the actual test bottles was not determined, and can be assumed to be within the range cited by Monsanto for the old type bottle. In the "new" Monsanto bottle, the maxi-

mum level of acrylonitrile in the bottle is 5 ppm, and the average is 3.3 ppm. (Monsanto App. at 2, footnote.) The only difference between the "new" bottle and the "old" bottle is the difference in the level of residual acrylonitrile in the bottle walls, i.e. an *average* of approximately 3 ppm in the new bottle versus 15 ppm in the old. Nevertheless, Monsanto regards it as "a specious line of reasoning" to expect migration from the new bottles because it has been observed in the old and argues that "resort cannot be had to mathematical postulation of migration from the 'new' bottles." (Monsanto App. at 17, 21, citing Monsanto Brief at 28, 63–68.)

NRDC argues in its reply that Monsanto cannot make the difference between the bottles significant "merely by designating one set of bottles 'new' and the others 'old'." (NRDC Reply at 13.) (The estimates of residual acrylonitrile used by NRDC for the old bottle were lower than those stated by Monsanto and cited in this Decision, but the NRDC argument is unaffected by this difference.) The Bureau maintains that acrylonitrile migration may reasonably be expected from all acrylonitrile copolymer beverage containers on the basis of the principle of diffusion.

The Commissioner concludes that migration of acrylonitrile monomer may reasonably be expected to occur in all the acrylonitrile copolymer beverage containers at issue here, including the "new" Monsanto bottle. The Commissioner reaches this conclusion because, as discussed below, he believes it is valid to use extrapolation models, based on the principle of diffusion and confirmed through appropriate means, to show that migration may reasonably be expected under the intended use of a food packaging substance, even though migration of the substance is not analytically detectable.

Monsanto, the Bureau, and the other parties to this proceeding submitted evidence concerning the use of mathematical models to project migration of acrylonitrile monomer from acrylonitrile copolymer beverage bottles (M–82, M–84, G–77, G–78). All the models, including Monsanto's, are based on the principle of diffusion and use the diffusion equation to project levels of migration from bottles for which no actual extraction data are available. The projections are made from a base of actual extraction data. The models indicate that acrylonitrile migration from acrylonitrile copolymer bottles varies in a linear fashion as a function of three principal parameters—concentration of residual acrylonitrile monomer in the bottle wall, time of storage, and temperature of storage. All acrylonitrile copolymer beverage bottles contain at least some residual acrylonitrile monomer, and the models indicate that some migration of the acrylonitrile monomer occurs under all anticipated conditions of use of the copolymer bottles.

The validity of these diffusion models for projecting migration is supported by the testimony of the manufacturers' witnesses as well as the Bureau's. Monsanto's Dr. Dixler discusses the diffusion principle and refers to the diffusion equations used to project migration as "reasonable and reliable." (M–82 at ¶¶ 6–10 and 25 and Appendix A.) Monsanto's witness Dr. Salame confirmed the validity of the basic parameters affecting the migration models (M–84 at ¶¶ 4, 12–18, A–1, A–11). The testimony of Bureau witnesses Holtz (G–77 at ¶ 27) and Livingston (G–78 at ¶¶ 5–16, Exh. A–C) provides additional support for the validity of the migration models, including their validity for projecting migration from bottles with varying RAN concentrations on the basis of data from a particular bottle.

Monsanto points out in its Brief that its models were intended to estimate the maximum migration that could be expected and that the equations underlying them do not anticipate changes in migration behavior that might occur at low RAN levels and thus invariably predict migration (Monsanto Brief at 25–27). Monsanto suggests that the premises underlying the models make them inapplicable to the present determination. The Commissioner believes, however, that the models illustrate that the reasonable assumption, absent contrary information, is that the diffusion process observed to operate at levels at which migration is detectable continues to operate even at the levels at which it is not detectable.

It is possible to envision conditions under which the applicability of the diffusion principle to a particular packaging material could not be extended through the full range of a controlling physical parameter. For example, extremes in temperature may produce changes of state in the container or fluid that in turn might induce discontinuities in the solubility of residual acrylonitrile monomer in the bottle walls or the contained fluid. Also, a physical barrier might be formed at the interface between the plastic and the enclosed liquid. However, the parameters that are important in the analysis of migration of acrylonitrile monomer—time, temperature, and the concentration of RAN in the container—do not interact in such highly nonlinear ways with the diffusion process over the observed range of these parameters.

Because of the possibility that there are nonlinearities in the diffusion curve under extreme conditions, the Commissioner believes it important to confirm the operation of the diffusion process under circumstances reasonably related to the intended use of the substance at issue. The direct observation of migration in the "old" Monsanto bottle under normal use conditions in three studies (G–79, G–80 and G–81), as found in the Initial Decision, provides an appropriate confirmation of the diffusion process and its applicability to other acrylonitrile copolymer bottles. The Commissioner finds that the demonstration of migration at a temperature, concentration and storage time reasonably close to the values associated with normal use of acrylonitrile bottles justifies application of the diffusion principle to bottles having lower concentrations of residual acrylonitrile, shorter storage times and lower use temperatures. The confirmation of the diffusion process for acrylonitrile was made under normal use conditions and thus is clearly appropriate. The confirmation may also be made using food simulating solvents or using exaggerated conditions that are appropriate for evaluating whether migration may occur during intended use.

Once the applicability of the diffusion principle has been reasonably confirmed, projections based on the diffusion process are sufficient to satisfy the burden of proof with respect to migration, even though the amounts projected to migrate are below the level of analytical detectability. The reasonable expectation of migration, arrived at on the basis of the diffusion principle, is not unalterable, however. The expectation can be rebutted, but only if an adequate showing is made that migration is not reasonably to be expected. Such a showing could be made through a demonstration that an unusual or different physical process occurs at some point that prevents migration.

Acceptance of the diffusion process as sufficient to show a reasonable expectation of migration is a corollary of the conclusion that a substance can be a food additive even though the amount migrating is below the level of detectability. If the amount of migration is below the level of detectability, the fact of actual migration cannot be shown. Instead, migration of the substance must be projected from data obtained from observed migration occurring at higher RAN levels and storage times and higher temperatures. The projections drawn from these data rest upon scientific principles, notably that of diffusion. The diffusion principle provides a reasonable and scientifically valid means of making projections from the available data and it is reasonably applied to the acrylonitrile bottles at issue.

Based upon the foregoing analysis, the Commissioner rejects the Monsanto argument that the direct observation of acrylonitrile monomer migration from Monsanto's "old" bottle is irrelevant to the question of whether monomer migrates in the "new" bottle. As noted, the only difference between the "old" and the "new" bottle is the RAN concentration, and the diffusion principle, as confirmed by extraction data from the "old" bottles, makes it reasonable to expect that there will be some migration from the "new" bottle despite the difference in RAN concentration.

Monsanto has suggested some additional arguments, discussed below, for not applying the diffusion principle as a basis for projecting migration from its new bottles.

1. In its Brief, Monsanto refers to a theory which says that when the concentration of residual acrylonitrile monomer is very low "the migration will be far below what the model predicts or there may be no migration at all." (Monsanto

Brief at 28, citing M-84 at ¶ 16, Tr. 526.) The theory is principally that at low levels the residual acrylonitrile monomer will become bonded to the copolymer and not migrate. Even as articulated by Monsanto, the theory raises only a possibility that there will be no migration. The bonding theory is, furthermore, only speculative; the Commission believes that it provides an insufficient basis for concluding that diffusion ceases and no migration occurs at some low RAN level. (Tr. at 147-48; M-84 at ¶18; Bureau Brief at 73.)

ii. Monsanto excepts to the Initial Decision not only because it discussed the data from the "old" bottles—which Monsanto views as irrelevant—but also because it did not take sufficient account of the extraction data for its "new" bottle—which Monsanto does consider to be relevant. (Monsanto App. at 16-23.) The extraction testing done by Monsanto on its "new" bottles shows no detectable migration with a method sensitive to 10 ppb. The levels of migration projected by migration models for the "new" bottles under the conditions at which the "new" bottles were tested is below 10 ppb. (G-78 at ¶10, 11 Exhibit A.) Thus, Monsanto's contention that the extraction data for the "new" bottles is significant is simply a reformulation of its argument that a substance is not a food additive if the amount of migration cannot be analytically detected. The Commissioner has rejected this argument for the reasons discussed above.

Monsanto also points out that the Administrative Law Judge disregarded its extraction study on the "new" bottles partly because of a supposedly conflicting preliminary report on extraction studies being conducted by the Bureau. (Monsanto App. at 20-23). The Commissioner believes that the Monsanto extraction data should be disregarded on the basis of the analysis set forth above and that it is unnecessary to disregard it on the basis of the "preliminary report." The Bureau has apparently undertaken some investigation to determine independently the levels of migration from the "new" bottles, including tests under more exaggerated test conditions, but no reliable results are available yet and no written report exists. (Breder, Tr. at 161; Bureau Reply at 13-14)

iii. Monsanto's position that the new bottle is not a food additive appears to be based in part on the argument that migration must be shown under the "actual intended conditions of use" and that this requires at least a showing of migration through extraction studies done specifically on the new bottles. (Monsanto App. at 2-3, 15, 18-23.) The Commissioner disagrees. The diffusion models already discussed make it reasonable to expect migration from all acrylonitrile copolymer beverage containers. Furthermore, the food additive definition in section 201(s) of the Act, 21 U.S.C. 321(s), does not require that either actual migration or a reasonable expectation of migration be shown under the "actual intended conditions of use" of a substance. Under the definition, the showing may be made with respect to the "intended use" of a substance. This term indicates that the showing may be made with only a limited inquiry into the specific conditions of use of a substance and that migration need not be shown individually with respect to each particular variation in the intended use of a substance. The definition clearly permits a conclusion to be drawn based on a showing of migration in one specific application of a substance that migration may reasonably be expected from other similar intended uses of the substance. (See Bureau Brief at 18-20).

b. *Borg-Warner Bottles*, Borg-Warner views the Initial Decision as accepting the validity and reasonableness of migration models only when actual migration has been confirmed using the actual bottle and the actual product. Since the confirmation of migration cited by the Administrative Law Judge was obtained in tests with the Monsanto bottles, not the Borg-Warner bottles, Borg-Warner excepts to the conclusion that the Borg-Warner acrylonitrile bottles are food additives. (Borg-Warner App. at 11.)

The Commissioner doubts that the Initial Decision should be read as narrowly as Borg-Warner suggests. The Administrative Law Judge, having confirmed that migration occurs in acrylonitrile copolymer beverage containers under normal use conditions, apparently considered it reasonable to conclude that migration occurs in all acrylonitrile copolymer beverage containers. In any event, the Commissioner concludes that it is reasonable to expect migration to occur from the Borg-Warner bottles based upon the analysis set forth in connection with the Monsanto bottles. The Borg-Warner bottles contain residual acrylonitrile monomer which, as the Commissioner's analysis demonstrates, may reasonably be expected to migrate. Contrary to Borg-Warner's exception, confirmation of migration need not be made with the actual product, in its case apple juice. There is nothing in the evidence or in the diffusion equation which suggests that a change in the solvent material will cause a complete cessation of migration. In fact, the evidence is to the contrary. Borg-Warner's own extration tests detected migration of acrylonitrile monomer from its own bottles containing apple juice (BW-1 and BW-2). These tests were conducted under storage conditions reasonably close to those associated with normal use—specifically, storage for 14 months at room temperature.

Borg-Warner also excepted to the Initial Decision because it stated that the data on conditions of use were not clearly defined. Borg-Warner considers this to establish that the Bureau did not meet what Borg-Warner described as its burden to show that acrylonitrile migrates under the "intended conditions of use." (Borg-Warner App. at 7-8.)

Under the food additive definition in section 201(s) of the Act, 21 U.S.C. 321 (s), the food component status of a substance (i.e. whether it migrates or may reasonably be expected to migrate) is to be judged under the intended use of the substance, not the specific "conditions of intended use." Specific conditions of intended use are relevant to safety evaluations, not to food component status. Thus, use data need not be as clearly defined to show migration as to show safety or establish GRAS status. In any event, the Administrative Law Judge did reach conclusions about the conditions of use, finding 6 months storage at room temperature to be well within the normal conditions of use for all beverage containers, a finding that is adequately supported by the record. (ID at 9-11.) That finding applies to apple juice containers as well as soda containers.

In judging whether a reasonable expectation of migration exists, the Commissioner has looked primarily at whether migration may be expected from the bottles under the conditions of use cited by the Administrative Law Judge as being well within normal conditions of use, specifically storage for 6 months at room temperature. The Commissioner notes, however, that these conditions are not exceptional and do not make allowance for atypical use of beverage bottles. He believes the conditions suggested by the Bureau for extraction testing for safety purposes of 6 months at 90° F to be more suitable conditions for extraction testing since they allow for atypical use and the variety of beverages for which the bottles could be used.

c. *Vistron Bottles*. Vistron acknowledges in its exceptions that the "amount of acrylonitrile migrating from acrylonitrile copolymer bottles is importantly a function of the amount of residual acrylonitrile monomer in the bottle wall." (Vistron App. at 12.) Vistron states that the walls of its current bottles contain 1.7 ppm of residual acrylonirile and that the amount of acrylonitrile migration into the contents can be projected to be 1.5 ppb after 6 months at 90°, and 1.7 ppb after 29 months at room temperature.

Vistron apparently concedes that migration may reasonably be expected from its bottles and rests its exception primarily on the grounds that the amount that migrates is small and even lower than that from the other manufacturers' bottles. The point appears to be that the amount of migration from the Vistron bottles is even more "toxicologically insignificant" than that from the other bottles. (Vistron App. at 12-14.) Toxicological insignificance is discussed later. At this point, the Commissioner concludes that it is reasonable to expect migration of acrylonitrile from the Vistron bottles based upon both the Vistron projections and the general analysis given above in connection with the Monsanto bottles.

d. *Reliability of Methods Used To Detect Acrylonitrile*. The Administrative Law Judge found that the Breder (G-79), Gajan (G-80), and Sphon (G-81) analyses showed actual migration of acrylonitrile into Coca-Cola from Monsanto's 32 oz. acrylonitrile beverage bottles stored for 6-7 months at ambient temperatures. The Commissioner agrees and concludes that the three methods

taken together reliably detect actual migration of acrylonitrile monomer and thereby provide adequate confirmation of the applicability of the diffusion principle to acrylonitrile copolymer beverage containers.

i. Monsanto takes exception to the Administrative Law Judge's reliance on these three studies for showing actual migration. (Monsanto App. at 44–46.) Monsanto argues that (1) the analyses do not meet FDA's own minimum requirements for establishing the reliability and applicability of analytical methodology, (2) the amount of migration reported using the direct liquid injection chromatography method is below the lowest reliable quantitation level for that method, (3) at this level of quantitation peaks on the chromatograph are not sufficiently distinguishable from background noise to support a conclusion that they reflect the presence of acrylonitrile, (4) the head space analysis technique is experimental, and (5) the confirmatory analyses performed by Gajan and Sphon use a concentration technique the reliability of which has not been adequately established.

The Commissioner rejects these arguments. First, the reliability of the three methods is attested to in the testimony of Breder, Gajan, and Sphon. The qualifications of these analysts were not challenged on cross-examination, and the testimony in the record does not contradict their testimony that the methods are reliable. (See Bureau Brief at 61–62). Furthermore, even assuming that the three methods of analysis at issue do not comply with the FDA Guidelines referred to by Monsanto, the Commissioner, in determining whether there is a reasonable expectation that migration will occur, is not bound to rely upon analytical methods that meet FDA Guidelines. The question is whether, on the basis of a fair evaluation of the entire record, there is substantial evidence supporting a conclusion that acrylonitrile does become, or may reasonably be expected to become, a component of food when put to its intended use. Non-compliance with FDA Guidelines does not render an analytical method unreliable per se for this purpose. The testimony is convincing that the tests were reliable.

Second, the arguments that the amount detected using the chromatography method is below the lowest reliable quantitation level for that method and might not be distinguishable from background noise is not persuasive. The chromatographic analysis is being relied upon not to show the quantity of acrylonitrile migrating but only the fact of migration, and the polarography and mass spectrometry analyses of Gajan and Sphon confirm the chromatographic finding of actual migration.

Third, the experimental data of the head space head space is not significant since the results obtained by the established FDA chromatography technique are similar to those found using the head space analysis and, again, were confirmed by the polarography and mass spectrometry analysis.

Fourth, there is nothing in the record to contradict the testimony of the Bureau's witnesses that the concentration technique used by Gajan and Sphon is a reliable method.

Finally, the Monsanto comparison of its analytical method with the three relied upon by the Administrative Law Judge is not persuasive. (Monsanto App. at 46–47.) It is important to remember that the Bureau's burden is only to show that migration may reasonably be expected. The Administrative Law Judge relied upon the three methods discussed above only for purposes of showing migration—not for quantifying it. (ID at 12–14.) The Bureau places strict requirements on analytical methods used by manufacturers submitting data intended to show the safety of a food additive because, in that circumstance, the manufacturer must accurately show the quantity migrating in order to establish a safe level.

ii. Vistron excepts to the Initial Decision for failing to recognize that "background interference" in the laboratory "will substantially increase" the levels of apparent migration detected in the Breder, Sphon and Gajan tests. (Vistron App. at 16–19.)

As stated above, the Bureau's witnesses were confident of the procedures they used, and this would encompass the possibility of background interference (G–79, G–80 and G–81). To the extent the exception goes simply to the level of migration, the Commissioner regards the levels of migration as important for safety issues, but not as pertinent to the determination of whether some migration may be expected. (See Bureau Reply at 41–42.)

3. *GRAS Status Of Acrylonitrile Copolymers In Beverage Bottles.* The second element of the food additive definition, upon which the Bureau bears the burden of proof, is that the:

> • • • substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use; • • • 21 U.S.C. 321(s).

The Administrative Law Judge concluded that the use of acrylonitrile copolymers in beverage containers is not generally recognized as safe (GRAS) because "the scientific community at large has not considered this question," the witnesses in this proceeding "represent almost evenly split opinion on the question," and "it has not been convincingly shown that the scientific community would inevitably form a consensus in either direction should they consider the matter." (ID at 35.)

The manufacturers take exception to the Administrative Law Judge's conclusion on the GRAS issue. As stated above, their arguments are based primarily on their theory of toxicologically insignificance and will be discussed in the next section of the decision. However, they also argue that the Bureau failed to meet its burden of proof on the GRAS issue as evidenced by the split of opinion cited by the Administrative Law Judge (ID at 36) and the absence of affirmative evidence of lack of safety to offset the positive opinions of safety offered by the manufacturer's witnesses. (Monsanto App. at 25–26.)

These arguments misapprehend the kind of showing the Bureau must make to show that a substance is not generally recognized as safe under its intended conditions of use and are rejected by the Commissioner. Since acrylonitrile copolymers were not used to fabricate beverage containers before January 1, 1958, the GRAS status of acrylonitrile in beverage bottles must be based on "scientific procedures." Thus, GRAS status will be achieved only if (1) there is scientific evidence of the actual safety of acrylonitrile in beverage bottles under their intended conditions of use of the same quantity and quality required for proof of safety under 21 U.S.C. 348, and (2) this scientific evidence is commonly known throughout the scientific community knowledgeable about the safety of food ingredients and is reflected in scientifically reliable published studies. See 21 CFR 170.30 (formerly 21 CFR 121.3).

The Commissioner concludes that there is no scientific evidence of the quantity and quality required for proof of safety and, thus, even if the existing evidence were commonly known throughout the knowledgeable scientific community—which it is not—it could not form the basis for a consensus that acrylonitrile has been shown to be safe. The existing evidence is incomplete, and safety risks are indicated by the data that are available. As discussed later under the heading "Safety of Acrylonitrile," the record shows that acrylonitrile is a frank teratogen in the rat, a tumorigen and probable carcinogen in the rat, a possible carcinogen in man, and a mutagen in several test systems. The Commissioner agrees with the Bureau's contention that under these circumstances it is inconceivable that the scientific community could recognize that any level of acrylonitrile has been shown through scientific procedures to be safe. (Bureau Brief at 113–14.) When a food component has been found wanting under the safety criteria applied in the context of 21 U.S.C. 348, it cannot, as a matter of law, be deemed generally recognized as safe within the meaning of 21 U.S.C. 321(s), and thereby escape regulation as a food additive.

Though the foregoing conclusion makes it unnecessary to consider the extent of knowledge in the relevant scientific community about the safety of acrylonitrile, the record supports the conclusion that it does not have general knowledge of the scientific evidence concerning the safety of acrylonitrile. (Tr. at 590.) Under section 201(s) of the Act, this alone is sufficient to justify the conclusion that acrylonitrile is not GRAS, regardless of the nature of that evidence.

Finally, in not a single usage by one of the manufacturing parties' witnesses of the phrase "generally recognized as safe," or words to that effect, is it stated that acrylonitrile is generally recognized as safe. Instead, the witnesses state that at the levels present in beverages it "should be," "must be," or "ought to be" generally recognized as safe. (See, for example, M–82 at ¶ 5; M–90 at ¶ 8; M–96 at ¶ 6.) Furthermore, on cross-examination, each of those witnesses confirmed what their testimony implied: that the scientific community knowledgeable about the safety of food ingredients does not now generally recognize acrylonitrile to be safe for use in beverage bottles. (Tr. at 466, 589–590, 690–691.)

On the basis of the foregoing analysis, the Commissioner concludes that the use of acrylonitrile copolymers to fabricate beverage containers has been shown by the Bureau not to be generally recognized as safe. The manufacturers' exceptions to the Administrative Law Judge's conclusion on the GRAS issue are based largely upon their theory of toxicological insignificance and will be discussed below in connection with the Commissioner's discussion of that theory.

4. *Toxicological Insignificance.* The manufacturing parties except to the Initial Decision because the Administrative Law Judge did not adopt their concept of "toxicological insignificance" as a basis for concluding that acrylonitrile in beverage containers is not a food additive (Monsanto App. at 23–27; Borg-Warner App. at 4–6; Vistron App. at 3–11). The concept of "toxicological insignificance" is used in several ways by the manufacturing parties. Their central argument appears to be that at levels of migration below the level of detectability a food packaging substance should either be considered not present in the food or, if considered to be present, be deemed "toxicologically insignificant" and therefore not subject to regulation as a food additive. (Monsanto Brief at 23–27; Borg-Warner Brief at 25–30.)

The term "toxicologically insignificant" does not appear in the statutory definition of food additive, 21 U.S.C. 321 (s), and the Commissioner concludes that the term has no legal significance as an element of the food additive definition. Food additive status should be judged by the statutory criteria already noted relating to whether (1) use of the substance "results or may reasonably be expected to result" in its becoming a component of food; and (2) at the level at which the substance does become a component of food it is generally recognized as safe. It is against these statutory criteria that the manufacturers' various arguments about toxicological insignificance should be evaluated.

1. To the extent that the term "toxicologically insignificant" is used to refer to some level of migration so low that it must, as a legal matter, be treated as zero migration and, thus, not a component of food (M–82 at ¶ 4), its use is inconsistent with the definition of food additive. The definition does not require that any minimum amount of migration be shown, and the definition thus permits any migration of acrylonitrile to satisfy the component element of the food additive definition.

2. To the extent that the term "toxicologically insignificant" is intended by the manufacturers to be used interchangeably with the statutory concept of "generally recognized as safe" (M–82 at ¶ 5), as the Administrative Law Judge apparently intended when he incorporated it in his statement of the issues at the urging of Monsanto, its use is merely confusing, and the Commissioner chooses not to use it as a substitute for the statutory language.

3. If the argument is that a certain quantity of a migrating substance, presumably any amount that happens to fall below the current level of detectability, can be considered GRAS per se, or safe per se, the Commissioner disagrees. (Monsanto App. at 3–5, 9.) The statute leaves no room for a contention that the presence of a migrating substance at a sufficiently low level by itself warrants a conclusion that the substance is GRAS, or safe, or unworthy of government concern. The Commissioner believes that the safety of a substance cannot be decided on the basis of quantity alone. Safety depends on many factors, including the toxicity of the substance, and it cannot be determined simply on the basis of amount (G–88 at ¶17; G–78.) Safety is appropriately determined through scientific procedures. It is for this reason that the argument that total lifetime exposure to acrylonitrile from beverages bottles might be only ½ of a teaspoon is meaningless. (Monsanto App. at 3–5.) No substance can be assumed to be "toxicologically insignificant" and safe simply because it is present at levels below the level of detectability. It follows that general recognition of safety cannot be based on quantity alone. Even if a certain quantity of a migrating substance (e.g., any quantity below the level of detectability) were determined to be safe through scientific procedures, GRAS status would not be achieved unless such evidence were known generally to experts qualified by training and experience.

4. At least implicit in some of the arguments made by the manufacturing parties is the novel position that the term "toxicologically insignificant" describes a third element of the Bureau's burden of proof on the food additive status issue, i.e., that the Bureau must show the anticipated levels of migration to be actually unsafe or harmful. (Monsanto App. at 23–25; Borg-Warner App. at 2–6.) The manufacturers in effect argue that (1) the Bureau, in proving the food additive status of acrylonitrile, must show not only that it may migrate and that it is not GRAS but also that acrylonitrile is "toxicologically significant" (i.e., actually unsafe or harmful) at the anticipated levels of migration, and (2) a showing of lack of safety is part of the Bureau's burden of proof on the GRAS issue. These views about the burden of proof account for the manufacturers' argument, referred to above, that the Bureau did not submit enough evidence to show that acrylonitrile is not GRAS. The manufacturers believe the Bureau must prove that acrylonitrile is toxicologically significant or actually unsafe in order to show that it is not GRAS. Both the Bureau and the Administrative Law Judge disagreed with this positon and the Commissioner rejects it.

As stated above, the term "toxicologically insignificant" has no legal significance as an element of the food additive definition. In establishing the food additive status of acrylonitrile, the Bureau is not required in any way to show that it is actually unsafe or harmful, either under the "toxicologically insignificant" concept or as part of its burden of proof on the GRAS issue. The burden is on the manufacturing parties to demonstrate the safety of a food additive by competent evidence, not on the Bureau to show lack of safety. Thus, the fact that no Bureau witness concluded that acrylonitrile is actually unsafe under intended conditions of use is irrelevant to the GRAS inquiry, as is the testimony of the manufacturers' witnesses that acrylonitrile should be considered safe under intended conditions of use. GRAS status depends on the existence of general recognition of safety, arrived at on the basis of adequate scientific procedures. Therefore, countrary to the Monsanto assertions (Monsanto App. at 25–26), it was proper for the Administrative Law Judge to cite the even split of opinion on the issue of acrylonitrile's safety among the expert witnesses at the hearing for his conclusion that acrylonitrile is not GRAS. (ID at 36). If the Bureau's burden were to show that acrylonitrile is actually unsafe, the even split of opinion might warrant a conclusion that the Bureau had not met its burden, but since the burden is merely to show lack of general recognition of safety the even split of opinion is highly probative of the conclusion that acrylonitrile is not GRAS. As already discussed, the record clearly establishes that acrylonitrile is not generally recognized as safe. (Bureau reply at 15–17.)

5. The manufacturing parties argue at several points that the Bureau has in the past used a "virtually nil" or "toxicologically insignificant" concept in deciding the food additive status of some packaging materials. Though such language had no doubt been used informally in the past by Agency employees in describing food additive status, it has never been Agency policy to use such language in any of the ways suggested by the manufacturing parties in this proceeding. The phrase does not replace the statutory definition of food additive. When used at all, it has been to describe the situation in which any occurring migration will be below the level at which the substance can be considered to be safe (G–87 at ¶¶ 6, 7) or has been found to be GRAS under the applicable legal standards.

6. Borg-Warner excepts to the Administrative Law Judge's references to acrylonitrile as a "known toxic sub-

stance" in discussing its food additive status. (ID at 8.) Borg-Warner contends that the Bureau has failed to prove that small amounts of acrylonitrile are known to be toxic. Moreover, according to the exception, the Administrative Law Judge ignored the concept of toxicological insignificance in evaluating whether acrylonitrile is a known toxic substance. (Borg-Warner App. at 4–6.)

The reference in the Initial Decision to known toxic substances was apparently a shorthand statement that acrylonitrile is not generally recognized as safe at the levels at which it migrates. (See Bureau Reply at 34–35.) The phrase may also have been intended to reflect the discussion in the Initial Decision, quoted above, about the policy concerns underlying the Act (ID 13–14) as well as to indicate that safety questions exist about acrylonitrile. The phrase does not, and should not, indicate that the Bureau has the burden to prove toxicity before a substance can be considered to be a food additive. The Administrative Law Judge recognized that the migration of any amount of a substance is sufficient to make it a food additive, unless the substance is generally recognized as safe in the amount in which it migrates. As stated above, the Commissioner has concluded that the Bureau is not required to show acrylonitrile to be toxic at the levels at which it may be expected to migrate, only that it is not generally recognized to be safe at those levels. Once again, there was no need for the Administrative Law Judge to consider the "toxicological insignificance" in evaluating acrylonitrile since that term is extrastatutory and has no separate meaning in this proceeding independent of the food additive definition.

7. The manufacturers also have argued that the "toxicological insignificance" concept reflects the Sensitivity of the Method (SOM) regulation (21 CFR 500.80–500.98) which the Commissioner has promulgated for determining residue levels for animal drugs. (Monsanto Brief at Appendix H.) The Commissioner discusses later why it is inappropriate to apply that regulation in this proceeding, or to decide in this proceeding whether the regulation could ever be applied to food additives. The Commissioner does note at this point, though, that the manufacturers' concept of "toxicological insignificance" would impose a burden of proof, and a burden of developing safety data, contrary to that which exists under the Sensitivity of the Method regulation. Under that regulation, the proponent of an animal drug must come forward with complete and adequate tests in two test animal species as one step in applying the procedures in the regulation. Similarly, under the current statutory scheme, the proponent of a food additive must come forward with data adequate to establish safety and has the burden of proof on safety. If the manufacturers' view of toxicological insignificance were adopted for food additives, FDA, in establishing food additive status, would have the burden to show that amounts of a substance migrating below the level of detectability are unsafe. Only if that burden were met and the substances were not generally recognized as safe would the manufacturers have the burden to establish its safety. This reversal of the burden of proof would be inconsistent with the policy implicit in both the SOM regulation and the current statutory scheme governing food additives.

5. *Comparison Of Acrylonitrile With Other Containers And Substances.* Monsanto and Vistron take exception to the Administrative Law Judge's failure to (1) consider the safety of acrylonitrile copolymer beverage containers in comparison with other food containers and other substances which may become a component of food, and (2) treat acrylonitrile copolymer beverage containers in a manner they consider consistent with the treatment afforded other such containers and substances. (Monsanto App. at 27; Vistron App. at 2–11.) Monsanto also argues that if the diffusion principle is sufficient to show that acrylonitrile may migrate, it will be sufficient to show that other substances and packaging materials migrate, and, as a result, subject these other materials to the food additive provisions of the Act. Monsanto maintains that the standards applied to acrylonitrile bottles should be applied consistently and be the same as those that have been applied to other substances. (Monsanto App. at 9–10.)

The Commissioner believes consistency is an important regulatory objective, and he endeavors to give equivalent treatment to similar cases. The Agency, though, cannot be prevented from taking warranted regulatory action on the grounds that it has not yet acted on other cases that are argued to be the same. As the Bureau states (Bureau Reply at 17):

> The Act does not require the Bureau to develop a comprehensive scheme of relative toxicity for all beverage containers before it can proceed against one. Such an approach would immobilize the Bureau's efforts to ensure the safety of food additives. The Government is not required to "choose between attacking every aspect of a problem or not attacking the problem at all." *Dandridge v. Williams*, 397 U.S.C. 471, 486–87 (1968).

It is true that the Administrative Law Judge's Initial Decision did not consider other food containers or other substances, indicating implicitly a conclusion that the status of such other containers and substances has no direct bearing on the issues in this proceeding. The Commissioner agrees with this conclusion. The issue in this proceeding is not acrylonitrile beverage bottles rank with other food containers in terms of safety, but whether acrylonitrile beverage containers are lawfully approved under the food additive provisions of the Act.

Likewise, the regulatory status of the specific substances mentioned in the Monsanto and Vistron Appeals, selenium and aflatoxin, are irrelevant to an evaluation of the safety of acrylonitrile beverage containers. The regulation of aflatoxins as a poisonous and deleterious substance under section 406 of the Act is not relevant to the regulation of acrylonitrile under the food additive provisions of the Act. The selenium animal feed regulation, 21 CFR 573.920, is consistent with the food additive provisions of the Act. Selenium is distinguishable from acrylonitrile on several grounds, and the Commissioner has stated that the available information does not support its classification as a carcinogen. (See FEDERAL REGISTER of April 27, 1973, 38 FR 10458; Blumenthal Tr. at 816–17.)

Other food packaging substances may also be food additives, because they may migrate at low levels and are not GRAS. (See Bureau Reply at 5, n. 8.) Food additive status does not necessarily mean that the substance cannot be used in food. If a substance can be shown to be safe, its use is permissible pursuant to a food additive regulation. In the next section of this Decision, the Commissioner examines whether the safety of acrylonitrile has been established.

III. SAFETY OF ACRYLONITRILE

Once acrylonitrile has been shown to be a food additive, its use can be permitted pursuant to a food additive regulation under section 409(c) of the Act, 21 U.S.C. 348(c), only if the manufacturers can show through scientific procedures that its use is safe under the intended conditions of use.

The Administrative Law Judge described the process for making these safety determinations as follows:

> The normal procedure in determining the safety of a product is to find, through animal experimentation, the possible safety hazards that could result from its usage, determine levels at which these effects do not occur, and through the utilization of an appropriate safety factor, extrapolate that data to the human case. (ID at 25.)

Stated below are the Administrative Law Judge's general findings about the kinds of safety risks indicated for acrylonitrile and his general basis for believing that no safe level for humans can be determined with respect to any of these risks through the use of any safety factors or risk assessment methods. The Commissioner also has stated his general conclusions. Thereafter in this section, the Commissioner discusses each specific type of risk indicated for acrylonitrile, examining the Administrative Law Judge's basis for believing the risk exists, the contentions of the participants that relate particularly to that risk or the existence of a no-effect level for it, and the Commissioner's specific responses. In the last part of this section, the Commissioner examines the participants' other contentions relating to risk assessment and consumption patterns.

A. GENERAL FINDINGS AND CONCLUSIONS

The Administrative Law Judge made the following determinations:

> An overview of the analysis of these studies shows a pattern of adverse effects, (i.e., simple toxicity, mutagenicity, teratogenicity and tumorigenicity) which appear in increasing numbers and at lower dosage levels as the studies progress. The most recently reported of these effects are

of a severe and irreversible nature. (ID at 28.)

• • • • •

• • • The record consists of two types of data: short-term experiments designed to demonstrate acute toxic effects and long-term studies which implicate AN as a mutagen, a teratogen, a tumorigen and possibly as a carcinogen. (ID at 36.)

• • • • •

An analysis of the risk-assessment methods described reveals that their accuracy depends on the validity of the no-effect level upon which they are based. None make provisions for overcoming incomplete studies, studies in one species, or assessing the cumulative impact of multiple effects.

It appears that unless the final outcome of these ongoing chronic animal studies can be accurately predicted, the use of a safety factor of the types described here does not overcome the basic defects in the manufacturers' conclusions as to the safety of AN. The 20-year latency period found in the development of cancers attributed to exposure to AN in the du Pont worker study suggests that the animal case of late development of tumors finds a counterpart in the human situation. Since there is a parallel in tumor types developed in animals in the inhalation and ingestion situations, the use of positive human inhalation data to predict potential human ingestion effects is justified. Using a simple multiplication of safety estimates from incomplete studies to assess a safe human consumption level does not cure the basic defects in the animal studies and the storage and consumption data.

In extrapolating from a population of rats which generally runs under 50 in number to a population of millions of humans, that which would appear as borderline effects at low dosage levels could easily compute to several thousand affected humans. The results of the animal and human studies raise health questions which are more insiduous than simple acute toxicity. A finding of toxicological insignificance would be premature pending a more complete evaluation of the effects in question. When a history of the research shows effects appearing only after longer exposure times, incomplete studies cannot form a legitimate basis for determining a no-effect dose for a human population which could conceivably encounter the chemical on a chronic basis. (ID at 32–33.)

• • • • •

It appears from an evaluation of the testimony and evidence presented in this proceeding that a finding of safety for AN at this time would be premature and unwarranted, particularly, in view of the severe irreversible effects which have been potentially attributed to AN. This is so, despite the fact that such a determination might well have been possible were the adverse effects of AN limited to acute toxicity. (ID at 38; see also ID at 23.)

After reviewing the record, including the findings of the Administrative Law Judge, the Commissioner concludes that acrylonitrile is a frank teratogen in the rat, a tumorigen and probale carcinogen in the rat, a possible carcinogen in man and a mutagen in several test systems. A safe level for human consumption cannot be determined because of the inadequacy of the present data and the probable carcinogenicity of acrylonitrile.

B. SPECIFIC RISK AREAS

1. *Teratogenicity*—a. *Initial Decision.*—The Initial Decision found the DOW–MCA study[2] to be the only fully-reported study available investigating the teratogenic potential of acrylonitrile (i.e. the potential to cause birth defects) and concluded that this study showed acrylonitrile to be a teratogen in the rat (ID at 21, 23). The Administrative Law Judge stated that the one-generation DOW–MCA study "shows such effects as missing vertebrae, short tails, and right-sided aortic arches." (ID at 21.)

The Administrative Law Judge found that the effects of teratogenicity are severe and irreversible (ID at 23). In reaching his conclusions, the Administrative Law Judge stated that determinations of safe levels for tumorigenicity and teratogenicity involved:

not a matter of passing malaise, with disappearing symptoms, but rather a heritage of cancer and birth defects. In view of such serious possibilities, it would be unwise to base such a weighty determination on half-completed studies. (ID at 23.)

As stated above, the Commissioner agrees with the Administrative Law Judge's conclusion that it would be premature to derive a safe level on the basis of the presently incomplete data for any of the chronic effects posed by acrylonitrile, including teratogenicity.

b. *Exceptions and Commissioner's Response*—i.—In their exceptions, Monsanto and Borg-Warner maintain that a safe level for humans can be derived from the no-effect level shown for rats in the DOW–MCA study (Monsanto App. at 56, 58–59, 64; Borg-Warner App. at 18–19). They criticize the Initial Decision for not pointing out that the Bureau agrees that a no-effect level for rats exists in the DOW–MCA study at the lowest feeding level. They contend that on the basis of this no-effect level and other data a safe level for human consumption can be derived using either a Mantel-Bryan risk assessment analysis or the 1000-fold safety factor that the Bureau uses in practice on frank terata. Monsanto also criticizes the above-quoted statement of the Administrative Law Judge for being an "unscientific appeal to emotion" and for being "misleading" in its reference to "half-completed" studies since the DOW–MCA study, among others, is complete. (Monsanto App. at 58–59.)

The Commissioner disagrees with these contentions insofar as they maintain that a safe level for humans should be established based on the DOW–MCA Study or the other information presently available. The present data are inadequate to derive a safe level for humans with confidence. The DOW–MCA study is indeed complete, and it has a no-effect level for rats at the lowest level, as both the manufacturers and the Bureau agree. However, it would be inappropriate to project a no-effect safe level for humans based on this one rat study, no matter what safety factors or risk assessment methods are used. At least another complete study of the teratologic effects in another species is needed, and a reproduction study would be desirable. (Tr. at 195–98.)

The teratogenic effects of a compound may vary from species to species. (Tr. at 208). Another animal species may be more sensitive to the teratogenic potential of acrylonitrile than the particular test species used. The relative human sensitivity to the teratogenic potential of acrylonitrile is not known and, of course, humans cannot be subjected to feeding studies involving potential teratogens. Thus, the risk to humans must be projected from animal tests. (Tr. at 184–185, 214). In view of the seriousness of the risks posed, acrylonitrile must be tested in at least one more animal species before any conclusions can be confidently projected about its teratogenic potential in humans. (Tr. at 195–199, 201, 208–209, 211; G–86 at ¶ 11b, 14a.) If another species were tested and found more susceptible to the teratogenic effects of acrylonitrile, the no-effect level for teratogenesis could be lowered. Without more testing, it is improper to assume that where the no-effect level is now is where it should stay for purposes of estimating a safe level for human consumption. (Bureau Brief at 82–85, 111–112, 138–139.)

The Commissioner believes that no safety factor should be applied until adequate studies are done to establish the level of risk posed. The 1000 fold safety factor referred to in the exception is a higher than normal safety factor which the Bureau ordinarily uses when the data show frank teratogenic effects on animals. (G–87 at ¶¶ 14, 15.) If the data show positive teratogenic effects, the Bureau requests data from a teratology study in at least another species before determining a safe level (G–87 at ¶ 15). The Bureau uses a larger than normal safety factor in computing the safe level due to the greater level of concern with reproductive effects. The concern that warrants a higher than ordinary safety factor also warrants not applying any safety factor, no matter how high, until the data base for acrylonitrile is complete enough to evaluate the risk posed with an adequate degree of confidence. (Tr. at 187, 195–89.) Another complete study in another species is needed for that purpose.

The Mantel-Bryan analysis referred to in the exception was applied to the teratology data by Monsanto's witness Dixler, based upon the "analogous" use of that analysis in FDA's Sensitivity of the Method regulation. (M–82 at ¶¶ 31–43; Monsanto Brief at 85–86.) That regulation has a different purpose than that proposed for it by Monsanto, and the Commissioner discusses later his reasons for believing the SOM regulation and risk assessment analysis generally to be inapplicable in this proceeding. It is particularly pertinent to note at this point that the SOM regulation provides for complete and adequate studies in two test animal species (42 FR at 10417, Sec. IV, col. 3; 10431, 21 CFR 500.87). Thus, the regulation does not support the determination of safe levels for teratologic effects through a Mantel-

[2] The DOW–MCA study (G–58) is also referred to in the record as Dow study, and MCA-sponsored teratogenicity study.

Bryan analysis on the basis of incomplete data.

The Commissioner believes that the Administrative Law Judge's reference to "half-completed" teratology studies was to the requirement for an additional study before the data base would be complete enough to determine a safe level for human consumption of acrylonitrile. In this sense, the statement is correct. The Commissioner also agrees with the Administrative Law Judge's remarks concerning the seriousness of the risk of birth defects and cancer and his conclusion that it warrants special care and a conservative approach in the making of safety determinations. His remarks in this regard were not an unscientific appeal to emotion. Rather, they reflect the policy concerns that underlie the Act, and were appropriately made in evaluating the safety issues in this proceeding.

ii. The manufacturers make further exception to the finding of teratogenicity based on the DOW–MCA study because the teratogenic effects seen at the higher dose levels have been "seriously questioned" both by the experimenters and by Bureau witnesses. (*Monsanto App. at 60–61; Borg-Warner App. at 18–19.*)

The questions relate to whether the maternal toxicity observed at the higher levels could have resulted from overdosing and whether that maternal toxicity "accentuated" the fetal deformities. In addition, some question was raised about the presence of rat mumps and the effect it might have had. The reviewers of the study believe that the malformations were not the effect of maternal toxicity alone and that any effects of rat mumps were probably negligible. (G–58 at 14–15.) The Bureau recognizes that questions can be raised about this study. (Bureau Reply at 31.) These questions, though, do not dispel the concerns about the teratogenic potential of acrylonitrile. As Dr. Collins, the Bureau witness whose testimony is cited by the manufacturers, stated after being cross-examined about these questions:

> I would not allow [acrylonitrile] to be used until I had the complete data * * * you have some very serious abnormalities here that are very rare, and they seem to be related to the compound, and I would not want the stuff to be utilized until we had the complete toxicological data. (Tr. at 197.)

It would be rash, in view of the rare and serious abnormalities seen in this study, to assume that the study is invalid, and that the teratogenic effects observed are all due to rat mumps or overdosing, without having complete data investigating the teratogenic potential of the substance. It might also be noted that Monsanto has described this study as "well designed." (Monsanto App. at 59.)

This study, moreover, is the only adequate investigation into the teratologic potential of acrylonitrile. If the manufacturers are correct in assuming that the questions they cite invalidate the study, it will not establish that acrylonitrile has been shown by the manufacturers to be safe through scientific procedures. There are no other chronic studies considered adequate by contemporary standards which establish that acrylonitrile is safe. If this study is invalid, it means that at least another fully adequate and complete study must be done before acrylonitrile can be considered to be safe.

iii. Monsanto also contends that a safe level for humans for the teratogenic and other adverse effects of acrylonitrile can be derived based on the no-effect levels seen in early chronic studies, specifically the Tullar study[2] and the Svirbely and Floyd study.[4] (Monsanto App. at 59.) The Tullar study is inadequate by contemporary standards, as discussed in more detail, below. The Svirbely and Floyd Study was never fully reported; only a preliminary report was introduced into evidence. (ID at 23.) The Bureau has "never relied" on this study because "the data were never fully reported and a reliable appraisal of the results is therefore not possible" (Bureau Brief at 94). The Commissioner concludes that the absence of a full report from the Svirbely and Floyd study makes it an inadequate basis for use in determining a safe level for the teratogenic risks or other adverse chronic effects of acrylonitrile. The Administrative Law Judge seems to have regarded the preliminary results of the Svirbely and Floyd study to suggest a teratogenic potential for acrylonitrile. (ID at 21, 23.) This may be, but the Commissioner believes that the teratogenic potential of acrylonitrile is sufficiently demonstrated by the DOW–MCA study, without refernce to Svirbely and Floyd.

Finally the Commissioner notes that even if a no-effect level for human teratogenic were to be derived for acrylonitrile based on the present data, the compound could not be considered to have been shown to be safe. As discussed below in this Decision, no adequate studies exist to establish the safety of acrylonitrile with respect to the other chronic risks it poses, and there are indications that acrylonitrile is a probable carcinogen.

2. *Tumorigenicity*—a. *Initial Decision.*—The tumorigenicity of acrylonitrile is shown by the interim reports from the on-going Dow chronic feeding study[5] in the rat. The report (G–57) of the interim sacrifice "showed" a higher incidence of "subcutaneous masses" in the mammary region, and "masses of the ear canal," "polyp formation and hyperplasia of the stomach" and "proliferate lesions of the central nervous system" (CNS) at the higher or highest feeding levels. (ID at 19.) A later interim report (G–71), made in April, 1977, indicated that 2 rats at the lowest feeding level had developed the CNS tumors previously seen at the higher levels (ID at 20). A subsequent interim report (G–73) diagnosed the ear tumors, CNS tumors and mammary masses as malignant (ID at 20 and see ID at 22, Yodaiken, NRDC–94). The Administrative Law Judge stated that the "interim reports from this study become increasingly alarming with the passage of time." (*ID at 23–24.*) He also noted that "these irreversible effects appear regularly only after a year's exposure time and increase beyond that point (as evidenced by the increase in tumors and the percent classified as cancers in each interim report)." (ID at 28.) He concluded that the determination of a safe level for humans would be "inappropriate on the basis of the available evidence which indicates potentially severe adverse effects from the ingestion of AN." (ID at 39.)

b. *Exceptions And Commissioner's Response.* The manufacturing parties believe that acrylonitrile can be considered to have a safe level for humans with respect to tumorigenicity.

i. They argue that a no-effect level exists at the lowest level in the Dow chronic feeding study (Monsanto App. 56–57, 61–64; Borg-Warner App. at 16–17). They dispute the number of tumors observed at the lowest level, pointing out that NRDC witness Yodaiken (NRDC–94 at ¶ 7) believed only one rat, not two, had developed CNS tumors at the lowest feeding level. They also cite the testimony of a Bureau witness that the tumors at the lowest level may have occurred spontaneously and might be "washed out" when the study is complete. (Cueto, Tr. at 290). They urge that a 1000-fold safety factor or a Mantel-Bryan analysis be applied to the lowest feeding level in this study to derive a safe human level, and they complain that the Initial Decision did not state their projected safe levels and their positions correctly.

The Commissioner rejects the contentions that a safe level should be derived for tumorigenicity based on the incomplete Dow chronic feeding study. The data available from the study at this point indicate that acrylonitrile is a tumorigen in the rat, and probably a carcinogen as well, since some of the tumors have been diagnosed as malignant. It is conceivable that the tumor effects at the lowest level could be spontaneous and that at the end of the study there will be an equivalent number of tumors at this level in the control and test groups. It would not be appropriate, however, to speculate now on what the result of the study will be and what the exact number of tumors will be at this level. Since the study is not yet complete, it cannot be assumed, contrary to the suggestion of the manufacturers, that there will be a no-effect level. Even if no tumors had yet been seen at this level, it would be inappropriate to make this assumption. If a safe level for tumorigenicity is to be established for humans, it must be done on the basis of complete data, not on the basis of a single half-complete study. Furthermore, in view of the probable carcinogenicity indicated by this study so far, it would be

[2] The Tullar study (G–54) is also referred to in the record as an early chronic study.

[4] The Svirbely and Floyd study (G–86) is also referred to in the record as the Svirbely study, a long-term study, and an early chronic study.

[5] The Dow chronic feeding study (G–57) is also referred to in the record as: Dow chronic rat feeding study, Dow chronic ingestion study, Dow rat feeding study, Dow ingestion study, MCA ingestion study, chronic ingestion study, long-term study, Norris study.

inappropriate to postulate any safe level pending resolution of whether acrylonitrile is indeed a carcinogen in animals.

ii. The manufacturing parties contend that a dose-response relationship and a no-effect level for tumorigenicity and the other chronic toxic effects of acrylonitrile have been shown by other studies, specifically the Tuller study, the Svirbely and Floyd study, and the Maltoni studies (Monsanto App. at 53–54; Borg-Warner App. at 13, 15–16).

a. The Tullar study was reported in 1947 and is inadequate by contemporary standards (G–87 at ¶ 18), because of the small number of animals in the experimental groups, the use of male animals only, and the failure to use a full range of toxicological criteria. (G–86 at ¶ 7.) When considering the Tullar study, it should also be noted that the manufacturing parties have excepted to the Administrative Law Judge's reference to a report of the investigator in the Tullar study who commented that tumor-like growths were seen in four rats. (Monsanto App. at 65–66, citing ID at 36.) The manufacturers view the suggestion that the Tullar study "adds significance" to the recent tumorigenicity findings as being in conflict with the Commissioner's earlier assessment, quoted by the manufacturers, that the Tullar study did not demonstrate carcinogenicity. The Commissioner made the latter assessment "because of the inadequacy of this study and the lack of dose relationship," and because "the fact the tumors were of different kinds suggests no relationship to the agent fed." (FEDERAL REGISTER of November 4, 1974 (39 FR 38907, 38908) quoted in Monsanto App. at 66.) The Commissioner's assessment of the inadequacy of the Tullar study for evaluating the safety of acrylonitrile has not changed, and, at least on this matter, the Commissioner and the manufacturers are in agreement on the inappropriateness of reliance on that study.

b. The deficiencies of the Svirbely and Floyd Study have already been discussed, and the study can no more be considered adequate for purposes of evaluating tumorigenicity than it can be for teratogenicity.

iii. The Maltoni studies are ongoing, long-term studies on rats which have not been published or reported on in the manner usual for scientific studies. Monsanto put great emphasis on the Administrative Law Judge's failure to discuss this study or give it any apparent weight. (Monsanto App. at 14, 53–54, 67–68.)

Dr. Levinskas testified that Maltoni has not released reports to anyone except the sponsors of the study. (Tr. at 757.) Apparently, Maltoni does not believe in releasing negative data before a study is completed "because they may turn out positive before the study is over" and he did not give any written or printed material to Dr. Levinskas. (Tr. at 779–80.)

The Administrative Law Judge originally excluded from the record Dr. Levinskas' account of this study. In his Initial Decision, he concluded that it should be admitted into evidence, but he did not discuss it further and gave it no apparent weight. The Commissioner agrees that the Maltoni studies described in Dr. Levinskas' testimony should properly be given no weight. The Maltoni data are incomplete and the studies have not been officially reported by Maltoni. Furthermore, given the strong evidence that acrylonitrile is a carcinogen. Maltoni's unreported and incomplete data cannot be used to establish a "safe level" for acrylonitrile. The Act does not acknowledge the existence of a "safe level" for a carcinogenic food additive.

iv. Monsanto also excepted to the Dow chronic feeding study on the grounds that its "design and validity has been challenged." (Monsanto App. at 53.) The criticism, as stated in the manufacturers' Briefs, relates primarily to whether the maximum tolerated dose was exceeded.

There is convincing testimony that this study is appropriately designed. (Cueto, G–85 at ¶ 5 and Tr. at 269–70.) The maximum tolerated dose is a criteria of the National Cancer Institute that is aimed at ensuring that enough animals survive the test to draw meaningful conclusions when negative results are found; when enough survive, or when positive results are found, as was true here, the fact that the dose was exceeded does not invalidate the study. (Cueto Tr. at 270–73, 297–98.) In any event, the Administrative Law Judge did not find that the maximum tolerated dose was exceeded, and the Commissioner concludes that it has not been established that it was exceeded. (See Bureau Brief at 104–07.) Furthermore, even if the validity of this study were to be undercut, this would not permit a conclusion that acrylonitrile is safe since no other chronic studies that are adequate by contemporary standards establish that acrylonitrile is safe.

v. Vistron excepts to the asserted misinterpretation by the Administrative Law Judge of Vistron's position on the contamination of the acrylonitrile and the acrylonitrile water solutions used in the Dow chronic feeding study and the effect of such contamination upon the results of the study. (Vistron App. at 14–16.)

NRDC replies aptly to Vistron's exception by saying "This argument does not explain the fact that acrylonitrile causes cancer when inhaled, or why acrylamide [the impurity] would not be formed in beverages and pose a cancer risk to humans." (NRDC App. at 19.) Furthermore, the contamination possibility could not be viewed as explaining the tumorigenic and carcinogenic effects in the Dow chronic feeding study until further studies are done to establish the effects of the contaminant and to show that acrylonitrile is safe. (See Bureau Reply at 41.)

3. *Carcinogenic Potential.* a. *Initial Decision And Commissioner's Analysis.* The interim results from the Dow chronic feeding study show malignant tumors, including a highly important incidence of rare microgliomas (central nervous system tumors) and an increased incidence of Zymbal gland tumors. (ID at 20, 22; G–86 at ¶ 14b; G–87 at ¶¶ 25–28; G–85 at ¶¶ 7–8.) The higher incidence of malignant tumors in the treated animals at the 12 month stage implicates acrylonitrile as a carcinogen in rats. Thus, the ongoing Dow chronic feeding study shows not only that acrylonitrile is tumorigenic in the rat, but also that it probably carcinogenic as well. Since this study is not yet complete, it cannot be finally determined that acrylonitrile is a carcinogen. However, in view of the tumor findings so far in that study and the other indications in the record that acrylonitrile may be carcinogenic, the Commissioner believes acrylonitrile cannot now be considered to have been shown by the manufacturers to be safe.

The Administrative Law Judge found that there are other data in the record indicating the possible carcinogenicity of acrylonitrile:

> The two inhalation studies, one in rats and one in humans are also pertinent to this discussion. The rats tested showed the same central nervous system tumors, ear canal tumors and breast masses as did their counterparts in the chronic ingestion studies. This similarity makes comparisons between the groups appropriate. It also gives relevance to the human data, which showed a threefold increase in cancer among workers exposed to AN industrially. The necessity of chronic studies in unearthing these effects is paralleled by the 20-year latency period noted in the human case, as well as the systemic nature of the cancer, this similarity being noted by the du Pont researchers. (ID at 23.)

Based on this the Administrative Law Judge concluded:

> While it would be inappropriate to find AN unsafe or label it as a definite carcinogen on the basis of incomplete tests, the interim results from chronic feeding and inhalation studies raise considerable doubt as to its safety and require its exclusion from food. This is necessary to protect the public from the harm that could result from subjecting it to what is a potentially harmful substance unless, or until the safety of such substance, or the lack thereof, is reasonably established. (ID at 24.)

b. *Exceptions And Commissioner's Response*—i. The manufacturers object to the determination that acrylonitrile is a potential carcinogen. (Monsanto App. at 57–58, 63, 66–68; Borg-Warner App. at 16–17.) Most of their exceptions have been dealt with already in discussing the tumorigenicity data. However, the manufacturers' suggestion that a safe level can be derived for acrylonitrile, notwithstanding its carcinogenic potential, warrants further comment. As the Administrative Law Judge stated, if the data establishes the carcinogenicity of acrylonitrile the Delaney Clause would preclude determination of any safe level for its use as a food additive. 21 U.S.C. 348 (c) (3) (A). When evaluating whether a possible carcinogen has been shown to be safe by the manufacturers, the policy embodied in that clause is pertinent. Given the strong indications that acrylonitrile is a carcinogen, the Commissioner does not believe that the manufacturers can show a safe level for its use at any level, even assuming that their determinations were being made from adequate and complete studies.

ii. NRDC contends that the Commissioner should conclude now that acrylonitrile is carcinogenic because of the finding of a high incidence of tumors, including malignant ones in the interim sacrifice in the Dow chronic feeding study. (NRDC Reply at 18–21.)

The Commissioner believes the final determination of the carcinogenicity of acrylonitrile should await the final results of the Dow chronic feeding study. *The determination of carcinogenicity* should be based on a finding that the sole experimental variable between the control and experimental groups is the absence or presence of the test compound, as well as upon a finding that the incidence of tumors is statistically significant. The statistical significance of the tumors cannot be determined until the study is complete and the number of tumors known. At this point, acrylonitrile is a suspect carcinogen, but not yet a proven carcinogen.

iii. Monsanto excepts to the Initial Decision for stating that no evidence has been submitted characterizing the metabolites of acrylonitrile (Monsanto App. at 65, excepting to ID at 28.) Monsanto points out that it has submitted metabolite data in support of its theory that at low levels acrylonitrile is metabolized in the body in a way that renders it harmless. The Commissioner notes, however, that the metabolism data submitted by Monsanto are not complete, and the company's own witnesses testified that more study is necessary to prove their theory. (Tr. at 642, 691, 695; Bureau Brief at 107–10.) The Bureau also submitted testimony that more data is needed before this theory can be considered. (Blumenthal, G–88 at ¶¶ 9, 20.)

Monsanto also criticized the Initial Decision for not discussing the "uncontradicted testimony" by Bureau witnesses Cueto and Blumenthal that the human body contains defense and repair mechanisms for carcinogenesis. (Monsanto App. at 14.) The very testimony cited by Monsanto provides a sufficient explanation of why this theory cannot be used to postulate a safe level for acrylonitrile. Dr. Blumenthal testified that he personally thought there might be such mechanisms, but—

> * * * for any individual compound, each of these parameters has to be determined individually. * * * Therefore, it would seem to me that the important point to establish with respect to acrylonitrile is whether in fact there are any data available that would define a threshold for toxicologic responses in rats, mice and humans to acrylonitrile exposure. (G–88 at ¶ 15.)

That data for acrylonitrile has not been submitted. Whether there is a threshold, and where it may be, is not now known. Accordingly, the Commissioner concludes that acrylonitrile cannot be considered to be safe based on Monsanto's as yet unsubstantiated theories.

iv. Monsanto also excepts to the Administrative Law Judge's reliance on the duPont workers study* (G–74) and the Dow inhalation study† in rats (G–71) in his evaluation of carcinogenicity (Monsanto App. at 57–58, citing ID at 23.) The principal basis of the objection is that the Maltoni studies were not also discussed, but, in addition, Monsanto questions the relevance of these two inhalation studies in view of the tumor distributions in the duPont study.

The Commissioner has already discussed why it is inappropriate to give any weight to the Maltoni studies. The rats in the 80 ppm group in the Dow inhalation study exhibited central nervous system tumors similar to those seen in the Dow chronic feeding study (G–87 at ¶ 29). The duPont workers study demonstrated an increased incidence of cancer among workers exposed to acrylonitrile (Kokoski, Tr. at 441). Although some of the tumor sites found in this study in humans differed from those found in rats in the Dow chronic feeding study, this difference was not unexpected since different species often manifest different tumor sites when exposed to the same toxic substances. (Kokoski, Tr. at 441–42.) Inhalation studies are not directly relevant to ingestion toxicity; however, the inhalation data "gives evidence of the systematic nature of the apparent carcinogenic effect of acrylonitrile after absorption." (G–87 at ¶ 29; Tr. at 440–42.) The Commissioner believes that the inhalation studies suggest that acrylonitrile is a carcinogen and that they provide evidence supportive of the interim results from the Dow chronic feeding study. All these studies taken together preclude a conclusion that acrylonitrile beverage containers have been shown to be safe.

v. Monsanto also excepts to the Administrative Law Judge's statements that the manufacturers used the duPont workers study to project a no-effect level. Monsanto maintains that this study is too flawed to be used for any purpose. (Monsanto App. at 55.) If any weight is to be given to the results of this study, though, Monsanto regards them as consistent with an apparent no-effect level.

The Commissioner accepts Monsanto's exception claiming that it did not in fact use this study to derive a no-effect level. He too is aware of the limitations of this study, including the fact that it is not complete. (G–87 at ¶ 30; Tr. at 820). Nonetheless he believes the Administrative Law Judge was correct in giving this study weight in considering whether acrylonitrile had been shown to be safe because the study suggests that acrylonitrile may be a human carcinogen. This study, taken together with the other data in the record, raises serious suspicions about the carcinogenic potential of acrylonitrile that need to be resolved by complete and adequate studies.

4. Mutagenicity. a. *Initial decision.* The Administrative Law Judge summarizes his findings on the mutagenicity studies as follows:

> The present data raise certain implications of adverse effects of acrylonitrile. The microbial system screening for animal carcinogenicity has produced several clear, highly reproducible positive findings, with negative results occurring only when a technique meant to overcome the problems of toxicity or volatility of AN was not utilized. In this situation, with the same number of studies finding positive results as those finding negative results, it would be improper to discount the positive findings. This view results in a strong implication of acrylonitrile being a carcinogen in higher animal systems. (ID at 22.)

b. *Exceptions and Commissioner's response.* Monsanto excepts to the above statement on the grounds that the "great majority" of the mutagenicity tests have shown a negative response. (Monsanto App. at 50–52.) Monsanto makes this calculation by counting as separate tests the testing done on each of 33 bacterial strains used in the six mutagenicity tests discussed in the Initial Decision. Monsanto describes all the positive results as weak. The exception also maintains that the manufacturers have never contended that negative results automatically outweigh positive results, but that they believe, on the other hand, that positive results should not automatically outweigh negative. Monsanto also criticizes the failure to note that negative mutagenicity results have been observed even when precautions were taken to prevent volatilization.

The Commissioner finds that Monsanto's approach of dividing each study into its component bacterial strain is inappropriate, since, as the Bureau notes, "many of the strains were never tested by procedures designed to inhibit the volatilization of the acrylonitrile nor designed specifically to detect mutagens that are not strong enough to demonstrate a mutagenic effect in the standard plate test." (Bureau Reply at 27.) Furthermore, Monsanto's effort to discount the positive results by emphasizing that they were "weak" overlooks the fact that the volatilization process used makes it impossible to conclude whether acrylonitrile is a weak or potent mutagen." (Prival, Tr. at 228.)

The mutagenicity testing is primarily important for indicating whether acrylonitrile may be a carcinogen. Microbial testing "has been shown to be about 90 percent accurate in predicting animal carcinogens." (ID at 17.) Consequently, the positive results are highly important in indicating the need for further investigation into the carcinogenic potential of acrylonitrile. The negative results do no dispel these concerns. (See ID at 17–19.) The laboratories reporting positive findings used appropriate methods (ID at 17–19), and nothing in the exceptions indicates that the positive

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* The duPont workers study (G–74) is also referred to in the record as the epidemiological study, human study, inhalation study and duPont study.

† The Dow inhalation study (G–71) is also referred to in the record as the rat inhalation study.

tests are invalid, apart from the existence of negative results, some of which can be attributed to the failure to use techniques to prevent volatilization.

The Administrative Law Judge believed that the positive results warranted the completion of a "cancer-profile test protocol" before acrylonitrile could be determined to be noncarcinogenic (ID at 17). The Commissioner believes this conclusion is still valid. Complete animal testing of the carcinogenic potential of acrylonitrile is needed to resolve the differences between the positive and negative results in the highly predictive mutagenicity testing.

C. RISK ASSESSMENT AND OTHER CONTENTIONS

1. Monsanto contends that the Administrative Law Judge ignored its position that in making risk assessments corrections can be made to compensate for incomplete studies, studies in one species, and cumulative effects. (Monsanto App. at 68–69.)

This may indeed be Monsanto's position, but it is not the Commissioner's position and the Administrative Law Judge rightly did not adopt it. Safety decisions should be made on complete data. If safety calculations are made on incomplete data, they inherently rest on a guess that the further studies will not demonstrate a greater risk than the compensation factor used. The Commissioner is not willing to make such assumptions in connection with the severe risks indicated for acrylonitrile. It is particularly inappropriate in view of the carcinogenic potential of acrylonitrile. Furthermore, the validity of statistical extrapolations to determine safety risks from incomplete data is conjectural. (See Bureau Brief at 131–33, 146–50.)

2. As part of his discussion of risk assessment, the Administrative Law Judge discussed not only the traditional use of safety factors to determine a no-effect level but also the Mantel-Bryan procedure which he equates with the "Sensitivity of the Method" (SOM) regulation[*] recently issued by FDA. (ID at 31, n. 20.) The Administrative Law Judge correctly found, as already discussed, that no risk assessment procedure, including the Mantel-Bryan procedures, could be used because of the absence of complete and adequate animal studies from which to extrapolate the risk level to humans with confidence. In its exceptions, Monsanto still argues for the use of the Mantel-Bryan procedure to calculate safe exposure levels for carcinogens (Monsanto App. at 63), and all the participants devoted considerable attention to the SOM regulation in their briefs to the Administrative Law Judge. Accordingly, the Commissioner believes he should elaborate upon his conclusion that the SOM regulation is inapplicable to this proceeding.

The SOM regulation applies by its terms to animal drugs and was issued under a statutory exception to the Delaney Clause (the so-called DES exemption) that permits the use of a carcinogenic animal drug in meat producing animals if no residue is found in the meat by a method approved by the Agency. (21 U.S.C. 348(c)(3)(A), 360b(d)(1)(H), and 376(b)(5)(B).) The regulation establishes criteria for how sensitive a method has to be before the agency will approve it. The regulation provides for the use of the Mantel-Bryan procedure to calculate how sensitive the method must be. The SOM regulation deals with the development of methods, pursuant to a statutory provision, for determining whether residues of a carcinogenic animal drug is present in meat, not with determining a safe level for carcinogens, as some of the submissions would have it. The regulation is currently under judicial review. (*Animal Health Institute* v. *FDA*, C.A. No. 77-0806 (D. D.C.), filed May 12, 1977.)

The Commissioner believes that if the SOM regulation were ever to be applied to food additives it should be done by regulation after public notice and opportunity for comment. It is by no means clear that the criteria and manner of calculation used for animal drugs should be adopted for food additives. NRDC, for example, maintains that the risk criteria in the SOM regulation are not sufficiently conservative for food additives. (NRDC Brief at 49–50; see Bureau Brief at 121–22, 126–29, 133–36.)

The general public has received no notice that the SOM regulation might be considered for application to food additives in this proceeding. The notice of hearing did not mention this issue and, indeed, the Commissioner did not anticipate that it would arise. A petition (77P-0122) has recently been filed by the Society of the Plastics Industry requesting the Commissioner to initiate a rulemaking proceeding to adopt the sensitivity of the method criteria for use in regulating food additives.

The legal issues regarding the applicability of an SOM approach to food additives are extremely complex and difficult. (Bureau Brief at 120–21.) The only explicit provision in the statutory section governing food additives which authorizes the agency to establish methods for determining the presence of a substance is the DES exemption, which is limited in its applicability to animal drugs. (21 U.S.C. 348.) NRDC maintains that the SOM regulation cannot appropriately be applied in this proceeding or for indirect food additives (NRDC Brief at 48–50.) The Commissioner will not attempt to resolve these legal questions here because he does not view this proceeding as a suitable forum to address the issue. More consideration of the issue is needed both by the public and by the agency before the applicability of the SOM regulation to food additives is addressed and resolved.

3. Monsanto states in its general exceptions that the degree of risk from small amounts of a substance like acrylonitrile can never be precisely known; it can only be estimated. Furthermore, safe levels can be determined by extrapolation from toxic effects seen at high levels, and the more data available the more confident the projections. Monsanto then states that more data exist on the safety of acrylonitrile than on any other beverage container migrant and, from this, concludes that the Administrative Law Judge was wrong in believing that the degree of risk from acrylonitrile is not presently known. (Monsanto App. at 28–30.)

The Commissioner agrees with Monsanto's position as summarized in the first two sentences above, but he finds the conclusion drawn by Monsanto to be unsound. Safety determinations are not precise and some uncertainties remain even when they are drawn from complete data. When incomplete studies or inadequate data are used to project risks, the estimates are more likely to be incorrect. The adequacy of data is not determined, as Monsanto would have it, on volume or on a comparative basis. To be adequate the data must satisfy scientific procedure and be sufficient to determine with confidence a safe level for each type of risk posed. By that standard the level of risk from acrylonitrile has not been adequately determined, as the Administrative Law Judge found.

4. Monsanto has also excepted to the discussion of consumption patterns in the Initial Decision because it reports the contentions of the participants without accepting Monsanto's figure. (Monsanto App. at 48–50, citing ID at 29–30; see Borg-Warner App. at 13.) Monsanto also objects to the Initial Decision for apparently agreeing with the Bureau's criticisms of Monsanto's estimate.

The Administrative Law Judge determined that a safe level could not be established for acrylonitrile in view of the incompleteness of the safety data. (ID at 33, 37 and 38.) Consumption patterns become relevant only if a calculation is to be made of a safe level for human consumption of a substance. Since a safe level cannot be determined, there is no need at present to resolve issues about the consumption pattern for acrylonitrile. Thus, it was appropriate for the Initial Decision not to reach any conclusion about this matter.

Furthermore, before Monsanto's estimate of the total dietary concentration of acrylonitrile can be accepted, the issues raised by the Bureau need to be considered. (Bureau Reply at 24–26.) The Bureau criticizes the Monsanto estimate because it relates to total diet, rather than total fluid diet, because it is based on migration estimates that are not sufficiently exaggerated with respect to time and temperature conditions, and because it does not make any allowance for the higher absolute amount of acrylonitrile consumed by the above average consumer, even though the concentration of acrylonitrile remains the same. If a safe level is to be determined for acrylonitrile

[*] The correct title of this regulation is Criteria and Procedures for Evaluating Assays for Carcinogenic Residues. The Commissioner will refer to it by the term Sensitivity of the Method (SOM) because this terminology has been used in this proceeding, but he has reservations about the terminology, as noted in the FEDERAL REGISTER of February 22, 1977 (42 FR 10412, 10427–28).

in the future, based on complete safety data, the issues raised by the Bureau need to be taken into account in evaluating Monsanto's estimate.

IV. MISCELLANEOUS MATTERS

The Commissioner discusses below some miscellaneous exceptions raised by the participants and the nature of the order that should be issued in this proceeding.

A. FORMAL REQUIREMENTS AND ADEQUACY OF THE INITIAL DECISION

The manufactures object to the Initial Decision on the ground that it made broad general findings, did not contain formal findings of fact and conclusions of law, and did not discuss all the testimony and points they consider significant. (Monsanto App. at 13–16, 28–29, Borg-Warner App. at 12–19, and Vistron App. at 19.) They conclude from this that the Administrative Law Judge did not fairly evaluate the whole record. They also deduce from the fact that the Administrative Law Judge did not state the governing legal standards with respect to the burden of proof and other matters that he did not in fact apply the correct legal standards and did not, for example, impose on the Bureau the burden of proof on the food additive question (Monsanto App. at 12, Borg-Warner App. at 2–8.) Monsanto also criticizes as "misleading" the Administrative Law Judge's statement of Monsanto's position on a number of safety issues and his description of the details of the different studies in the record. (E.g., Monsanto App. at 54–69.)

The Commissioner concludes after reviewing this matter carefully that these objections go primarily to form and that there is no merit in the suggestion that the Initial Decision is inadequate or unfair. The Administrative Law Judge's Initial Decision reflects a thorough evaluation of the submissions under the appropriate statutory standards and a careful analysis of the points he considered significant. He did not need to recite all the governing legal standards, and his not doing so with respect to the matters raised in the exceptions seems attributable to the fact that it was clear and undisputed which standards applied. The Bureau clearly acknowledged, for instance, that it had the burden of proof on the food additive issue (Bureau Brief at 6–7).

In preparing this Final Decision, the Commissioner has addressed all the contentions raised by the participants that he considers significant. He also has expressly stated his positions on some of the minor contentions, simply to avoid further dispute about the need for an express statement to demonstrate they were considered. Time did not permit, though, an express treatment of each exception or item in the record that the participants may have wanted discussed, and a specific discussion of each was not needed in view of the satisfactory responses in the Bureau reply. Furthermore, the Commissioner believes the issuance of a Decision should not be an exercise in mentioning details. Instead, the time and attention of the decisionmaker should be addressed to presenting a reasoned discussion of the important issues, as the Commissioner believes has been done in this proceeding.

A narrative presentation of findings of fact and conclusions of law, as incorporated in the Initial Decision, is permissible under the provisions of the Administrative Procedure Act, 5 U.S.C. 557(d). *Gilbertsville Trucking Co.* v. *United States*, 196 F. Supp. 351 (D. Mass. 1961); *State Corporation Commission* v. *United States*, 184 F. Supp. 691 (D. Kan. 1959). The other applicable provisions, 21 U.S.C. 409(f) and 21 CFR 12.120, do not establish a mandatory form for the required findings of fact and conclusions of law. The Commissioner believes, though, that a formal statement of the findings and conclusions of law is the most useful format for providing a concise presentation of the basic elements of the decision. Accordingly, he has included formal findings of fact and conclusions of law in this final decision in numbered paragraph form.

Monsanto's criticisms of the Initial Decision as being inaccurate or misleading are related to specific exceptions it takes to the discussion of the safety data. The Commissioner has discussed a number of these criticisms in connection with the safety data to which they relate. In many repects, the exceptions fault the Initial Decision as being inadequate or misleading simply because the decision did not accept the theories offered by the manufacturer. (E.g., Monsanto App. at 58–59.) Some objections are a quibbing over details, though Monsanto's exceptions did correctly point out some inaccuracies. (See, e.g., Bureau Reply at 26, n. 36 and 31, ¶¶10–11 agreeing with Monsanto's exceptions.) The Commissioner has responded to some other exceptions reporting errors or imprecision by stating the point correctly when the discussion of the point was pertinent in this Decision. The inaccuracies in the Initial Decision do not, however, have any material bearing on the basic findings of the Initial Decision or its conclusions, and, after considering them the Commissioner finds that they are, as a whole, inconsequential.

B. COMPENSATION ARRANGEMENT FOR WITNESS AND BIAS

The Administrative Law Judge noted in his opinion that one of the expert witnesses for a manufacturing party was an employee of one of the law firms representing that part (ID at 5–6). The Administrative Law Judge stated that he was raising this matter in his Initial Decision "merely to point out the potential inroads to a witness's freedom from 'financial inducements' which could conceivably result from such circumstances." (ID at 6.) The manufacturing party involved raised a strenuous and lengthy exception to the Administrative Law Judge's reference to this matter and asked the Commissioner to have the Administrative Law Judge's discussion "expunged from the record of this proceeding," (Monsanto App. at 30–37). The comment of the Administrative Law Judge quoted above was viewed as a "gratuitous slur" of the witness, and his raising of the issue, without resolving it, was viewed as indicating bias on his part against all the manufacturers' witnesses. (Monsanto App. at 33, 35.)

The Commissioner views the Administrative Law Judge's purpose as having been either to note a factor that might conceivably have some bearing on the weight to be given the testimony of the witness involved or to raise an issue that might be considered for treatment in the Agency's procedural regulations. His raising of the matter does not demonstrate bias. As the exception itself maintained, the compensation arrangement for a witness "is simply a factor to be considered in weighing the testimony". (Monsanto App. at 35.)

After reviewing the matter, the Commissioner finds no reason to alter the weight that should be given to the testimony of the witness because of the compensation arrangement noted in the Initial Decision. The Commissioner has carefully considered the testimony of this witness on its merits.

The Commissioner regards the manufacturer's request for an expungement of the record as being novel. He is neither convinced of its merits nor certain of the mechanics. Under FDA's general procedural regulations, 21 CFR 10.70(c)(6), once a document is final and part of the Agency's administrative file, it cannot be deleted. The record of this proceedng is public, and what is in the public record should remain there.

The Commissioner also rejects the suggestion that the Initial Decision reflects bias against all the manufacturers' witnesses. The principal grounds given in the exception for asserting bias, aside from the matter discussed above, are the failure to rely on the Maltoni studies and the failure to mention the testimony of "eminent scientists," specifically Dr. Robert Olson (M–96), and Professor Robert Wilson (M–90). (Monsanto App. at 35–37.) The Maltoni studies are discussed earlier in this Decision and the testimony of Dr. Olson and Dr. Wilson is discussed below.

As the Bureau points out, bias is not demonstrated simply "because the Court fails to invoke the name or discuss explicitly the testimony of every witness in the proceeding." (Bureau Reply at 20.) The Administrative Law Judge did not specifically discuss the testimony of some "key" Bureau witnesses, namely Holtz, Cueto and Livingston (Bureau Reply at 20), yet there is no suggestion that he was biased against the Bureau. Furthermore, the Commissioner believes that omission of any specific discussion of the Olson and Wilson testimony is justified by its content. The testimony of Dr. Olson discussed in general terms the metabolism of acrylonitrile and the threshold concept and, without referring to any actual toxicity data, drew a conclusion about the safety of acrylonitrile which was based on the manufacturers' theory of toxicological insignificance.

Since the Commissioner has rejected that theory in this proceeding, it is unnecessary to deal in detail with Dr. Olson's testimony. Professor Wilson's testimony dealt with a risk assessment of acrylonitrile which was not significantly different from others presented by the manufacturers and was based on incomplete data. Since the Commissioner has concluded that the presently available data are not adequate to confidently evaluate the risks posed by acrylonitrile, it is not necessary to evaluate in detail risk assessments such a those offered by Professor Wilson.

C. APPLICABILITY TO OTHER USES AND SUBSTANCES

The manufacturing parties except to the Administrative Law Judge's suggestion that the Commissioner consider revising or staying the regulations governing the use of acrylonitrile copolymers in non-beverage containers. (Monsanto App. at 37–38, Borg-Warner App. at 20–23; Vistron App. at 1–3.) They urge that the Commissioner not issue an order in this proceeding that applies to non-beverage containers.

The Commissioner believes the Administrative Law Judge's suggestion warrants further consideration, but he views any action to be taken in that regard to be a distinct matter that should be handled in a separate proceeding. The issues as framed for this proceeding concern only beverage containers, and affected persons must be afforded an opportunity to be heard before any action is taken with respect to other uses.

Monsanto suggests that this proceeding should be viewed as having determined that hydrogen cyanide and other substances which may be in acrylonitrile copolymer beverage bottles are non-migratory or safe merely because they were not discussed in the Initial Decision. (Monsanto App. at 12, footnote.) The Commissioner disagrees. The record shows that, due to the migration of acrylonitrile monomer, acrylonitrile copolymers used to fabricate beverage containers are food additives which have not been shown to be safe. Therefore, it is not necessary to consider whether other substances in the beverage containers migrate or are safe, and this proceeding should not be considered to have decided those questions.

D. PRIOR HISTORY

Monsanto excepts to the Administrative Law Judge's summary of the origins of this proceeding. (Monsanto App. at 39–41.) The Administrative Law Judge attributed the Agency's reconsideration of the safety data for acrylonitrile to the development of improved methods for detecting migration. Monsanto insists that the reconsideration of the safety data was prompted by a concern about the possibility of delayed extraction from a reversible mercaptan complex, a possibility which has not been pursued by the Bureau in this proceeding. (Tr. at 114.) Monsanto also excepts to the description of the requirements of the interim regulations. (Monsanto App. at 40–41.)

Whatever the particular factor was that caused the initiation of some reconsideration of the safety data for acrylonitrile copolymers, the Commissioner believes the reconsideration to have been warranted, as this record amply demonstrates. The Commissioner regards as pointless any further effort to settle disputes about the prior history of acrylonitrile regulation.

E. NATURE OF THE ORDER

The Initial Decision provides for a stay of the regulations at issue "until further notice." (ID at 40.) In its brief to the Administrative Law Judge, the Bureau proposed an order providing for an amendment of the regulations to eliminate the use of acrylonitrile in beverage containers. The Commissioner has adopted essentially the Bureau's proposed order, by making the appropriate changes in the codified text of the regulations, with a deletion of the stay note and termination of the stay published in the FEDERAL REGISTER of March 11, 1977 (42 FR 13546). Under § 409(f)(3) of the Act, 21 U.S.C. 348(f)(3), the Commissioner's final order is not effective until 90 days after publication.

In *Monsanto Corp.* v. *Gardner*, the Court held that in effect the Commissioner's stay action was taken on his own initiative and that the situation was governed by sections 409(d) and (h) of the Act, 21 U.S.C. 348(d) and (h). These statutory provisions authorize the Commissioner to issue regulations on his own initiative and to establish procedures to amend or withdraw food additive regulations. Thus, the Court viewed this proceeding as being one taken on the Commissioner's initiative to withdraw or amend food additive regulations. The Commissioner agrees.

The Commissioner believes that it would be inappropriate to adopt the order contained in the Initial Decision which simply stays the regulations indefinitely until further notice. It is not clear what procedures would be involved in terminating such a stay, nor what circumstances would warrant termination. Treating this proceeding as an action to amend the regulations, rather than merely to stay them, will ensure that future developments are governed by the regular procedures for regulation of food additives. Any future changes in the status of acrylonitrile as a food additive should be made through the regular procedures of public notice of a proposed regulation, opportunity for comment, and a hearing on objections. By regarding this proceeding as one to amend the regulations rather than merely stay them, the Commissioner reduces the likelihood that there will be confusion about the legal status of acrylonitrile copolymers used to fabricate beverage containers.

V. FINDINGS OF FACT AND CONCLUSIONS OF LAW

A. FINDINGS OF FACT

1. Acrylonitrile monomer is used to fabricate acrylonitrile copolymer beverage containers (G–77 at ¶ 17; 21 C.F.R. 177.1020, 177.1030, 177.1040, 177.1050, 177.1480).

2. Acrylonitrile monomer was not used prior to January 1, 1958 to fabricate beverage containers (G–77 at ¶ 17).

3. None of the containers manufactured in accordance with any of the regulations that currently authorize their use is free of residual acrylonitrile monomer (M–1; M–84, at ¶ 11 and Table A; BW–1; BW–2; V–4 at ¶ 18; V–12).

4. The physical process known as diffusion causes residual acrylonitrile monomer in the containers to migrate into the beverage under all conditions of time and temperature to which the containers would be exposed in normal usage (M–82 at ¶¶ 6–10; M–84 at ¶¶ 13–18, 21.B, Appendix; M–86 at ¶¶ 2(a), (b); G–77 at ¶¶ 30–32; G–78 at ¶¶ 11–12, 18 and Exhibit A; Tr. at 132, 136, 139, 143, 144).

5. Extraction tests with food simulants and with beverages conducted under conditions reasonably close to those associated with normal use and intended use confirm that the diffusion process causes migration of acrylonitrile monomer from the beverage containers of Monsanto, Borg-Warner, and Vistron (G–77 at ¶ 30; G–78 at ¶¶ 8, 10–11, 14–16; G–79; G–80; G–81; M–84, Appendix at A–2, A–3, Table IV; BW–1; BW–2; V–1, Table 2; V–7; V–10).

6. The diffusion process may be expressed in the form of a mathematical equation that can be used to predict the occurrence of migration of acrylonitrile monomer at levels that cannot be measured by analytical techniques. Models based on this equation predict that migration will occur, under all time and temperature conditions to which beverage containers would normally be exposed, from containers with low levels of residual monomer that produce amounts of migration too small to be detected analytically (G–78 at ¶¶ 5–7, 8, 11–12, Exhibits A, C; M–84 at ¶¶ 12–18, Appendix; M–86 at ¶¶ 2(a), (b); Tr. at 132, 136, 139, 143, 144).

7. No demonstration has been made that the diffusion process fails to operate for acrylonitrile copolymer beverage containers. The theory that, in unusual circumstances, the molecules of acrylonitrile monomer are indissolubly bound to the copolymer matrix is speculative and has not been established with respect to the levels of residual acrylonitrile monomer present in the copolymer materials most recently produced by Monsanto, Borg-Warner, and Vistron (M–84 at ¶¶ 18, 21.B; Tr. at 147–148).

8. The use of acrylonitrile monomer to fabricate acrylonitrile copolymer beverage containers may reasonably be expected to, and in fact does, result in acrylonitrile copolymer beverage containers becoming a component of beverage foods packaged in such containers (G–77 at ¶ 33; G–78 at ¶ 18; Findings Nos. 1–7, supra).

9. Laboratory testing of acrylonitrile copolymer beverage containers under exaggerated time and temperature conditions with food simulants is an appropriate means of confirming whether the intended use of the containers results in

migration of acrylonitrile monomer and of determining what the levels of migration are or may be assumed to be for purposes of evaluating the toxicity of acrylonitrile monomer under the intended conditions of use of acrylonitrile copolymer beverage containers (G–77 at ¶¶ 5–16; G–78 at ¶ 17; Tr. at 63, 70–71, 79–80, 124).

10. The purpose of extraction testing of acrylonitrile copolymer beverage containers is to determine the maximum amount of acrylonitrile monomer to which the consumer may be exposed under the intended conditions of use of the containers. In conducting extraction tests, it is scientifically appropriate to use conditions of time and temperature that exaggerate those that would be expected for a particular product in order to account for extreme conditions of use and to compensate for the fact that food simulants do not necessarily possess the same extraction characteristics as the numerous different foods that might be packaged in the containers (G–77 at ¶¶ 11–12, 14–16, 23, 25–26. Exhibit F, at 12–13; Tr. at 61, 120, 125, 145).

11. The conditions of 6 months and 90° F are appropriately assumed to represent the intended conditions of use of acrylonitrile copolymer beverage containers in accordance with accepted principles of extraction testing (G–77 at ¶¶ 24–29; M–85 at ¶¶ 22–25).

12. For purposes of assessing the toxicity of acrylonitrile monomer in beverages, data must be derived that show approximately how much monomer will migrate under the intended conditions of use of the containers. These data may consist of the results of extraction tests, projections from mathematical models, or the level of analytical detection that has been achieved. (G–77 at ¶¶ 5–7, 27–28; G–78 at ¶¶ 5–6, 9, 12; M–83; M–84; BW–1; BW–2; V–4 at ¶ 13; V–6; V–7; V–8; V–10; Tr. at 69, 70–72, 79–80, 104–106, 129, 137, 146–147.)

13. Extraction data exist for the acrylonitrile copolymer beverage containers of Monsanto, Borg-Warner, and Vistron (Finding No. 5, *supra*).

14. The available extraction data do not permit a determination of how much monomer migrates from the most recently produced beverage containers of Monsanto and Vistron, although in the case of Vistron its presence was detected and in the case of Monsanto its presence was probably detected (M–83 at ¶¶ 2.d, 9; V–4, ¶ 16; V–10).

15. The mathematical models developed by Monsanto predict migration of 4.3 ppb or more of the monomer under the intended conditions of use of acrylonitrile copolymer beverage containers. The models are as applicable to Borg-Warner's and Vistron's containers as to Monsanto's. The models are not intended to be precise, but to provide an approximation of the levels of migration that can reasonably be expected to occur (G–78 at ¶ 9, Exhibits A and C; M–84, Appendix and Table IV; M–88, Table IV; Tr. at 137, 139, 146).

16. The lowest reliable limit of detection yet achieved for acrylonitrile monomer is 10 ppb (M–83 at ¶ 8; BW–1; V–10).

17. Taken together, the available data indicate that migration of acrylonitrile monomer from acrylonitrile copolymer beverage containers now being produced is in the range of several parts per billion to ten or more parts per billion under the intended conditions of the containers' use. Greater precision would be required if a safe level for human consumption of arcylonitrile were capable of being established at this time (Findings Nos. 9–16, *supra*).

18. Acrylonitrile is a frank teratogen in the rat (G–58; G–82; G–83; Tr. at 187).

19. Because animal species differ in their susceptibility to teratogenesis, a teratology study in at least one more animal species must be performed before a "no-effect" level for acrylonitrile monomer can be determined for purposes of estimating a safe level of exposure for human (G–82 at ¶ 6; G–86 at ¶ 11.b.; G–87 at ¶¶ 15, 23; Tr. at 195, 197, 199, 201–203, 208–209, 210–211).

20. Because of the teratologic effects of acrylonitrile monomer in the rat, a reproduction study must also be conducted before the toxic potential of the monomer can be regarded as completely characterized (Tr. at 195).

21. Based on the Dow-MCA study in rats, acrylonitrile monomer may be teratogenic in humans (G–82 at ¶ 6; Tr. at 214).

22. Acrylonitrile monomer is mutagenic in several bacterial test systems (G–67; G–70; G–84; BW–7; NRDC–92).

23. A chemical that is mutagenic is probably carcinogenic in mammals (G–84 at ¶¶ 3, 20; Tr. at 219–221, 261).

24. The Dow chronic feeding study (G–57; G–72) is appropriately designed to determine the potential carinogenicity and other toxic effects of acrylonitrile monomer in rats (G–85 at ¶ 5; Tr. at 269–270).

25. The interim one year results of the Dow chronic feeding study demonstrate that acrylonitrile monomer is tumorigenic, and create a strong inference that it is carcinogenic (G–85 at ¶¶ 8–9; G–86 at ¶¶ 11.c, 14.b; G–87 at ¶¶ 25–28; Tr. at 303; NRDC–94).

26. The Dow chronic feeding study is incomplete, and the preliminary results indicate at best only the level of risk from acrylonitrile monomer after about the first half of a rat's lifetime (G–72; Tr. at 560, 611–612). At least one tumor has been observed in rats at the lowest feeding level in the ongoing phase of the study that are similar to the tumors observed in rats at higher feeding levels in the interim phase of the study (G–71; G–86 at ¶ 13.b; G–87 at ¶¶ 25–27; Tr. at 290). Consequently, the Dow chronic feeding study does not permit the determination of a "no-effect" level (G–86, ¶ 15; G–87, ¶ 38).

27. Epidemiological data from the duPont workers study suggest that acrylonitrile monomer is carcinogenic in humans (G–86 at ¶ 13.g; G–87 at ¶ 30), but the study does not involve exposure to acrylonitrile by ingestion, does not contain data indicating what the lifetime risk is from exposure to acrylonitrile, and does not report the level of exposure to acrylonitrile monomer undergone by the subjects of the study (G–74).

28. The Tullar Study (G–54) and the Svirbely and Floyd Study (G–55), early chronic toxicity studies of acrylonitrile monomer, are scientifically inadequate for purposes of drawing reliable conclusions about the toxicologic potential of acrylonitrile (G–41; G–84 at ¶¶ 6–9; G–87 at ¶¶ 18–19).

29. The available toxicology data demonstrate that acrylonitrile is a teratogen, a mutagen, a tumorigen, and probably a carcinogen (Finding Nos. 18–28, *supra*.).

30. Whether there is a true biological threshold for the toxic effects of acrylonitrile monomer or where that threshold lies, if it exists, are not now known (G–88 at ¶¶ 9, 14–15, 16–21; Tr. at 650–651, 660, 692).

31. A safe level of human exposure to a toxic chemical is established by applying appropriate safety factors to a "no effect" level determined from the available toxicology data (21 U.S.C. 348(c)(5)(C); G–87 at ¶¶ 12–15).

32. It is not possible on the basis of the available toxicology data to establish a safe level for human consumption of acrylonitrile monomer by applying safety factors: the data are incomplete, a "no effect" level for the chronic toxicity demonstrated in the 2-year Dow chronic feeding study has not been reliably determined, and it is not possible to establish a safe level for human consumption of a substance that is probably carcinogenic (G–82 at ¶ 6; G–86 at ¶¶ 11.b, 15; G–87 at ¶¶ 13–16, 23, 24–36, 41; Tr. at 195, 197, 199, 201–203, 208–209, 210–211, 284, 290).

33. For the same reasons, it is impossible to establish the degree of toxicity of acrylonitrile monomer for use in performing a "risk assessment" of any level of human exposure to acrylonitrile monomer in beverages.

34. For the same reasons, there do not now exist "scientific procedures" that adequately show that acrylonitrile is safe under the conditions of its intended use to fabricate beverage containers and that could be relied on by qualified experts for that conclusion.

35. Qualified experts in fact do not generally recognize that acrylonitrile has been adequately shown through scientific procedures to be safe under the conditions of its intended use in beverage containers (G–82 at ¶ 6; G–86 at ¶ 16; G–87 at ¶ 41; M–82 at ¶ 5; M–90 at ¶¶ 8, 52; M–96 at ¶ 6; M–97 at ¶ 11; M–98 at ¶ 11; Tr. at 466–467, 589–590; NRDC at ¶¶ 19–22).

36. Factors that are considered in evaluating the safety of a toxic substance under the conditions of its intended use as a food packaging material include the amount of possible migration into food, the types of food packaged in the material, the extent of consumption of foods packaged in the material, and the degree of toxicity of the substance (G–87 at ¶ 5).

37. Since acrylonitrile cannot be considered safe at present because of the deficiencies in the toxicology data (Finding Nos. 19–35, *supra*), it is unnecessary to determine the extent of dietary exposure to acrylonitrile monomer in this proceeding.

B. CONCLUSIONS OF LAW

1. The intended use of acrylonitrile monomer in fabricating acrylonitrile copolymer beverage containers may reasonably be expected to, and does, result in its becoming a component of food.

2. The actual or reasonably expected presence of acrylonitrile monomer in food may be established by reference to any probative scientific evidence, and need not be shown by actual measurement.

3. Whether acrylonitrile monomer becomes, or may reasonably be expected to become, a component of food within the meaning of 21 U.S.C. 321(s) does not depend on whether it does or may migrate in any particular amount. "Toxicological insignificance" is not a statutory term; it does not have a precise meaning or an independent significant or relevance for food additive determinations.

4. The "conditions of . . . intended use" of acrylonitrile monomer in beverage containers are relevant to evaluating the toxicity or safety of the monomer; migration under the "conditions of . . . intended use" need not be shown, but may be used, to establish whether the "intended use" of the monomer "results or may reasonably be expected to result . . . in its becoming a component" of food within the meaning of 21 U.S.C. 321(s).

5. The "conditions of . . . intended use" of acrylonitrile monomer in beverage containers are properly assumed to be those conditions determined to be appropriate for extraction testing.

6. For purposes of toxicological assessment, the amount of acrylonitrile monomer that migrates under extraction testing conditions may be determined by analytical measurement, by the use of mathematical models, or by the lower limit of analytical detection. If mathematical models are used, their limitations must be clearly kept in mind, and the Bureau is not bound to accept the predictions of such models as determinative of the amount of monomer that is present for purposes of making toxicological judgments. If the lower limit of analytical detection is used, in the absence of a contrary showing, monomer should be assumed to be present in an amount equal to the lower limit of detectability.

7. For a substance to be generally recognized among qualified experts as having been adequately shown to be safe under the conditions of its intended use, the relevant community of experts must have actual, present knowledge of the toxic potential, or the absence of toxic potential, of the substance at the levels present under those conditions of use; they must actually have concluded from such knowledge that the substance has been adequately shown to be safe; their knowledge must be based on scientific procedures, which must be of the same quality and quantity as those necessary to demonstrate safety for purposes of issuing a food additive regulation; and such evidence must be reflected in published studies in the relevant body of scientific literature. Evidence that qualified experts would or should recognize a substance as having been adequately shown to be safe if they were aware of the data and information about a substance does not establish the existence of general recognition of safety among such experts.

8. "Safe" or "safety," as those terms are used in 21 U.S. 321(s) and 348, mean a reasonable certainty in the minds of competent scientists that a substance is not harmful under the intended conditions of its use. A substance may be safe even though the toxicological data do not definitively demonstrate that it is safe. However, if the toxicology data make it reasonably certain that the substance may be seriously harmful to some people under its intended conditions of use, the substance is not safe within the meaning of the Federal Food, Drug and Cosmetic Act even though the people who will not be harmed by it greatly outnumber those who may.

9. In evaluating whether a food additive has been shown to be safe, FDA must consider the probable consumption of the additive. 21 U.S.C. 348(c)(5)(A). Probable consumption includes consumption by individuals likely to be exposed to the additive in amounts that significantly exceed the average level of exposure.

10. The Delaney Clause, 21 U.S.C. 348(c)(3)(A), creates a conclusive presumption that a carcinogenic substance present in food as a food additive is unsafe. Accordingly, a carcinogenic substance *per se* cannot be considered generally recognized as safe under 21 U.S.C. 321(s). A substance that is the subject of testing whose preliminary results strongly indicate that it will be shown to be carcinogenic cannot be considered generally recognized as safe under 21 U.S.C. 321(s).

11. Since the Dow chronic feeding study is not yet complete, acrylonitrile monomer cannot at this time be "found to induce cancer when ingested by man or animal" within the meaning of the Delaney Clause, 21 U.S.C. 348(c)(3)(A). No other carcinogenicity data here in evidence have been shown at this time to be "appropriate for the evaluation of food additives" within the meaning of the Delaney Clause.

12. In evaluating the safety of a food additive, FDA must consider safety factors which in the opinion of experts qualified by scientific training and experience to evaluate the safety of food additives are generally recognized as appropriate for the use of animal experimentation data. 21 U.S.C. 348(c)(5)(C). Safety factors may not be applied to a carcinogenic or potentially carcinogenic substance to determine a safe level of human exposure to the substance as a food additive.

13. Acrylonitrile monomer used to fabricate acrylonitrile copolymer beverage containers is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures to be safe.

14. The proviso in 21 U.S.C. 321(s) for substances used in food prior to January 1, 1958, applies only when a substance to which the proviso is sought to be applied was used prior to January 1, 1958, in the same way that it is, or is sought to be, used now. The proviso is inapplicable to acrylonitrile used to fabricate beverage containers.

15. Acrylonitrile copolymers used to fabricate beverage containers are food additives within the meaning of 21 U.S.C. 321(s).

16. The data of record in this proceeding fail to establish that the use of acrylonitrile to fabricate acrylonitrile copolymer beverage containers is safe, as required by 21 U.S.C. 348(c)(3)(A).

FINAL ORDER

Therefore, on the basis of the foregoing Findings of Fact and Conclusions of Law and the record in the above proceeding and under the Federal Food, Drug and Cosmetic Act (secs. 201(s), 402, 409, 701, 52 Stat. 1046–1047 as amended, 1055–1056 as amended, 72 Stat. 1784–1788 as amended (21 U.S.C. 321(s), 342, 348, 371)) and under the authority delegated to the Commissioner (21 CFR 5.1): *It is ordered*, That the stay of §§ 177.1020, 177.1030, 177.1040, 177.1050 and 177.1480, insofar as those sections permit the acrylonitrile copolymers identified in those sections to be used to fabricate beverage containers, as ordered in the FEDERAL REGISTER of March 11, 1977 (42 FR 13546), be terminated, and that Part 177 be amended as follows:

1. In § 177.1020, by deleting the stay note at the end of the section, and by adding a new paragraph (f) to read as follows:

§ 177.1020 Acrylonitrile/butadiene/styrene copolymer.

• • • • •

(f) Acrylonitrile copolymers identified in this section are not authorized to be used to fabricate beverage containers.

2. In § 177.1030, by deleting the stay note at the end of the section, and by adding a new paragraph (f) to read as follows:

§ 177.1030 Acrylonitrile/butadiene/styrene/methyl methacrylate copolymer.

• • • • •

(f) Acrylonitrile copolymers identified in this section are not authorized to be used to fabricate beverage containers.

3. In § 177.1040, by deleting the stay note at the end of the section, and by adding a new paragraph (e) to read as follows:

§ 177.1040 Acrylonitrile/styrene copolymer.

• • • • •

(e) Acrylonitrile copolymers identified in this section are not authorized to be used to fabricate beverage containers.

4. In § 177.1050, by deleting the stay note at the end of the section, and by adding a new paragraph (g) to read as follows:

§ 177.1050 Acrylonitrile/styrene copolymer modified with butadiene/styrene elastomer.

* * * * *

(g) Acrylonitrile copolymers identified in this section are not authorized to be used to fabricate beverage containers.

5. In § 177.1480, by deleting the stay note at the end of the section, and by adding a new paragraph (d) to read as follows:

§ 177.1480 Nitrile rubber modified acrylonitrile-methyl acrylate copolymers.

* * * * *

(d) Acrylonitrile copolymers identified in this section are not authorized to be used to fabricate beverage containers.

Effective date: This final decision is effective upon signature on September 19, 1977. The order terminating the stay and amending the regulations shall be effective December 22, 1977.

Dated: September 19, 1977.

DONALD KENNEDY,
Commissioner of Food and Drugs.

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