acted in bad faith, or whether special circumstances make an award unjust.

(h) *Agency review*. Either the applicant or complaint counsel may seek review of the initial decision on the fee application by filing a notice of appeal under § 3.52(a), or the Commission may decide to review the decision on its own initiative, in accordance with § 3.53. If neither the applicant nor complaint counsel seeks review and the Commission does not take review on its own initiative, the initial decision on the application shall become a final decision of the Commission 30 days after it is issued. Whether to review a decision is a matter within the discretion of the Commission. If review is taken, the Commission will issue a final decision on the application or remand the application to the Administrative Law Judge for further proceedings.

(i) *Judicial review*. Judicial review of final Commission decisions on awards may be sought as provided in 5 U.S.C. 503(c)(2).

(j) *Payment of award*. An applicant seeking payment of an award shall submit to the Secretary of the Commission a copy of the Commission's final decision granting the award, accompanied by a statement that the applicant will not seek review of the decision in the United States courts. The agency will pay the amount awarded to the applicant within 60 days, unless judicial review of the award or of the underlying decision of the adjudicative proceeding has been sought by the applicant or any party to the proceeding.

By direction of the Commission.

Benjamin I. Berman,

Acting Secretary.

[FR Doc. 98–17803 Filed 7–2–98; 8:45 am]

BILLING CODE 6750–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 172

[Docket No. 90F–0220]

Food Additives Permitted for Direct Addition to Food for Human Consumption; Acesulfame Potassium

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the food additive regulations to provide for the safe use of acesulfame potassium (ACK) as a nonnutritive sweetener in nonalcoholic beverages. This action is in response to a petition filed by Hoechst Celanese Corp. (Hoechst).

DATES: This regulation is effective July 6, 1998; written objections and requests for a hearing by August 5, 1998.

ADDRESSES: Submit written objections to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Patricia A. Hansen, Center for Food Safety and Applied Nutrition (HFS–206), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–418–3093.

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I. Introduction

In a notice published in the **Federal Register** of July 30, 1990 (55 FR 30983), FDA announced that a food additive petition (FAP 0A4212) had been filed by Hoechst Celanese Corp. (Hoechst), Route 202–206 North, Somerville, NJ 08876, proposing that § 172.800 *Acesulfame potassium* (21 CFR 172.800) be amended to provide for the safe use of acesulfame potassium (ACK) as a nonnutritive sweetener in nonalcoholic beverages, including beverage bases. (Recently, Hoechst has reorganized; the division of Hoechst now responsible for ACK is known as Nutrinova, Inc., 25 Worlds Fair Dr., Somerset, NJ 08873.) The present petition contains data and other information relevant to the safety of ACK under the proposed conditions of use; the present petition also relies on certain data and information contained in previous petitions for ACK.

FDA's food additive regulations were first amended to permit the use of ACK on July 28, 1988 (53 FR 28379, the ''dry uses final rule''), in response to a petition filed by Hoechst. In its original evaluation of the safety of ACK, FDA concluded that a review of animal feeding studies showed that there is no association between neoplastic disease (cancer) and consumption of this additive (53 FR 28379 at 28380 and 28381). The agency further concluded that ACK was safe under the conditions of use proposed in the initial petition, and amended its food additive regulations to permit the use of the sweetener.

Following publication of the dry uses final rule, the agency received timely objections from the Center for Science in the Public Interest (CSPI). CSPI submitted four separate objections, two of which asserted that the long-term studies of ACK in rodents were inadequate to evaluate ACK's potential carcinogenicity, and two of which asserted that certain of these studies showed that the additive was potentially carcinogenic. CSPI requested a stay of the regulation and also requested a hearing on each of its objections. FDA, after careful consideration of CSPI's objections, found that none of the objections raised issues of fact that justified granting a

hearing or otherwise provided a basis for revoking the regulation. Thus FDA denied both the request for a stay of the regulation and a hearing, and confirmed the effective date of the regulation. The agency published a detailed response to CSPI's objections in the **Federal Register** of February 27, 1992 (57 FR 6667).

Since its initial approval decision on the use of ACK, FDA has approved the following additional uses for ACK in response to petitions: In baked goods and baking mixes, including frostings, icings, and fillings for baked goods; in yogurt and yogurt-type products; in frozen and refrigerated desserts; in sweet sauces, toppings, and syrups; and in alcoholic beverages (59 FR 61538, 59 FR 61540, and 59 FR 61543, December 1, 1994, and 60 FR 21700, May 3, 1995). No objections were received in response to the December 1, 1994, final rule. However, CSPI filed timely objections to the agency's May 3, 1995, final rule authorizing the use of ACK in alcoholic beverages (60 FR 21700). The agency's response to those objections is published elsewhere in this issue of the **Federal Register**.

With respect to the present petition, Hoechst's original submission contained data and information from several toxicity studies of ACK, as well as data and information regarding the stability of ACK in aqueous solutions.[1] Because hydrolysis of ACK can occur under certain conditions, the petitioner also conducted toxicity studies of the principal hydrolysis products of ACK.

In response to an issue raised by FDA's review, Hoechst submitted additional information regarding ACK hydrolysis products, including a report prepared by a panel of experts in various scientific disciplines who independently evaluated the results of certain toxicity studies of the ACK hydrolysis products. Hoechst also submitted an indepth analysis of the potential health risk from one of the ACK hydrolysis products, acetoacetamide (AAA). FDA's Center for Food Safety and Applied Nutrition (CFSAN) conducted its own indepth analysis of the data and information on AAA, and, in reaching a final decision on this issue, also obtained the advice of additional experts from within and from outside the agency.

FDA notes that CSPI has submitted comments on the present petition for use of ACK in nonalcoholic beverages, and has transmitted comments on that petition from other interested parties as well. Further, Hoechst has transmitted additional comments from two of these same parties. Several other comments were also received. The agency's response to all comments on the present petition is presented in section IV of this document.

II. Evaluation of Safety

Under the general safety standard of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 348(c)(3)(A)), a food additive cannot be approved for a particular use unless a fair evaluation of the data available to FDA establishes that the additive is safe for that use. FDA's food additive regulations in § 170.3(i) (21 CFR 170.3(i)) define safe as ''a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.''

The food additives anticancer, or Delaney, clause of the act (21 U.S.C. 348(c)(3)(A)) provides that no food additive shall be deemed safe if it is found to induce cancer when ingested by man or animal. Importantly, however, the Delaney clause applies to the additive itself and not to impurities in the additive. That is, where an additive itself has not been shown to cause cancer, but contains a carcinogenic impurity, the additive is properly evaluated under the general safety standard using risk assessment procedures to determine whether there is a reasonable certainty that no harm will result from the intended use of the additive (*Scott* v. *FDA*, 728 F.2d 322 (6th Cir. 1984)).

III. Evaluation of the Safety of the Petitioned Use of the Additive

A. ACK—Background

As previously noted, FDA's original evaluation of the safety of ACK established that there was no association between neoplastic disease (cancer) and consumption of this additive (53 FR 28379 at 28380 and 28381). That evaluation also established a lifetime-averaged acceptable daily intake (ADI) for ACK of 15 milligrams per kilogram of body weight per day (mg/kg bw/d), equivalent to 900 mg per person per day (mg/p/d).

B. ACK—New Information

In the present petition, Hoechst included several ACK toxicity studies that had been conducted since the agency's original evaluation of the safety of this additive. These included studies on mutagenicity, antigenicity, and potential for dermal and eye irritation; an acute toxicity study in fish; and a subchronic toxicity study in diabetic rats.

The mutagenicity studies demonstrated that ACK is not mutagenic at histidine loci in *Salmonella typhimurium* or at a tryptophan locus in *Escherichia coli*. These results are consistent with the negative results of the mutagenicity and genetic toxicity studies previously considered by FDA in its original evaluation of the safety of ACK. The results of all the ACK genetic toxicity tests establish that ACK is not genotoxic.

The results of the other ACK toxicity studies listed above did not show toxicologically significant ACK-related adverse effects. Importantly, these ACK toxicity studies contain no new information that would change the agency's previous conclusion that there is no association between neoplastic disease and consumption of this additive. Thus, FDA has evaluated the safety of the petitioned use of ACK in nonalcoholic beverages under the general safety standard, considering all available data.

In determining whether the proposed use of an additive is safe, FDA considers, among other things, whether an individual's lifetime-averaged estimated daily intake (EDI) of the additive will be less than the ADI established from toxicological information. Importantly, the new studies on ACK listed above do not contain any new information that would cause the agency to alter the previously determined ADI for ACK. Thus, FDA concludes that the ADI for ACK is 15 mg/kg bw/d (equivalent to 900 mg/p/d). The present petition contains information regarding dietary consumption of ACK-containing food products, including nonalcoholic beverages, and the agency has considered consumer exposure to ACK resulting from its use in nonalcoholic beverages, as well as all currently listed uses. FDA has calculated the mean EDI from these combined uses to be 1.6 mg/kg bw/d, which is equivalent to 96 mg/p/d; and the 90th percentile EDI from these combined uses to be 3.0 mg/kg bw/d, which is equivalent to 180 mg/p/d (Ref. 1). These levels of dietary exposure to ACK, which represent measures of the average and the high chronic intake, respectively, are both well below the ADI.

C. Methylene Chloride

Residual amounts of reactants and manufacturing aids are commonly found as contaminants in chemical products, including food additives. In its evaluation of the safety of ACK, FDA reviewed both the safety of the additive

[1] Stability studies of ACK in aqueous solutions were also submitted in the original petition for ACK.

and the safety of the chemical impurities that may be present in the additive from the manufacturing process.

In the current manufacturing process for ACK, methylene chloride, a carcinogenic chemical, is used as a solvent in the initial manufacturing step. Subsequently, the product is neutralized, stripped of methylene chloride, and recrystallized from water. Data submitted by the petitioner show that methylene chloride could not be detected in the final product at a limit of detection of 40 parts per billion (ppb).

FDA has previously discussed the significance of the use of methylene chloride in the production of ACK. The agency incorporates those discussions, published in the **Federal Register** of December 1, 1994 (59 FR 61538, 59 FR 61540, and 59 FR 61543) and of May 3, 1995 (60 FR 21700), in full, into the agency's safety determination on the present petition.

Specifically, in evaluating the safety of the uses of the additive that are currently listed, FDA concluded, using risk assessment procedures, that the estimated upper-bound limit of individual lifetime risk from the potential exposure to methylene chloride resulting from these uses of ACK, together with the petitioned use of ACK in nonalcoholic beverages, is 2.6×10^{-11}, or less than 3 in 100 billion. The agency also concluded that, because of the numerous conservative assumptions used in calculating this estimated upper-bound limit of risk, this upper-bound limit would be expected to be substantially higher than any actual risk (59 FR 61538 at 61539, 59 FR 61540 at 61542, 59 FR 61543 at 61544, and 60 FR 21700). FDA has received no new information that would change the agency's previous conclusion. Therefore, the agency concludes that there is a reasonable certainty of no harm from the exposure to methylene chloride that might result from the proposed use of ACK in nonalcoholic beverages.

In conducting its evaluation, the agency also considered whether a specification is necessary to control the amount of potential methylene chloride impurity in ACK. At that time, FDA concluded that there is no reasonable possibility that methylene chloride will be present in amounts that present a health concern, and that there would thus be no justification for requiring manufacturers to monitor compliance with a specification (59 FR 61538 at 61539, 59 FR 61540 at 61542, 59 FR 61543 at 61544, and 60 FR 21700). Because no new information has been received that would change FDA's previous conclusion regarding the need for a specification, the agency affirms its prior determination that a specification for methylene chloride impurity in ACK is unnecessary.

D. Special Conditions Relevant to Use in Nonalcoholic Beverages

The use of ACK as a nonnutritive sweetener in nonalcoholic beverages may subject the sweetener to conditions other than those considered in the evaluation of the currently listed uses of this additive. FDA has evaluated data in the present petition and other information regarding the stability of ACK under a variety of conditions that characterize the proposed use in nonalcoholic beverages. Based on these data and information, the agency concludes that ACK is stable under almost all circumstances expected to be encountered for the proposed use in nonalcoholic beverages.

However, FDA has determined that there is a limited possibility that some nonalcoholic beverages could be stored under conditions that could lead to the formation of ACK hydrolysis products. Specifically, small amounts of hydrolysis products may be formed in highly acidic aqueous food products (which would include some, though not all, nonalcoholic beverages) under conditions of prolonged storage at elevated temperatures. As part of its safety evaluation, FDA has reviewed toxicological data and supporting information regarding the hydrolysis products of ACK, as well as estimates of human dietary exposure to the hydrolysis products. The substantive aspects of the agency's safety assessment of the hydrolysis products, as they relate to the use of ACK in nonalcoholic beverages, are discussed in detail in sections III.D.1 and 2 of this document.

1. Hydrolysis Products—Consumer Exposure

Both the present petition and the petition supporting the initial approval of ACK contain studies of the stability of ACK in aqueous solutions. These studies show that ACK hydrolyzes, in strongly acidic or strongly basic aqueous solutions, to acetoacetamide-N-sulfonic acid (AAS). AAS subsequently hydrolyzes to acetoacetamide (AAA). The AAA that is formed is also subject to hydrolysis; the eventual endproducts are acetone, carbon dioxide, and ammonia. Data and other information submitted by the petitioner and evaluated by the agency establish that both AAS and AAA are transient intermediates in the overall ACK hydrolysis pathway and that no significant buildup of AAS or AAA will occur in ACK-sweetened nonalcoholic beverages.

Studies in the two petitions also establish that hydrolysis of ACK is dependent on two other factors in addition to pH: Time and temperature. Prolonged storage at elevated temperatures is required to produce detectable amounts of AAS and, particularly, its byproduct, AAA, even in test solutions containing over 100 times the amount of ACK that would ordinarily be used in a nonalcoholic beverage. Specifically, data in the petition show that such a concentrated, buffered, carbonated solution of pH 3.0 (representative of the lower end of the pH range for carbonated diet soft drinks), after storage at 20 °C (68 °F) for 8 weeks, contained AAS at a level of 0.35 percent of the original ACK level. Even with a sensitive analytical method (limit of detection, circa (ca.) 1 ppb, corresponding to 0.001 percent of the original ACK level), no AAA was detected in this system. More severe storage conditions were required to produce detectable levels of AAA (e.g., 8 weeks storage at 30 °C (86 °F) or 50 weeks storage at 20 °C).

The combination of conditions necessary to produce measurable amounts of hydrolysis products in beverages (i.e., low beverage pH and extended storage at high temperatures) is not expected to be frequently encountered. The stability studies also establish that AAA and AAS will not build up in beverages over time. Accordingly, FDA believes that any consumer exposure to AAA and AAS from consumption of ACK-sweetened nonalcoholic beverages will be at extremely low levels and also both intermittent and infrequent.

Nevertheless, using data from the stability studies and other information regarding consumption patterns, FDA has estimated a potential lifetime-averaged ''daily'' dietary intake of ACK hydrolysis products that might result from consumption of ACK-sweetened nonalcoholic beverages. In its calculations, the agency has deliberately incorporated several assumptions that, taken together, will produce an estimated ''daily'' intake that is likely to be an overestimate rather than an underestimate. First, FDA has assumed that all nonalcoholic beverages ingested by consumers will have been sweetened only with ACK, that ACK will be used at the highest levels characteristic of each type of nonalcoholic beverage, and that the consumer will have ingested such beverages at the 90th percentile consumption level. Second, FDA has assumed certain values for beverage pH,

storage time, and storage temperature that are also likely to produce an overestimate of the ''daily'' intake of ACK hydrolysis products. The basis for the agency's particular choice of beverage pH, storage time, and storage temperature is discussed in more detail in the next two paragraphs.

FDA has chosen to use a pH of 3.0 in its analysis because this pH is representative of the lower end of the range in which beverages containing nonnutritive sweeteners are formulated. The agency has chosen to use a storage time of 8 weeks because FDA considers 8 weeks to be representative of a storage period that is significantly longer than the average storage period for nonalcoholic beverages. Data in the petition and in the agency's files show that ca. 90 percent of diet cola (representative of beverages formulated at low pH) is sold within 8 weeks of bottling; these data also show that even when additional flavor categories are considered, ca. 90 percent of nonalcoholic beverages are still sold within 9.5 weeks of bottling, with an average time from bottling to sale of just under 4 weeks (Ref. 2).

With respect to temperature, FDA has chosen to use 20 °C in its analysis because this temperature is representative of the high end of the range of in-home or in-store storage temperatures, when periods of both refrigerated and room temperature storage are taken into account.[2] The agency also reviewed climate data for different geographical locations in the United States, which were chosen to cover the range of possible temperature extremes for beverages stored under ambient conditions (no temperature control). This review shows that few locations have annual average temperatures above 20 °C (Ref. 2). Accordingly, for all of the foregoing reasons, the agency has used 20 °C as representative of the temperature conditions likely to be encountered over an extended storage period.

FDA has calculated estimated dietary exposure to AAS and AAA based upon data reflecting the foregoing assumptions regarding beverage formulation and storage conditions (see Ref. 2). The agency concludes that, for the 90th percentile consumer of ACK-sweetened nonalcoholic beverages, exposure to AAS would be no more than 2.5 micrograms (µg)/kg bw/d, which is equivalent to 0.15 mg/p/d. In estimating consumer exposure to AAA, the agency incorporated an additional conservative assumption: that AAA would be present at a level corresponding to one-half the limit of detection (Ref. 3), even though it was not actually detected. The agency concludes that, for the 90th percentile consumer of ACK-sweetened nonalcoholic beverages, exposure to AAA would be no more than 3.3 nanograms (ng)/kg bw/d, which is equivalent to 0.2 µg/p/d.

2. Hydrolysis Products—Evaluation of Toxicological Information

In support of the safety of ACK for use as a nonnutritive sweetener in nonalcoholic beverages, the petitioner submitted toxicity studies of AAS and AAA, the two principal hydrolysis products of ACK. The agency's evaluation of these toxicological data and other related information follows.

a. *Acetoacetamide-N-sulfonic acid (AAS).* Hoechst submitted a set of toxicity studies of AAS in support of the safety of the proposed use of ACK in nonalcoholic beverages including: Short-term tests for genetic toxicity; acute, short-term and subchronic studies in rats; a subchronic study in dogs; short-term and subchronic studies in monkeys; an acute study in humans; a reproduction and developmental toxicity study in rats; and metabolism studies in rats and humans. The key studies of AAS relevant to FDA's safety decision regarding the petitioned use of ACK are discussed in the next sections of this document.

i. *Genetic toxicity testing.* AAS was tested in several in vitro and in vivo genetic toxicity tests. In the absence of bioassay data, such tests are often used to predict the carcinogenic potential of the test compound.

AAS was not mutagenic at histidine loci in *Salmonella typhimurium* (Ames test), at a tryptophan locus in *Escherichia coli*, nor at the HGPRT locus in V79 cells treated in vitro. AAS did not induce unscheduled deoxyribonucleic acid (DNA) synthesis in strain A 549 human cells exposed in vitro. Finally, AAS was not clastogenic in V79 cells exposed in vitro nor in bone marrow cells of NMRI mice. The agency concludes that results of these tests establish that AAS is not genotoxic.

ii. *Subchronic toxicity studies in rats and monkeys.* The petitioner submitted the results of a subchronic toxicity study in which AAS was administered in the diet to 30 Wistar rats/sex/group at dose levels equivalent to 0, 800, 2,000, or 5,000 mg/kg bw/d for 90 days. Twenty rats/sex/group were sacrificed at the end of the dosing period. The remaining ten rats/sex/group were designated as ''recovery'' animals; that is, there was an interval of approximately 1 month between the time dosing ended and the time of sacrifice for these animals.

Increased relative kidney weights and decreased relative pituitary weights were observed in high-dose female rats. The mid- and high-dose groups (2,000 and 5,000 mg/kg bw/d, respectively) of male and female rats had softer feces, decreased body weight gain, and dose-related increases in feed consumption compared to controls. Other AAS-related effects observed in the animals in the mid- and high-dose groups included increased urine pH, and changes in various clinical chemistry parameters, some of which changes resolved by the end of the recovery period. Certain changes in the caecum were also observed; however, these effects had also resolved by the end of the recovery period, and were judged by FDA to be a probable physiological adaptation to osmotic changes in the gastrointestinal tract. Based on these data, FDA concludes that the no-observed-effect level (NOEL) from this study is 800 mg AAS/kg bw/d, the lowest dose level tested in this study (Ref. 4).

The petitioner also submitted the results of a subchronic toxicity study of AAS in Cynomologous monkeys. In this study, four monkeys/sex/group were administered gavage doses of 0, 100, 315, or 1,000 mg AAS/kg bw/d for 13 weeks. Marginal decreases in the absolute and relative weights of various organs in animals of the mid- and high-dose groups were observed; however, FDA does not consider these effects to be of toxicological significance because of the lack of corroborative evidence of organ toxicity. The only toxicologically significant effect observed in this study was a dose-related increase in incidence and severity of diarrhea in the mid- and high-dose groups. Thus, FDA concludes that the NOEL for AAS from this study

[2] FDA also considered the effect of extreme temperature conditions on dietary exposure to ACK hydrolysis products (see Ref. 2). However, the agency has concluded that, for several reasons, it is highly unlikely that beverages stored under extremely high temperatures for extended periods of time would be consumed on a continued basis. First, most in-home or retail storage is under refrigeration or other climate-controlled conditions. Second, it is a common and usual practice in the industry to discard diet beverages that have been stored under extreme conditions (e.g., 50 to 55 °C, equivalent to 120 to 130 °F) because the artificial sweeteners currently in use undergo significant decomposition that results in an unpalatable product. FDA expects that this practice would also be applied to beverages sweetened with ACK because the decomposition of ACK that occurs under such extreme conditions also results in an unpalatable product. Finally, consumers do not customarily store nonalcoholic beverages under extreme conditions for lengthy periods, and would not be expected to habitually consume the unpalatable products that result from extended storage at extremely high temperatures.

is 100 mg/kg bw/d, the lowest dose level tested (Ref. 4).

iii. *Reproduction and developmental toxicity study in rats.* The petitioner submitted the results of a two-generation reproduction study with a teratology phase conducted in Sprague-Dawley rats. In this study, AAS was administered in the diet to 25 rats/sex/group of the P- and F1-generation at dose levels equivalent to 0, 164, 492, or 1,780 mg AAS/kg bw/d. No adverse effects on reproduction or developmental parameters were observed at any dose level in this study. Thus, FDA concludes that the NOEL for this study is 1,780 mg AAS/kg bw/d, the highest dose used in the study (Ref. 4).

iv. *Assessment of AAS.* No adverse AAS-related effects were observed at 800 mg/kg bw/d in the subchronic rat study, at 100 mg/kg bw/d in the subchronic monkey study, and at 1,780 mg/kg bw/d and lower in the reproduction/teratology study in rats. The agency has no safety concerns about AAS at its anticipated level of intake (less than 2.5 μg/kg bw/day) because of the substantial margin between this level and the levels at which no adverse effects were observed in these studies (a margin of at least 40,000).

b. *Acetoacetamide (AAA).* Hoechst submitted a set of toxicity studies of AAA in support of the safety of ACK for use in nonalcoholic beverages, including short-term tests for genetic toxicity; an acute study, two short-term studies, and a subchronic study in rats; an acute and two short-term studies in dogs; a subchronic study in rabbits; metabolism studies in rats, dogs, hamsters, and humans; a developmental toxicity study in rabbits; and several other studies. The key studies of AAA relevant to FDA's safety decision regarding the petitioned uses of ACK are discussed in detail below.

i. *Genetic toxicity testing.* AAA was tested in several in vitro and in vivo genetic toxicity tests. As noted, in the absence of bioassay data, such tests are often used to predict the carcinogenic potential of the test compound.

AAA was not mutagenic at the HGPRT locus in V79 cells treated in vitro nor at histidine loci in *Salmonella typhimurium* (Ames test). AAA was not clastogenic in V79 cells exposed in vitro nor in bone marrow cells of NMRI mice. In addition, AAA did not induce unscheduled DNA synthesis in strain A 549 human cells exposed in vitro. The agency concludes that the results of these tests establish that AAA is not genotoxic.[3]

ii. *Short-term and subchronic toxicity studies in rats, rabbits, and dogs.* The petitioner submitted the results of one subchronic (90-day) and two short-term toxicity studies of AAA in rats. One short-term (30-day) study was designed to determine appropriate doses for the subsequent subchronic study. The second short-term (14-day) study was designed as a preliminary mechanistic study; the second short-term study is discussed in detail in section III.D.2.b.v of this document.

In the subchronic study, AAA was administered in the diet to 15 SPF Wistar rats/sex/group at dose levels equivalent to 0, 24, 157, 794, or 4,300 mg/kg bw/d for 13 weeks. The following AAA-related adverse effects were identified in the subchronic rat study: (1) Reduced body weights of males and females in the highest dose group over the entire study; (2) anemia in female rats in the highest dose group and male rats in the two highest dose groups; (3) increased numbers of both males and females with centrilobular fatty liver in the highest dose group; (4) increased group mean relative liver weights for male and female rats in the highest dose group; as well as (5) various adverse effects on the thyroid, which are discribed in the next paragraph.

The adverse effects on the thyroid observed in the subchronic rat study of AAA were: (1) Dose-related increases in the numbers of males and females with grossly enlarged thyroids; (2) increased relative thyroid weights for mid- and high-dose males and females; (3) dose-related increases in the numbers of males and females with follicular cell hypertrophy and hyperplasia; and (4) thyroid adenomas in one male rat in each of the two highest dose groups. No hypertrophy or hyperplasia was associated with enlarged thyroids in controls or in animals in the lowest dose group (24 mg/kg bw/d).

With respect to endpoints in organs other than the thyroid, no adverse toxicological effects were observed at doses corresponding to 157 mg/kg bw/day and lower. However, based on the gross and histopathological findings in the thyroid, FDA concludes that the NOEL from the subchronic rat study is 24 mg AAA/kg bw/d, the lowest dose tested in this study.

The petitioner also submitted the results of a subchronic study of AAA in albino Himalayan rabbits. In this study, six rabbits/sex/group were administered 0, 1,200, 6,000, or 30,000 mg AAA/kg drinking water/day (equivalent to 0, 96, 499, or 2,192 mg AAA/kg bw/d for male rabbits, and to 0, 93, 560, or 2,763 mg AAA/kg bw/d for female rabbits). The following effects were observed: (1) Significantly increased testes weights and signs of focal tubular hypospermatogenesis in the testes of all high-dose males; (2) significantly increased thyroid weights in high-dose males and females; and (3) thyroid follicular cell hypertrophy and hyperplasia in all high-dose males and females. One mid-dose female and one high-dose female in this study had grossly enlarged thyroids; the mid-dose female also had a thyroid follicular cyst that may have been part of a hyperplastic response.

With respect to endpoints in organs other than the thyroid, no adverse toxicological effects were observed at doses corresponding to 499 mg/kg bw/day and lower. However, based on the evidence that the thyroid is a target organ for AAA-related toxicity and the finding of possible thyroid hyperplasia in one female in the mid-dose group, FDA concludes that the NOEL for AAA in rabbits is 93 mg/kg bw/d, the lowest dose tested in females in this study (Ref. 4).

The petitioner submitted the results of two short-term (14-day) studies of AAA in dogs. In the first short-term study, two dogs/sex/group were gavaged with 0, 100, 500, or 2,500 mg AAA/kg bw/d for 14 days. Thyroid follicular cell hyperplasia was observed in males and females in all dose groups.

Because adverse effects were observed at all dose levels in the first study, the petitioner performed a second short-term (14-day) dog study using lower doses. In the second study, three dogs/sex/group were gavaged with 0, 4, 20, or 100 mg AAA/kg bw/d for 14 days; at the end of the dosing period two males and females from each group were sacrificed. The remaining male and female in each group were designated as ''recovery'' animals; that is, there was an interval of approximately 1 month between the time dosing ended and the time of sacrifice for these two animals. In this study, two of the males in the high-dose group developed thyroid follicular hyperplasia; no other males and no females in this study were reported to have thyroid abnormalities. However, of the two high-dose males that developed thyroid follicular hyperplasia, one was a ''recovery'' animal, indicating that the effect of AAA on the thyroid had persisted for 1 month after dosing ended. In an effort to identify a possible mechanism for AAA's action on the thyroid in the second dog study, the investigators

[3] The petitioner also submitted results of genetic toxicity tests of β-hydroxybutyramide (BHB), the principal metabolite of AAA in humans. The Ames test of BHB was well conducted and showed that BHB is not mutagenic. Although several of the other genetic toxicity tests of BHB had deficiencies, none of these tests indicated that BHB is genotoxic.

measured serum levels of thyroid hormones T3 and T4 at the end of the study; no compound-related changes in serum T3 or T4 levels were observed. (The investigators did not measure levels of thyroid stimulating hormone (TSH).)

FDA concludes that the results of the short-term and subchronic toxicity studies in rats, rabbits, and dogs demonstrate that AAA has a proliferative effect on the thyroid (i.e., diffuse follicular cell hypertrophy and hyperplasia). The agency's assessment of the significance of the observed thyroid lesions is discussed in detail in section III.D.2.b.v of this document.

iii. *Developmental toxicity study in rabbits*. The petitioner submitted an embryotoxicity study of AAA in Chinchilla rabbits in which groups of 16 rabbits were gavaged with 0, 100, 300, or 1,000 mg AAA/kg bw/d on days 6 through 18 of pregnancy. FDA has determined that there were no toxicologically significant effects of AAA on reproductive or developmental parameters in this study; thus, the NOEL for reproductive and developmental effects is 1,000 mg AAA/kg bw/d, the highest dose used in this study (Ref. 4).

iv. *Assessment of AAA—nonthyroid endpoints*. For organs other than the thyroid, no AAA-related adverse effects were observed at 157 mg/kg bw/d and lower in the subchronic rat study, at 499 mg/kg bw/d and lower in the subchronic rabbit study, and at 1,000 mg/kg bw/d and lower in the developmental toxicity study in rabbits. With respect to endpoints in organs other than the thyroid, the agency has no safety concerns about AAA at its anticipated level of intake (less than 3.3 ng/kg bw/day) because of the substantial margin between this level and the levels at which no adverse effects were observed in the studies discussed previously (a margin of at least 5 million).

v. *Assessment of AAA—thyroid endpoints*. No adverse AAA-related effects on the thyroid were observed at 24 mg/kg bw/day in the subchronic rat study, at 93 mg/kg bw/day in the subchronic rabbit study, and at 20 mg/kg bw/day and lower in the second short-term dog study. Although the study results permit FDA to identify NOEL's for certain thyroid endpoints in the rat and rabbit subchronic studies,[4] the major histological findings in these studies, thyroid follicular cell hypertrophy and hyperplasia, raise a question regarding the possible tumorigenic activity of AAA. Thyroid follicular cell hypertrophy and hyperplasia were also observed at similar levels of AAA administration in the dog studies, which studies were of even shorter duration. The pronounced thyroid follicular cell hypertrophy and hyperplasia observed in rats, rabbits, and dogs, considered together with the occurrence of thyroid adenomas in two males in the subchronic rat study, suggest that AAA might induce thyroid tumors if administered in long-term oral studies (see Refs. 2 and 4).

In response to FDA's concerns regarding AAA's thyroid effects, the petitioner initially argued that application of an appropriate safety factor to the lowest NOEL for thyroid endpoints was a suitable approach, despite the possible tumorigenic activity of AAA. Hoechst maintained that the dose-related hypertrophy and hyperplasia of the thyroid follicular cells and, in a 90-day study, the progression of some cells to adenomas was consistent with a typical pattern of morphological changes clearly associated with sustained, elevated levels of TSH,[5] particularly in the rat. Hoechst also maintained that AAA was most likely to act on the thyroid gland by inhibiting the enzyme thyroperoxidase in follicular cells. Thyroperoxidase is required for synthesis of T3 and T4 in the thyroid; therefore, inhibiting this enzyme would lead to a reduction in the levels of T3 and T4 and, consequently, increased serum levels of TSH (see Refs. 5 and 6). As support for this hypothesis, Hoechst referenced an extensive body of scientific literature linking thyroperoxidase inhibition (and consequent elevated TSH levels) by other compounds to thyroid lesions that are similar in type, severity, and timecourse of development, to the thyroid lesions observed in the short-term and subchronic studies of AAA summarized previously in this document. Hoechst asserted that progression of the hypertrophy and the hyperplasia associated with AAA would be dependent on continued or chronic stimulation of the thyroid gland by TSH, again drawing upon comparisons with other compounds whose similar effects on the thyroid were mediated by chronic TSH stimulation.[6]

In further support of its argument, Hoechst submitted a set of publications addressing various aspects of thyroid function and toxicity, including thyroid carcinogenicity; a report authored by the ''Acesulfame K Scientific Expert Panel,'' a group of experts retained by the petitioner to perform an independent safety evaluation of AAS and AAA (Ref. 7); and a letter from one of the experts from the Acesulfame K Scientific Expert Panel elaborating on the significance of the thyroid effects of AAA (Ref. 8).

The petitioner also submitted the results of a short-term study of AAA in rats (the ''preliminary mechanistic study''). In this study, 5 male rats per group were fed diets containing 0, 50, 123, 410, 1,110, or 2,400 ppm AAA or 90 ppm methimazole (positive control) for a period of 14 days. The following AAA-induced thyroid effects were observed in the preliminary mechanistic study: (1) Significantly increased absolute and relative thyroid weights in all positive control rats and in all rats fed diets containing 1,110 or 2,400 ppm AAA; (2) grossly enlarged thyroids in all positive control rats and in all rats fed diets containing 1,110 or 2,400 ppm AAA; (3) diffuse thyroid follicular cell hypertrophy and hyperplasia in all positive control rats and in all rats fed diets containing 1,110 or 2,400 ppm AAA; (4) significantly increased levels of TSH in positive control rats, as well as in rats fed 410, 1,110 or 2,400 ppm

[4] In reaching a safety decision on a food additive, FDA typically uses NOEL's determined from studies of at least 90 days duration (a subchronic study) and uses the term ''NOEL'' to refer specifically to the no-observed-effect levels determined from such studies. Results from studies in which animals are exposed for shorter test periods are typically used for different purposes (e.g., to gather information for use in designing longer studies). The short-term studies in dogs and rats (14 days) are too short to determine a subchronic NOEL.

[5] Iodine is taken up by the thyroid and converted to the thyroid hormone thyroxine, also known as T4 (which contains four iodine atoms) or to tri-iodothyronine, otherwise known as T3 (which contains three iodine atoms). Thyroid hormone production and release into circulation are stimulated by TSH released by the pituitary in response to decreases in circulating levels of T3 and T4. The biological functions of T4 and T3 are similar. The thyroid hormones are primarily metabolized in the liver and, to a lesser extent, in the kidneys. T4 can be converted to T3 (biologically active) or to reverse T3 (inactive), and then to di-iodothyronine (DIT).

Thyroid hypertrophy, hyperplasia and neoplasia can be caused by a wide range of nongenotoxic compounds. The common factor is prolonged stimulation of the thyroid by TSH following disruption of the normal feedback mechanism that controls the serum level of TSH. This disruption of thyroid hormone economy can be caused by interference with iodide uptake and thyroid hormone synthesis or secretion, interference with the peripheral metabolism of T4 or T3, or increased metabolism and excretion of thyroid hormones (see Refs. 5 and 6).

[6] ''Ample information in experimental animals indicates a relationship between inhibition of thyroid-pituitary homeostasis and the development of thyroid follicular cell neoplasms. This is generally the case when there are long-term reductions in circulating thyroid hormones which have triggered increases in circulating thyroid stimulating hormone * * *. The progression of events leading to thyroid * * * neoplasms can be reversed under certain circumstances by reestablishing thyroid-pituitary homeostasis'' (Ref. 6).

AAA; (5) significantly decreased levels of T4 and reverse T3 in positive control rats and in rats fed diets containing 1,110 or 2,400 ppm AAA; and (6) significantly decreased T3 levels in positive control rats and in rats fed diets containing 2,400 ppm AAA (see Ref. 4).

In further support of its proposed mechanism, Hoechst also submitted the results of an in vitro investigation of the action of AAA on canine thyroperoxidase. In this study, AAA was shown to inhibit enzyme activity in a dose-related manner; the AAA concentration at which 50 percent enzyme inhibition occurred was calculated by Hoechst to be 28.6 micromolar. Hoechst pointed to the consistency between the results of both the preliminary mechanistic study and the thyroperoxidase inhibition study as further evidence for the link it hypothesized between thyroperoxidase inhibition and the thyroid-related effects observed in the oral toxicity studies of AAA.

Hoechst also argued that a substance acting through a TSH-dependent mechanism would be expected to show a threshold below which no excessive stimulation of thyroid follicular cells would occur. The petitioner acknowledged that it is difficult to actually determine thresholds for low-incidence effects because of the small numbers of animals ordinarily used in toxicity studies (see Ref. 8). However, Hoechst cited the results of the preliminary mechanistic study, the results of the in vitro thyroperoxidase inhibition study, and the results of the short-term and subchronic oral studies in rats, rabbits, and dogs as strong evidence of the existence of a threshold for AAA-induced thyroid effects. The petitioner also pointed to the negative results of the genetic toxicity tests of AAA as further support for its argument that a threshold level should exist, below which administration of AAA would not induce thyroid tumors. That is, hypertrophy and hyperplasia and, by extension, possible progression to tumors, would occur only at AAA doses high enough to increase circulating levels of TSH, and not through a genotoxic mechanism.

In summary, Hoechst proposed the following nongenotoxic or ''secondary'' mechanism for the AAA-induced effects observed in the thyroids of several species: (1) At high doses, AAA acts to disrupt thyroid hormone economy by inhibiting thyroperoxidase activity and thus decreasing serum levels of T3 and T4; (2) the disruption in thyroid hormone economy results in hypersecretion of TSH by the pituitary; (3) the elevated blood levels of TSH, if sustained, result in hypertrophy and hyperplasia of the thyroid follicular cells and, eventually, thyroid tumors; and (4) that AAA does not act through a genotoxic mechanism to initiate a neoplastic process.

Hoechst explicitly acknowledged that there was a distinct possibility that AAA, if tested in a 2-year rodent bioassay, would induce thyroid tumors. However, Hoechst also maintained that thyroid tumors would occur only as a result of chronic consumption of AAA in amounts high enough to induce excess TSH production. Hoechst argued that because AAA would be consumed only in extremely low amounts, well below any value they believed likely for the postulated threshold for stimulating excess TSH production, it would be appropriate to base an analysis of the potential health risk from AAA on a comparison between the NOEL's for certain thyroid endpoints and the anticipated low levels of intake (a ''safety factor'' or ''threshold concept'' approach). Hoechst concluded that because the NOEL's for AAA's thyroid effects exceeded its dietary exposure estimate by a factor of approximately 2 million, there would be essentially no risk to human health from dietary exposure to AAA resulting from consumption of beverages sweetened with ACK.

FDA agrees that the anticipated human dietary exposure to AAA is lower than the NOEL's for AAA-related thyroid hypertrophy and hyperplasia by several orders of magnitude. FDA does not agree, however, that Hoechst's approach of simply comparing these NOEL's with dietary exposure is sufficient for evaluating the potential health risk suggested by the AAA-related effects observed in the thyroid. As previously noted, the AAA-related histopathological findings in the thyroid (i.e., hypertrophy and hyperplasia in rats, rabbits, and dogs, together with adenomas in two AAA-treated male rats in the subchronic study) suggest that AAA may induce thyroid tumors in long-term studies. Hoechst's ''safety factor'' approach relies on the firm's proposed mechanism for AAA's action on the thyroid, which explicitly incorporates a presumed threshold for AAA's thyroid effects. FDA has concluded, however, that the available data do not establish the mechanism proposed by the petitioner. The strengths and weaknesses in the data submitted in support of Hoechst's proposed mechanism are discussed in the following paragraphs.

FDA has determined that there is strong evidence that AAA is not genotoxic. The agency also acknowledges that some of the results from the preliminary mechanistic study and the in vitro study of canine thyroperoxidase are consistent with Hoechst's argument that AAA-induced effects on the thyroid are mediated through disruption of thyroid hormone economy. In particular, because inhibition of thyroperoxidase would cause TSH serum levels to increase rapidly, the results of the in vitro thyroperoxidase inhibition study are consistent with results of the preliminary mechanistic study. The preliminary mechanistic study also provides some support for the hypothesis that AAA-induced thyroid effects in rats are mediated by dose-related perturbations in thyroid hormone economy because decreased circulating levels of T3 and T4 and increased serum TSH levels were associated with thyroid follicular cell hypertrophy and hyperplasia in this study.

However, a threshold level for thyroperoxidase inhibition in vivo cannot be determined from the available data, which were obtained in an in vitro system. In addition, a threshold level for AAA-induced TSH induction cannot be determined from the in vivo studies, which were conducted with too few animals. Finally, the in vivo studies of AAA-induced effects on thyroid hormone economy (the preliminary mechanistic study in rats and the second short-term dog study) were both limited to 14 days duration; there are no studies of the effects of longer periods of exposure to AAA on thyroid hormone economy.

Moreover, FDA has determined that some of the data from the short-term and subchronic toxicity studies appear to be inconsistent with Hoechst's proposed mechanism. For example, as discussed above, early AAA-related changes in the thyroid (e.g., hypertrophy and hyperplasia), if induced via the petitioner's proposed mechanism, would be expected to be reversible. However, in the second 14-day dog study, one of the two high-dose animals with thyroid follicular hyperplasia was a ''recovery'' animal (i.e., an animal sacrificed 1 month after dosing ended); the observation of hyperplasia in a ''recovery'' animal indicates that AAA's effect on the thyroid persisted for 1 month after dosing ended. This raises the possibility that the effect may persist for longer than 1 month and may not be readily or completely reversible.

Similarly, some of the data obtained from the subchronic rat study are not entirely consistent with certain features of the mechanism proposed by Hoechst.

Hoechst has advanced, as part of its argument, the observation that rodents are more susceptible to TSH-mediated thyroid effects than other species, and that male rats are ''particularly vulnerable.'' However, FDA notes that the available data do not show clear differences, between rats and dogs, in sensitivity to AAA-induced effects. For example, the NOEL for AAA-induced thyroid effects in rats in the subchronic study and the level at which no AAA-induced effects were observed in the second dog study are approximately the same. In addition, although FDA's review of the subchronic rat study showed that male rats may have been slightly more susceptible to AAA's thyroid effects than female rats, the differences were again small.

FDA concludes that, for several reasons, the petitioner's proposed mechanism has not been established. First, as noted, some of the results of the short-term and subchronic feeding studies (e.g., persistence of thyroid effects in recovery animal in the dog study; the lack of a clear difference, in sensitivity to AAA, between rats and dogs and between male and female rats) appear to be inconsistent with the proposed mechanism. Second, the data on AAA's effects on thyroid hormone economy are limited to short-term exposures of a relatively small number of animals; as previously noted, these limited data do not permit the determination of a threshold for AAA's effects. Thus, FDA has determined that although the mechanism proposed by Hoechst is plausible, it has not been established. Because Hoechst's approach to evaluating the health risk from AAA (a comparison of the NOEL's for certain thyroid endpoints with dietary AAA exposure) relies explicitly on the firm's proposed mechanism, and the proposed mechanism has not been established, FDA concludes that Hoechst's approach is not sufficient for an evaluation of the health risk from AAA.

vi. *Consideration of whether more testing of AAA is necessary—(1) Statement of the issue.* Because the findings in the short-term and subchronic toxicity studies of AAA suggest that AAA could induce thyroid tumors in a long-term study, FDA carefully considered whether conduct of such a study was necessary to evaluate the safety of ACK for use in nonalcoholic beverages. In particular, given the likely human dietary exposure to AAA, FDA considered whether the possibility that AAA might induce tumors in a long-term bioassay raised sufficient concern such that testing of the hypothesis should be required. Said differently, the issue was whether a long-term oral study of AAA, a hydrolysis product expected to be present at extremely low levels (if at all) in only certain nonalcoholic beverages, is needed to evaluate the safety of the petitioned use of the food additive, ACK. In addressing this question, FDA determined that it was critical to assess both the likely putative tumorigenic (neoplastic) potency of AAA and the likely patterns of dietary exposure to AAA resulting from consumption of ACK-sweetened nonalcoholic beverages.

As discussed in detail in the rest of this section, FDA considered several approaches to assessing the risk from AAA, and determined both that long-term testing of AAA is unnecessary and that the petitioned use of ACK in nonalcoholic beverages is safe.

(2) Risk assessment. The usual process of quantitative risk assessment is characterized by four steps. First, a possible toxicological hazard is identified. Second, mathematical modelling techniques are applied to the dose-response information from a toxicity study in order to estimate the probability, or, usually, an upper-bound limit on the probability, of the toxic effect of the substance at any given dose level (see for example, Refs. 9 through 11).[7] Typically, in a risk assessment of a carcinogen, this dose-response information is taken from tumor incidence data from a long-term animal study; most often, this long-term study is conducted in a rodent species. Third, the likely human dietary exposure to the substance is estimated. This estimate of dietary exposure may consider such factors as the age groups likely to be exposed and the type, magnitude, and duration of the anticipated exposures.[8] Finally, the information from the first three steps is combined to characterize the risk associated with the potential human exposure to the substance in question.

In the present case, as in the usual risk assessment process, a possible hazard, thyroid carcinogenicity, has been identified. There are similarities between the thyroid effects produced by oral administration of AAA in short-term and subchronic toxicity studies and those produced by oral administration of other substances known to induce thyroid tumors in long-term rodent studies. Thus, there is the possibility that AAA would also induce tumors if tested in a long-term rodent study and, thus, may ultimately present a carcinogenic hazard to humans.

The risk assessment process used in the present case differs from the usual process, however, in that AAA has not been demonstrated to be an animal (or human) carcinogen. That is, dose-response information from a long-term oral study of AAA in animals has not been used because such a study has not been conducted. As an alternative, FDA has used information from the many existing long-term oral studies of known thyroid tumorigens to assess the probable carcinogenic potency (or range of probable potencies) of AAA that might be determined, were a carcinogenicity study of AAA conducted in a rodent species. The agency believes this is a sound approach because of the substantial amount of information available for a large number of thyroid tumorigens.[9]

As in the usual risk assessment process for a known carcinogenic constituent of a food or color additive, a potential life-time averaged ''daily'' human dietary exposure to the substance in question (in this case, AAA, a putative tumorigen) has been estimated. In calculating this estimate, FDA has used estimates of the likely human dietary exposure to ACK, in conjunction with information from analytical testing conducted on model solutions under exaggerated conditions, to estimate a potential lifetime-averaged level of daily dietary exposure to AAA. FDA's exposure estimate is conservative in that it incorporates numerous assumptions and default values for certain parameters that, when combined, yield a value for ''daily'' dietary exposure to AAA that is likely to overestimate rather than underestimate such exposure. By combining the information regarding potential human dietary exposure with the information regarding the likely tumorigenic potency (or range of probable potencies) of AAA, FDA has characterized the potential human carcinogenic risk from AAA resulting

[7] In the absence of information that would support another approach, FDA uses simple linear extrapolation from the dose-response information in the experimental range to estimate the dose-response outside the experimental range (that is, at lower doses comparable to the anticipated human exposure).

[8] In the risk assessment of carcinogenic constituents of food and color additives used directly in food, FDA most often uses an estimate of the lifetime-averaged daily dietary exposure to the substance in question.

[9] Potency values at the thyroid and at other organ sites are available for a large number of thyroid tumorigens. In addition, the results of genetic toxicity testing, short-term studies, and other toxicity testing are available for many of the these compounds. Mechanistic information, though not complete in many cases, is also available for a significant number of these compounds, as well as information regarding structure-activity relationships.

from the consumption of ACK-sweetened nonalcoholic beverages.

The petitioner and the agency have separately analyzed the likely health risk suggested by the AAA-related thyroid findings in the short-term studies, by considering both estimates of the tumorigenic potency of AAA and the likely patterns of dietary exposure to AAA resulting from consumption of ACK-sweetened nonalcoholic beverages. In the course of its analysis, scientists from FDA's Center for Food Safety and Applied Nutrition consulted with several scientists (hereafter referred to as ''the FDA consultants''), from both within and outside the agency, with expertise in various scientific disciplines relevant to the agency's analysis. Details of the petitioner's analysis and the agency's analysis (including relevant comments from the FDA consultants) are discussed in the following paragraphs.

(3) Hoechst's analysis. In response to the agency's reservations regarding Hoechst's initial, threshold-based approach to evaluating the potential health risk from AAA, Hoechst performed two additional ''extreme-case'' or ''worst-case'' comparative risk assessments. In both assessments, Hoechst assumed that AAA would induce thyroid tumors in a long-term study, even though AAA has not been shown to be a tumorigen. In contrast to the firm's initial approach, neither of Hoechst's comparative risk assessments was predicated on a threshold for AAA's thyroid effects. That is, both of Hoechst's comparative risk assessments assumed that some risk of neoplastic disease would be present at all levels of exposure to AAA.

In presenting its assessments of the tumorigenic potential of AAA, Hoechst continued to argue strongly for the mechanism it had proposed to account for AAA's thyroid effects. Hoechst used several features of its proposed mechanism to select the set of chemicals against which to compare AAA and estimate AAA's tumorigenic potential; Hoechst's selection of these surrogates for AAA is described in the following paragraphs.

Using data from lifetime studies of thyroid tumorigens that Hoechst identified as acting with similar effect and through a mechanism similar to the one it had proposed for AAA, Hoechst estimated AAA's putative thyroid tumor potency. According to Hoechst, these estimates of AAA's putative thyroid tumor potency, coupled with an estimate of dietary exposure, would provide ''comparative risk assessments'' of AAA's potential to induce thyroid tumors. Hoechst drew upon several recognized sources to identify the thyroid tumorigens that it chose as surrogates for AAA. These sources included a publication analyzing target organs for more than 500 chemicals in the Carcinogen Potency Database (CPDB), a published review of the information in the data base maintained by the National Toxicology Program (NTP), the Integrated Risk Information System (IRIS), and a well known literature source on thyroid follicular cell carcinogenesis (Refs. 6 and 12 through 14).[10] From the group of thyroid tumorigens identified using these sources, Hoechst selected those for which long-term rodent bioassays had been conducted and in which the test substance displayed tumorigenic activity in either the thyroid alone or, if tumorigenic at other organ sites as well, with greater potency at the thyroid than at other sites. From this subset of thyroid tumorigens, only those compounds that Hoechst identified as both nonmutagenic and active in inhibiting thyroperoxidase (both of which are critical elements of Hoechst's proposed mechanism) were retained as AAA surrogates. Applying these criteria, Hoechst identified four compounds: Amitrole, methimazole, propylthiouracil, and sulfamethazine.

Hoechst used the same estimated dietary exposure in both of its comparative risk assessments. In calculating this estimate, Hoechst used data on ACK stability and nonalcoholic beverage consumption patterns, incorporating several conservative assumptions similar to those used by FDA and described previously. Hoechst estimated the high-level consumer's potential ''daily'' dietary exposure to AAA to be 3.5 ng/kg bw/day. Hoechst asserted that this estimate of potential ''daily'' dietary exposure was likely to overestimate significantly the actual exposure because of the numerous conservative assumptions used in deriving the estimate.[11]

In its first comparative risk assessment, Hoechst assumed that the putative induction of thyroid tumors by AAA would be directly related to an AAA-induced increase in serum levels of TSH. Using the literature sources listed previously, Hoechst identified three compounds (methimazole, propylthiouracil, and sulfamethazine) that the firm asserted have approximately the same quantitative effect on circulating TSH levels as AAA had on TSH levels in the preliminary mechanistic study in rats. Hoechst then estimated a hypothetical cancer potency for AAA by interpolating between the established tumorigenic potencies of these three substances;[12] the hypothetical cancer potency for AAA in this assessment was 2.3×10^{-3} (mg/kg bw/day)$^{-1}$. When coupled with the firm's estimated ''daily'' dietary exposure of 3.5 ng/kg bw/day, Hoechst's estimated upper-bound limit of lifetime human cancer risk, in its first assessment, was 8.1×10^{-9}.

In the second of Hoechst's nonthreshold risk assessments, the putative induction of thyroid tumors by AAA was assumed to be directly related to AAA-induced inhibition of thyroperoxidase (and thus, indirectly, to elevated serum TSH levels). Hoechst identified four substances (amitrole, methimazole, propylthiouracil, and sulfamethazine) for which it maintained that the induction of thyroid tumors in animals is known to occur as a result of thyroperoxidase inhibition. Hoechst then estimated a hypothetical cancer potency for AAA by calculating a weighted average of the established tumorigenic potencies of these four substances. In this second comparative risk assessment, Hoechst estimated the hypothetical potency of AAA as 4.0×10^{-2} (mg/kg bw/day)$^{-1}$. When coupled with the firm's estimated ''daily'' dietary exposure of 3.5 ng/kg bw/day, Hoechst's estimated upper-bound limit

[10] The CPDB summarizes results of carcinogenicity bioassays published in the open literature and in technical reports of the NTP. The NTP data base, also known as the NCI/NTP data base, contains the results of mouse and rat carcinogenicity studies conducted by NCI/NTP. The published review that was used by Hoechst summarized the results of 343 selected carcinogenicity studies conducted by NCI/NTP; in this subset of the NCI/NTP data base, 14 percent of the studies in male rats, 11 percent of the studies in female rats, 8 percent of the studies in male mice and 9 percent of the studies in female mice were identified as having positive or equivocal, chemically-related thyroid proliferative lesions. (The studies from the NCI/NTP data base are also included in the CPDB.) IRIS is an electronic data base prepared and maintained by the U.S. Environmental Protection Agency (EPA); it contains information on human health effects that may result from exposure to various chemicals in the environment.

[11] Hoechst's estimate of consumer exposure to AAA (3.5 ng/kg bw/d) is essentially the same as FDA's estimate (3.3 ng/kg bw/d, equivalent to 0.2 µg/p/d). FDA has determined that both Hoechst's and the agency's estimate of AAA dietary exposure, because of the particular assumptions used in deriving them, are likely to overestimate rather than underestimate exposure.

[12] The potencies of the AAA surrogates are properly described as tumorigenic potencies; the tumors observed in rodents are more often benign, rather than malignant, follicular cell tumors. In both the petitioner's and the agency's comparative risk assessments, the distribution of tumorigenic potencies of AAA surrogates is used to estimate the putative tumorigenic potency of AAA. This putative tumorigenic potency of AAA is then used as a direct substitute for a hypothetical human cancer potency in the comparative risk assessments.

of lifetime human cancer risk, in its second assessment, was approximately 1.4×10^{-7}.

The petitioner argued that both its estimates of AAA's upper-bound limit of lifetime human cancer risk were well below the level ordinarily regarded by FDA as commensurate with negligible risk. The petitioner also argued that any actual risk would be far lower than these estimated upper-bound limits of risk because of the numerous conservative assumptions used in calculating these estimates.

In addition, the petitioner noted that humans are less sensitive than rats to thyroid effects induced through TSH-dependent mechanisms. Hoechst referenced scientific literature in support of its contention that, although chronic TSH stimulation induces thyroid hypertrophy and hyperplasia in humans as well as in rodents, humans are less likely to develop tumors following chronic stimulation by TSH. Specifically, they noted that prolonged TSH stimulation is known to lead to thyroid enlargement or goiter in humans, but rarely leads to thyroid tumors (Refs. 15 and 16). Hoechst also maintained that the rat's significantly higher baseline TSH levels and more rapid metabolism of the hormone leave rats more vulnerable than humans to the development of thyroid tumors in response to chemically induced increases in circulating TSH levels (see Refs. 8 and 17). Hoechst argued that the lower sensitivity of human thyroid follicular cells to elevated TSH levels would further reduce the likely magnitude of any actual thyroid tumor risk to humans from exposure to any AAA in ACK-sweetened nonalcoholic beverages.

(4) FDA's analysis. FDA has carefully evaluated the petitioner's comparative risk assessments. The agency agrees that it is reasonable to perform an ''extreme-case'' risk assessment of AAA in order to evaluate the potential health concern raised by the thyroid findings in the short-term studies of AAA. To this end, FDA conducted its own analysis of the potential health risk from the low levels of AAA that may be ingested as a result of the consumption of ACK-sweetened nonalcoholic beverages. FDA's two principal comparative risk assessments of AAA, like the petitioner's, are essentially modified carcinogenic risk assessments; however, in several respects the agency's approach differs from the petitioner's.

Like Hoechst, FDA assumed that AAA would be tumorigenic if tested in a long-term bioassay. The agency also assumed, as did Hoechst in its comparative risk assessments, that there is no threshold for AAA's presumed tumorigenic activity. However, in contrast to Hoechst, FDA did not rely on assumptions regarding AAA's mechanism of action on the thyroid. Although FDA believes that it is plausible that AAA may induce thyroid tumors in long-term studies through the mechanism hypothesized by the petitioner, the data supporting the petitioner's hypothesis are limited in several key areas. First, as noted, there are no studies demonstrating long-term effects of AAA on thyroid hormone economy; thus, FDA, in its comparative risk assessments, did not assume a quantitative correlation between TSH induction and AAA's putative thyroid tumorigenic potency. Second, there is no direct evidence of AAA-induced effects on thyroperoxidase activity in vivo; consequently, FDA did not assume that AAA's putative potency would be similar to potencies of thyroid carcinogens known or asserted to act through inhibition of thyroperoxidase activity.

To provide assurance that the risk presented by AAA is not underestimated, FDA included in its set of AAA surrogates all substances it identified, using the 1996 CPDB (see Ref. 18), as having induced tumors in the thyroid, including substances that also induced tumors in other organs, regardless of the relative potencies involved.[13] This set of surrogates includes both genotoxic and nongenotoxic substances. Because the potency distribution for genotoxic chemicals is shifted to higher potencies than the potency distribution for nongenotoxic chemicals, FDA's set of 91 surrogates includes substances of higher potency than those in Hoechst's set of 4 surrogates (Ref. 2). FDA included this frank and deliberate conservatism to ensure that neither the putative potency of AAA nor the attendant estimate of AAA's potential carcinogenic risk would be underestimated.

In the first of FDA's comparative risk assessments, the agency used potency values from the distribution of the thyroid tumor potencies of the 91 surrogates. FDA chose this approach because the data from the short-term and subchronic studies of AAA in rats, rabbits, and dogs identify the thyroid as the potential target organ for putative AAA-induced tumors and do not suggest other likely target organs. The distribution of thyroid tumor potencies for the 91 surrogates has a peak, or ''most probable'' value, of 7.0×10^{-3} $(mg/kg\ bw/day)^{-1}$. FDA used this potency value as an estimate for the likely potency of AAA. This potency, coupled with the agency's estimated ''daily'' dietary exposure to AAA of 3.3 ng/kg bw/day, yields an estimated upper-bound limit of lifetime risk from AAA of 2.3×10^{-8} (Ref. 2). This hypothetical upper-bound limit of lifetime risk from AAA is well below the level that FDA ordinarily considers commensurate with negligible risk.

To provide further assurance that AAA's potential risk was not being underestimated, the agency performed a second risk assessment. In this second assessment, FDA hypothesized that AAA might, in addition to inducing thyroid tumors, induce tumors at sites other than the thyroid and that AAA's potency at these other sites could be higher than for tumors induced at the thyroid.[14] In essence, this scenario describes the most adverse outcome of a long-term bioassay with AAA, were such a bioassay actually conducted. Thus, FDA's second risk assessment included an assumption of the most adverse outcome for a study testing the hypothesis that AAA causes thyroid tumors so that the potential risk posed by AAA would not be underestimated.

In this assessment, to estimate AAA's most likely tumorigenic potency, FDA used the peak, or ''most probable value'' value from the distribution of highest tumor potencies at any organ site for FDA's 91 surrogates. Using this estimate of the putative tumorigenic potency of AAA (2.0×10^{-2} $(mg/kg\ bw/d)^{-1}$) and the agency's conservative estimate of ''daily'' dietary exposure to AAA of 3.3 ng/kg bw/d, FDA estimated the upper-bound limit of lifetime human cancer risk from exposure to AAA to be 6.6×10^{-8} (Ref. 2). This hypothetical upper-bound limit of lifetime risk from AAA, like the value obtained in FDA's first

[13] Taken together, the six plots of the 1996 CPDB include results of 5,002 experiments on 1,230 chemicals. The agency notes that of the 91 compounds in the CPDB that were reported to induce thyroid tumors in rodents, only three (methimazole, deltamethrin, and sulfamethazine) produced thyroid tumors only. Of the remaining 88 compounds, 70 percent had a higher cancer potency for tumors other than thyroid tumors. Thus, the majority of compounds that have been found to induce thyroid tumors (by any mechanism) have also been found to induce tumors at other sites, for which the estimated cancer potency is higher than the potency estimated for thyroid tumors alone (see Ref. 2).

[14] One of the FDA consultants noted that some, but not all thyroid peroxidase inhibitors lead to tumors at sites other than the thyroid, especially the liver of mice. This consultant further commented that ''* * * FDA is on strong ground to look at the potency for tumors other than thyroid, as well as looking at those for the thyroid.'' Including the higher potencies for tumors other than thyroid tumors in FDA's assessment is, however, a conservative measure in that the data in the studies of AAA submitted to the petition do not suggest that there are other likely target organs for neoplasia.

risk assessment, is well below the level ordinarily considered by FDA as commensurate with negligible risk.

Based on its risk assessments, the agency believes that AAA is highly unlikely to pose more than a negligible cancer risk to consumers. For example, even if, in FDA's first risk assessment, AAA's thyroid tumor potency were as high as that of the 90th percentile most potent compound in FDA's set of AAA surrogates, the estimated upper-bound limit of lifetime risk from AAA, using all of the conservative features and assumptions described previously, would still be less than 7×10^{-7}. To produce the same estimate of upper-bound risk from AAA using the approach in FDA's second risk assessment, AAA's potency at any organ site would have to approach that of the 90th percentile most potent compound in FDA's set of AAA surrogates. The agency considers these potency levels highly unlikely for several reasons. First, AAA's potency at the thyroid would need to approach that of methimazole, the positive control in the preliminary mechanistic study. That AAA would be as potent as methimazole is unlikely, however, given the fact that almost 100-fold greater doses of AAA than of methimazole were needed to induce comparable degrees of thyroid follicular cell hypertrophy and hyperplasia, the presumed precursors to any thyroid neoplasia (see Ref. 2). Second, the thyroid tumorigens in the set of 91 surrogates with potencies in this range (approaching the 90th percentile and above) are almost all genotoxic or have strong structural indicators of genotoxicity while the results of the genetic toxicity tests of AAA show that AAA is not genotoxic. As previously noted, the potency distribution for genotoxic compounds is shifted to higher values than the potency distribution of nongenotoxic compounds; thus, the probability that AAA, a nongenotoxic compound, will be more potent than the most potent genotoxic compounds in FDA's set of AAA surrogates is extremely low (see Ref. 2).

As noted previously, the agency's comparative risk assessments were based on numerous conservative assumptions so that any risk from AAA would not be underestimated; FDA believes that any actual risk from AAA would be substantially lower than either of its estimates of the upper-bound limit of lifetime risk. The agency also notes that all of the FDA consultants agreed that the numerous conservative assumptions used in the agency's comparative risk assessments were likely to lead to an overestimate, rather than an underestimate, of the risk from AAA.[15]

The conservative nature of FDA's risk estimates was amplified by the agency's assumption, in its comparative risk assessments, that consumers would be subject to ''chronic'' or ''daily'' dietary exposure to AAA through consumption of ACK-sweetened nonalcoholic beverages. In fact, frequent exposure to AAA is unlikely because few containers of beverages are likely to be stored under the conditions necessary to produce significant quantities of AAA. Thus, any actual dietary exposure to AAA through consumption of ACK-sweetened beverages is likely to be at very low levels, to be intermittent, and to be infrequent.[16]

In summary, the agency has used information from the many long-term oral studies of known thyroid tumorigens to estimate the range of possible tumorigenic potencies of AAA; this estimate has then been used to represent the tumorigenic potency for AAA that might be determined by a carcinogenicity study of AAA in a rodent species. FDA has combined this information with a conservative estimate of ''daily'' dietary exposure to AAA in order to assess the risk that might be posed to individuals consuming ACK-sweetened beverages. FDA's risk assessments for AAA all yield upper-bound limits of lifetime risk that are not only very low, but are also expected to be substantially higher than any actual risk from AAA.

(5) Resolution of the issue. FDA has carefully evaluated the data from the available short-term and subchronic oral toxicity tests of AAA. As previously noted, the findings in these studies suggested that AAA might induce thyroid tumors in a long-term oral study, raising the question of AAA's possible carcinogenic risk. Thus, FDA has considered whether conduct of a long-term study was necessary to assess the possible carcinogenic risk from AAA.

FDA has concluded that, for several reasons, it is not necessary to require the conduct of a long-term study of AAA. First, the primary purpose of such a study would be to determine whether AAA actually induced thyroid tumors. As an alternative, in its assessment of the potential health risk of AAA, the agency has simply chosen to assume that AAA would, indeed, induce thyroid tumors in a long-term study, thus obviating the first purpose of such a study.

The second purpose of a long-term study of AAA, in the event that AAA were found to be tumorigenic, would be to determine AAA's tumorigenic potency. As an alternative, in its risk assessments for AAA, FDA has conservatively estimated AAA's putative potency by considering the range of potencies of the many known thyroid tumorigens (AAA surrogates) for which long-term testing has been conducted. As noted previously, FDA believes this is a sound approach because the results of the short-term tests of AAA indicate the thyroid as a likely target organ for the assumed neoplasia, and because of the substantial amount of chemical and toxicological information available for a large number of thyroid tumorigens.

FDA has also used several deliberate conservatisms in constructing its set of surrogates in order to ensure that AAA's putative potency and any attendant estimate of AAA's hypothetical cancer risk are not underestimated: (1) FDA's set of surrogates includes genotoxic compounds which, as a group, are generally more potent than nongenotoxic compounds (AAA is nongenotoxic); (2) FDA's set of AAA surrogates also includes compounds for which genetic toxicity testing data are not available, but which have features in their chemical structures that are widely recognized as strong indicators of mutagenicity/carcinogenicity and, thus, are expected to be of higher potency than nongenotoxic compounds; and (3)

[15] One of the FDA consultants also provided two additional approaches to calculating a conservative upper-bound limit of lifetime human cancer risk, one that made use of a feature of the petitioner's proposed mechanism for AAA's action on the thyroid and one that did not. The estimates of AAA's upper-bound carcinogenic risk derived by these two additional approaches were 8.0×10^{-8} and 3.3×10^{-8}, respectively (see Ref. 2). Both of the consultant's estimates for the upper-bound risk from AAA, like the upper-bound risks calculated by FDA (2.3×10^{-8} and 6.6×10^{-8}) and by the petitioner (8.1×10^{-9} and 1.4×10^{-7}), are very low.

[16] FDA notes that approaches to modifying risk assessments for intermittent exposures to carcinogens generally reduce the estimated risk substantially (see for example, Refs. 19 and 20). Such modification can be particularly important for carcinogens that are nongenotoxic. In general, continuous exposure to such substances for a prolonged period of time is needed before tumors develop; removal of the carcinogen from the diet for a significant portion of that time, will stop progression toward tumor development and may even result in partial or complete reversal of the treatment-related preneoplastic changes (see Ref. 6). If AAA were to induce thyroid tumors, and if it were to do so through a nongenotoxic or indirect mechanism, the intermittent nature of the exposure to AAA from consumption of ACK-sweetened nonalcoholic beverages would reduce the risk from AAA so that it is even more likely to be significantly less than the value estimated by the agency's method, and perhaps to be zero. On this point, one of the FDA consultants also commented that explicit consideration of the expected intermittent nature of any dietary exposure to AAA was particularly important in placing the calculations of AAA's estimated risk into perspective.

FDA's set of surrogates includes thyroid tumorigens that are tumorigenic at sites other than the thyroid and with higher potency than at the thyroid. Using information regarding the AAA surrogates and the distribution of their potencies, FDA estimated a range of hypothetical carcinogenic potencies for AAA. Thus, by conservatively estimating the range of likely tumorigenic potencies for AAA, FDA believes that it has obviated the need to determine AAA's potency through long-term testing.

Using the estimates of AAA's likely tumorigenic potency, the agency performed several comparative risk assessments for AAA, combining the estimates of AAA's potency with a deliberately exaggerated estimate of dietary exposure to AAA to assess the possible risk from the compound; these conservative estimates of AAA's hypothetical upper-bound limit of cancer risk are very low. As previously noted, the risk estimates calculated by the FDA consultant and by Hoechst, though derived using different assumptions about the range of possible potencies for AAA, are also very low. In addition, the conservative nature of all of the risk estimates for AAA is amplified by the assumption that consumers would be subject to ''chronic'' or ''daily'' exposure to AAA through consumption of ACK-sweetened nonalcoholic beverages when, in fact, such exposure is likely to be both intermittent and infrequent.

FDA's risk assessments show that, even assuming that AAA were carcinogenic in a long-term test, the hypothetical upper-bound of risk associated with an exaggerated estimate of dietary exposure to the compound would be extremely small. Because of the numerous conservatisms used in calculating these upper-bound limits of risk, FDA concludes that any actual risk from AAA would be far lower than these limits and, in fact, negligible. In this way, the results of FDA's risk assessments corroborate the agency's determination that a long-term study of AAA is not necessary to assess the potential risk to the public health from consumption of this compound.

Thus, based on the available data and information, including the risk assessments described previously, FDA concludes that there is a reasonable certainty that no harm will result from the exposure to AAA that might result from the proposed use of ACK in nonalcoholic beverages. Accordingly, the agency has determined that requiring the petitioner to conduct further testing of AAA is not necessary and would not serve a useful purpose from the public health perspective.

E. Summary of FDA's Safety Evaluation

The safety of ACK has been thoroughly tested and the data have been carefully reviewed by the agency. FDA has considered the data and information submitted in the present petition as well as other information in its files, including data and information in previous petitions for ACK.

The agency has determined that the toxicological data on ACK establish that: (1) There is no association between neoplastic disease (cancer) and consumption of the additive and (2) the ADI for the additive is 15 mg/kg bw/day. FDA has also determined that the estimated dietary exposure to ACK from all currently permitted uses of the additive as well as the proposed use in nonalcoholic beverages (1.6 mg/kg bw/day for the mean consumer, 3.0 mg/kg bw/day for the 90th percentile consumer) is well below the ADI. In addition, the agency has concluded that there is a reasonable certainty of no harm from the exposure to methylene chloride (a chemical used in the manufacture of ACK) that might result from all currently permitted uses of the additive as well as the proposed use in nonalcoholic beverages.

Finally, FDA has considered the special conditions that are relevant to the proposed use in nonalcoholic beverages. In this regard, FDA has considered toxicological data and other information, including estimates of dietary exposure, regarding AAS and AAA, the principal hydrolysis products of ACK. Based on the data and information described previously in this document, including FDA's comparative risk assessments for AAA, the agency has concluded that there is a reasonable certainty of no harm from the exposure to AAS and AAA that might result from the proposed use of ACK in nonalcoholic beverages.

Thus, based on a full and fair evaluation of the relevant data and information, FDA concludes that the proposed use of ACK in nonalcoholic beverages is safe.

IV. Response to Comments

During the course of FDA's evaluation of the present petition, the agency received several sets of comments on the petition. FDA received multiple submissions from CSPI, who also transmitted comments from other interested parties. Later, Hoechst transmitted additional remarks from two of these same parties. Several letters were also received from trade groups and other organizations.

A. Summary of Comments

1. Center for Science in the Public Interest's (CSPI's) First Submission

The first of CSPI's submissions was a letter, dated October 18, 1990, in which CSPI referred to the organization's 1988 objections to FDA's initial approval of the use of ACK (the dry uses final rule). CSPI asked that FDA not consider expanding the permitted uses of ACK ''without first resolving [CSPI's] objections, hearing request, and petition[17] [sic].'' As noted previously in this document, FDA considered the issues raised by CSPI in its objections and responded, in detail, to those objections in the **Federal Register** of February 27, 1992 (57 FR 6667). After reviewing the objections, the agency concluded that no genuine issues of material fact had been raised that would justify either a hearing or a stay of the regulation and, accordingly, denied CSPI's requests. Because the agency has responded to CSPI's objections to the dry uses final rule and to the organization's related requests, no further discussion of CSPI's first submission is warranted.

2. CSPI's Second Submission

CSPI's second submission was a letter, dated January 29, 1996, in which CSPI asserted that the long-term toxicity testing of ACK was inadequate and that ACK was ''possibly carcinogenic.'' Once again, CSPI referred to its previous objections to the dry uses final rule, and urged FDA to deny the present petition and to require the petitioner to conduct additional carcinogenicity testing of ACK. CSPI did not, however, supply any substantive information to support these requests.[18] In its letter, CSPI also mentioned certain results from the toxicity tests of AAA[19] in support of its request for additional carcinogenicity testing of ACK, but did not supply any substantive information that had not already been considered by FDA or any explanation of how the AAA test results related to the organization's request for additional testing of ACK. Because CSPI did not provide any substantive information to support its requests, no

[17] CSPI uses the term ''petition'' to refer to its request for a stay of the dry uses final rule.

[18] In its January 29, 1996, letter, CSPI indicated that it intended to submit a detailed analysis of the ACK safety data at a future date.

[19] CSPI mentioned histologic changes in the thyroid glands of rats, rabbits, and dogs, referring specifically to ''hypertrophic and neoplastic changes'' when AAA was administered at high dose levels in short-term studies. As previously noted in this document, AAA-related thyroid follicular cell hypertrophy occurred in all three animal species; adenomas occurred only in two male rats in a subchronic study.

further discussion of this submission is warranted.

3. CSPI's Third Submission

CSPI's third submission consisted of a letter to FDA, dated May 29, 1996, in which CSPI reiterated its concerns about the carcinogenicity testing of ACK, and also included copies of the materials the organization had submitted to the National Toxicology Program (NTP) in nominating ACK for ''chronic toxicity (carcinogenicity) testing'' by NTP (''CSPI's NTP nomination package''). CSPI's NTP nomination package consisted of a cover letter, dated May 29, 1996, and a narrative describing CSPI's rationale for nominating ACK for testing under the NTP program (a document entitled ''Summary of Data on Acesulfame Potassium''), including a list of nine references and seven attachments.[20]

The seven attachments in CSPI's NTP nomination package were three FDA review memoranda; the final report for a subchronic toxicity study of ACK in rats; a letter from Hoechst responding to FDA questions regarding histopathology data from two of the long-term studies of ACK in rodents; and two FDA memoranda, each summarizing a different meeting of Hoechst and FDA representatives. The agency notes that the attachments are all copies of publicly available documents contained in the administrative record for the dry uses final rule. The agency also notes, however, that CSPI did not provide NTP with all of the information from the administrative record for the dry uses final rule.[21] Specifically, CSPI did not provide NTP with the reports on the long-term studies of ACK in rats or mice, the reports of the genetic toxicity studies of ACK, or any of the review memoranda from FDA's pathologists or FDA's Cancer Assessment Committee.

The narrative describing CSPI's rationale for nominating ACK for NTP testing raised various issues with respect to the three long-term ACK feeding studies in rodents that were submitted in the original ACK petition. FDA's analysis of the specific issues raised in CSPI's third submission is discussed in section IV.B.2 of this document.

4. CSPI's Fourth Submission

CSPI's fourth submission consisted of a letter, dated July 31, 1996, addressed to the Director of FDA's CFSAN, in which the organization reiterated its concerns regarding the long-term testing of ACK and also mentioned its nomination of ACK for chronic toxicity (carcinogenicity) testing by NTP. In addition, CSPI cited certain of the results from the toxicity testing of AAA and urged FDA to require the petitioner to conduct long-term testing of AAA. CSPI again asked FDA to deny the present petition and to revoke ''all existing regulations permitting the use of acesulfame potassium.''

In support of its requests, CSPI enclosed copies of letters from ''ten experts in the fields of carcinogenesis, toxicology, and statistics'' who had, at CSPI's request, ''reviewed the Hoechst test protocols and results'' (hereinafter, these individuals will be referred to as ''CSPI's ten consultants''). Seven of the letters were addressed to CSPI; the authors of these particular letters expressed support for CSPI's nomination of ACK for testing under the NTP program. Three of the letters were addressed to the Commissioner of the Food and Drug Administration. The authors of these three letters urged FDA to require additional carcinogenicity tests of ACK; one of the authors also urged FDA not to approve the present petition.[22] CSPI claimed that ''[b]ased on the experts' conclusions regarding Hoechst's tests, it is clear that Hoechst has failed to demonstrate a 'reasonable certainty of no harm' for the use of acesulfame potassium in soft drinks (or other foods).''

In partial response to CSPI's letter of July 31, 1996, FDA requested copies of the materials supplied to CSPI's ten consultants and on which, presumably, the consultants had based their comments. CSPI responded by submitting copies of materials that it characterized as ''a standard data set,'' consisting of ten complete documents and selected portions of several other documents (19 items altogether) drawn from the administrative record for the dry uses final rule.[23] Based on the ''standard data set'' submitted by CSPI, it appears that the ten consultants were not provided, however, with all of the Hoechst study reports and other relevant supporting information, nor were they provided with all of the FDA review memoranda filed in the administrative record for the prior approvals of ACK.[24] For example, neither the results of the ACK genetic toxicity testing nor FDA's final pathology review memorandum (Ref. 21), which articulated FDA's resolution of the outstanding questions regarding missing data and incomplete initial reporting of histopathology results raised in earlier FDA review memoranda, were included in CSPI's ''standard data set.''

As previously noted, most of the letters from CSPI's ten consultants did not raise specific issues regarding either the long-term testing of ACK or other safety data relevant to FDA's evaluation of the present petition; only one consultant provided detailed criticism of FDA's interpretation of the data. FDA's analysis of the few specific points raised in letters from the ten consultants is discussed below, along with FDA's analysis of the issues raised in CSPI's NTP nomination package.

5. Hoechst's Submission

In response to the letters from CSPI's ten consultants, Hoechst transmitted to FDA copies of letters from two CSPI

[20] FDA has assumed that the NTP nomination package is the detailed analysis of the safety data on ACK that CSPI indicated, in its letter of January 29, 1996, that it would send to the agency at a future date.

[21] The administrative record for the dry uses final rule contains all of the Hoechst study reports submitted in support of the original petition for ACK, other data and supporting information, FDA review memoranda, and other documents. Hoechst submitted reports for 6 genetic toxicity tests, 2 acute toxicity studies, a subchronic toxicity study, 4 reproduction or developmental toxicity studies, 3 long-term studies in rodents referred to previously in this document, a 2-year study in dogs, 11 metabolism studies, and 7 other specialized studies.

[22] Several of the letters to CSPI and to FDA raised specific issues regarding the procedures used in, or the interpretation of results from, the long-term studies of ACK in rodents. None provided any new data or other information that had not already been considered by the agency. FDA's analysis of the specific issues raised in these letters is discussed later in this document.

[23] The ten complete documents in CSPI's ''standard data set'' were six FDA review memoranda, including the final review memorandum from FDA's Cancer Assessment Committee; the dry uses final rule (53 FR 28379); FDA's response to CSPI's objections to the dry uses final rule (57 FR 6667); and two letters addressed to Hoechst from an independent pathology lab, supplying additional information regarding histopathology data (one letter in regard to a long-term study in rats, the other in regard to a long-term study in mice). The other items in CSPI's ''standard data set'' consisted primarily of narrative sections from, or excerpts from various tables (e.g., mortality data, tumor incidence data) included in, the study reports for the three long-term feeding studies of ACK in rodents.

[24] Judging from their remarks, some of CSPI's ten consultants may have been under the impression that all of the data and information on ACK had been made available to them. For example, one of these individuals stated: ''I agree strongly with [CSPI's] evaluation that the available data on this compound is at best incomplete * * * I could not find any information related to mutagenicity or other genotoxicity or any studies on reproduction and development.'' Another of CSPI's consultants also made similar remarks regarding the apparent lack of ACK genetic toxicity data.

However, as noted previously in this document, the ACK toxicity data base submitted to the original petition for ACK included the results of six genetic toxicity tests and four studies of reproductive or developmental toxicity. The agency concluded that the results of the genetic toxicity tests did not indicate ACK-induced genotoxic effects and that the results of the reproduction and teratology studies produced no evidence of ACK-related teratogenic or adverse reproductive effects (see 53 FR 28379 at 28380).

consultants to whom the firm had provided supplementary information regarding the toxicity testing of ACK. In their letters, these two individuals stated that, after reviewing additional information provided to them by Hoechst, they had concluded that the long-term testing of ACK was adequate and that the test results did not indicate that ACK was a carcinogen.

Hoechst also submitted to FDA copies of the materials it had provided to the two CSPI consultants for review. These materials included several documents from the administrative record for the dry uses final rule as well as a copy of the dry uses final rule. Also included in Hoechst's information package was a copy of a document entitled ''Executive Summary,'' a document that, according to Hoechst, was a summary of toxicology information on ACK that had been submitted to Health Canada as part of a petition for the use of ACK; and a book, entitled *Acesulfame Potassium*.[25]

Because the additional letters from these two particular consultants provided no data or other substantive information, FDA regards them solely as further elaboration of the earlier remarks from the two individuals in question. No further discussion of any of these remarks is necessary.

6. Other Submissions

FDA also received several letters from trade groups and other organizations urging FDA to approve the present petition. Because none of these letters provided any substantive information, no further discussion of these submissions is necessary.

B. Analysis of Specific Issues Raised in the Comments

1. AAA Test Results

CSPI, in its fourth submission, and two of CSPI's ten consultants, commented on the results of short-term toxicity tests of ACK's breakdown product, AAA, and raised the issue of AAA's possible carcinogenic potential.[26] FDA agrees that the results of the short-term studies of AAA raised concerns that required resolution. As discussed previously, the agency carefully evaluated the data from the short-term toxicity tests of AAA, along with other data and information from the petition and in its files. As discussed previously, FDA has concluded that AAA is highly unlikely to pose a significant cancer risk to individuals consuming ACK-sweetened beverages; none of the information in the comments provides a basis to reconsider that conclusion. Because the agency's detailed analysis of the issue of AAA's possible carcinogenic potential has already been presented (see sections III.D.2.b.v and vi of this document), that analysis will not be repeated here. The agency's analysis of the remaining issues raised in the comments on the present petition follows.

2. ACK Test Results

In its NTP nomination package, CSPI again raised some of the same questions regarding the adequacy of, and the results from, the long-term testing of ACK that it raised in its previous objections to the dry uses final rule; CSPI also raised some new points with respect to the safety testing of ACK. CSPI's NTP nomination package is clearly addressed to NTP and is not written as a comment, per se, on the present petition; the narrative in CSPI's NTP nomination package focuses on the differences between the designs of, and procedures used in, the long-term feeding studies of ACK and specific elements of NTP study designs or other ''NTP standards.'' Nevertheless, FDA has assumed that CSPI's NTP nomination package constitutes the ''detailed analysis of the safety data on ACK'' that CSPI had intended to send to the agency at a future date and that FDA had indicated it would treat as a comment on the present petition. Thus, FDA has attempted to extract from CSPI's NTP nomination package those remarks on specific issues that could be construed as comments on the present petition.

As noted previously, there is considerable overlap between the specific issues raised by certain of CSPI's ten consultants and those raised by CSPI. Because CSPI's NTP nomination package provides the most detailed discussion of specific issues, those remarks will be the focus of FDA's response. Where the other parties have raised additional points or points that differ substantively from those raised by CSPI, FDA will indicate that in its discussion.

a. *The second rat study*. In its original evaluation of the safety of ACK, FDA reviewed a long-term study conducted in CPB–WU Wistar rats in which ACK was administered at 0, 0.3, 1.0, or 3.0 percent in the test diet (the ''second rat study''). In the preamble to the dry uses final rule, the agency concluded that this study was adequate for an evaluation of a food additive and that it demonstrated the safety of acesulfame potassium (see 53 FR 28379 at 28380). Implicit in FDA's determination of the adequacy of the second rat study was that the dosing levels in this study were appropriate (see 57 FR 6667 at 6669).

i. *Issues raised previously—(1) Appropriateness of the dosing.* CSPI's NTP nomination package asserts that the second rat study was inadequate because the highest dose tested (3 percent in the diet) was too low. To support its assertion, CSPI compares the dosing regimen used in the second rat study with NTP ''requirements'': ''NTP requires that long-term feeding studies be carried out at the minimally toxic dose (MTD), which is functionally equivalent to the maximum tolerated dose * * *.'' CSPI also states that ''NTP requires that when a test chemical is administered in the diet, the high dose should not exceed 5 percent of the diet, but use of a 5 percent dose could meet NTP standards. Since rats in the subchronic test tolerated 10 percent acesulfame potassium in the diet with what were reported as only minimal effects* * *, 5 percent should have been the highest dose tested in the two rat studies.''[27] CSPI's submission does not, however, contain or identify any data or other evidence to establish that the dosing used in the second rat study was, in fact, too low to permit an assessment of ACK's carcinogenic potential.

CSPI implies that, in order for long-term toxicity (carcinogenicity) testing to be valid, it must conform to NTP ''requirements.'' FDA does not agree. The NTP document cited by CSPI[28]

[25] This book, co-edited by a Hoechst scientist and a professor at a German university, discusses various studies of ACK submitted in the original petition, including genetic toxicity studies, acute studies, the three long-term feeding studies in rodents referred to previously in this document, a subchronic feeding study, reproduction and teratology studies, metabolism studies and others. The book also discusses several additional studies of ACK (e.g., additional genetic toxicity studies), conducted after FDA's initial approval decision, that were submitted to the present petition and have been discussed previously in this document.

[26] One of these individuals referred to AAA as a ''metabolic breakdown product.'' FDA notes, however, that AAA has not been shown to be a metabolite of ACK. As discussed previously in this document, the ACK toxicity data base submitted to the original petition for ACK included the results of 11 metabolism studies. FDA carefully evaluated the results of these studies and concluded that they revealed no evidence that ACK was metabolized (53 FR 28379 at 28380, see also Ref. 4).

[27] FDA notes that, in the subchronic study, ACK was administered at dose levels of 0, 1.0, 3.0, or 10.0 percent in the diet. ACK-related reductions in body weight of greater than 10 percent, along with various other effects, were observed in the 10 percent dose group. Body weight reductions were also observed in the 3 percent dose group, but such reductions were less than 10 percent. Based on the findings in the 10 percent and 3 percent dose groups, Hoechst chose to use 3 percent as the highest dose level in the long-term study; there are no data to suggest that 5 percent was required.

[28] This document is entitled ''Specifications for the Conduct of Studies to Evaluate the Toxic and

Continued

establishes standardized protocol elements and reporting formats for certain toxicity and carcinogenicity tests conducted by contract laboratories under the auspices of the NTP program. The NTP document does not establish criteria for evaluating the scientific validity of toxicity and carcinogenicity tests in general, nor does it establish regulatory requirements with respect to safety decisions on food additives. The NTP document provides specifications that must be met in order for the results of a particular toxicity study to be included in the NCI/NTP data base (described previously in this document).

FDA notes that the agency's own guidelines, ''Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food'' (the FDA Redbook), do not establish regulatory requirements or requirements for establishing the scientific validity of testing. Rather, the Redbook represents the agency's best advice to manufacturers of food and color additives on how to satisfy the legal safety standard of ''reasonable certainty * * * that a substance is not harmful'' (see § 170.3(i)); and contains general toxicological principles that are to be applied using good scientific judgment.

It is important to note that although the details provided in the NTP document differ from those provided in the Redbook, a study that follows either the NTP ''specifications'' or the Redbook guidance[29] and is conducted in accordance with good laboratory practices will generally be appropriate for use in a safety evaluation. Strict adherence to any particular set of guidelines is not necessary, however, to ensure either scientific validity or suitability for a regulatory safety decision. Accordingly, in reaching a final decision on the safety of a food additive, FDA considers all of the relevant data and information available, including the design of, and results from, toxicity testing. The suitability and validity of any particular toxicity study submitted in support of a food additive is evaluated on its own merits, using good scientific judgment, by FDA.

The agency notes that, in its objections to the dry uses final rule, CSPI raised the same issue regarding the adequacy of the dosing in the second rat study, and FDA addressed this issue in its response to CSPI's objections (57 FR 6667 at 6668 and 6669). The agency incorporates that discussion, in full, into the safety determination on the present petition. Because CSPI has presented no new evidence to support its opinion regarding the adequacy of the dosing in this study, nor identified evidence that the agency overlooked in its previous evaluations, FDA reaffirms its earlier determination that the dosing in the second rat study was adequate for an assessment of the carcinogenic potential of acesulfame potassium (57 FR 6667 at 6669, see also 53 FR 28379, 28380).

With respect to dosing, one of CSPI's consultants asserted that the dose range in the second rat study was too narrow, citing ''[the] increased tumorigenesis at even the 'lowest' dose used * * *.'' FDA has previously concluded, however, that the data from the second rat study do not establish an association between tumors and treatment with ACK (53 FR 28379 at 28380 and 28381). The issue of tumor incidence in the second rat study is also discussed later in this document.

CSPI, in its NTP nomination package, also implies that the second rat study is inadequate because the subchronic testing of ACK, used as an aid in determining doses for the second rat study, did not conform in each and every respect to the standardized elements in the NTP guidelines. Specifically, CSPI stated that a subchronic study was not conducted in the same strain of rat as that used in the second rat study; CSPI also disagrees with the use, in the subchronic study, of fewer dose groups than the number NTP ''requires.''[30]

FDA disagrees. First, the agency notes that the purposes of subchronic testing are generally acknowledged to be twofold: To identify likely target organs in longer-term studies and to aid in determining doses for the longer-term testing. Second, as previously noted, the NTP document does not establish scientific or regulatory requirements for either subchronic or long-term toxicity testing, including carcinogenicity testing. In particular, the NTP document does not establish a subchronic testing regimen that must be followed in order for long-term testing to be valid. Moreover, FDA is not aware of any relevant guideline, including the NTP document, that states that deviations from the guidelines for a subchronic toxicity study conducted to determine appropriate dose levels in a subsequent carcinogenicity study necessarily invalidates the results of the carcinogenicity study.

Because CSPI has not provided any substantive information to support its assertions regarding the effect of the design of the ACK subchronic study on the validity of the long-term testing of ACK, it has provided no basis for FDA to reconsider its conclusions regarding the second rat study. Thus, FDA reaffirms its earlier conclusions that the dosing in the second rat study was appropriate for an assessment of the carcinogenic potential of ACK and that the study was suitable for a safety assessment of ACK (57 FR 6667 at 6669, see also 53 FR 28379 at 28380).

(2) Incidence of mammary tumors. In its NTP nomination package, CSPI stated that there was an increased incidence of mammary tumors in treated females in the second rat study. CSPI also claimed that ''* * * FDA discounted these data because [the] incidence was not strongly dose-related.'' CSPI thus implies that the lack of a strong dose-response was the only reason FDA concluded, in its previous evaluation, that the incidence of mammary tumors in female rats in the second rat study was not ACK-related. CSPI also criticizes the agency's use of historical control data in evaluating the results of the second rat study and asserts that more information on ''animals or test conditions'' (e.g., diets, animal husbandry) should have been obtained by FDA before using the data from ''previous studies'' conducted at the testing laboratory where the long-term studies of ACK were conducted.[31]

The agency notes that CSPI has previously raised these particular points in its objections to the dry uses final rule, and that FDA has previously addressed these points at length in responding to CSPI's objections (57 FR 6667 at 6674 and 6675). Specifically, in the original safety evaluation of ACK, FDA gave careful and detailed consideration to the incidence of mammary gland tumors in female rats in the second rat study. After a review of

Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP).''

[29] Other guidelines, such as those issued by EPA or the Organization for Economic Cooperation and Development (OECD), are also frequently used as resources in the design, conduct, and evaluation of toxicological tests (see for example, Ref. 22).

[30] CSPI specifically noted that the NTP document stipulates the use of five dose groups in addition to controls. FDA notes that the use of five dose groups is not a requirement, either for the scientific validity of the test, or for utility of the test in reaching a regulatory decision. FDA's own Redbook recommends (but does not require) the use of at least three dose groups in addition to controls; EPA's guidelines for subchronic toxicity testing contain a similar recommendation.

[31] One of CSPI's consultants criticized the petitioner's use of historical control data, commenting that the ''historical database'' is ''actually very small.'' CSPI's consultant did not, however, provide any information to indicate that FDA made inappropriate use of the relevant historical control data. (As previously noted, FDA's final pathology review memorandum, which discusses the agency's use of the historical control data, was apparently not included in the materials supplied by CSPI to its ten consultants.)

all the data, the agency concluded that mammary gland neoplasms were not associated with treatment with ACK. The preamble to the dry uses final rule cited several reasons for this conclusion, including the lack of a dose response. However, the agency also took into account the lack of evidence of progressive stages of mammary gland neoplasms and certain information obtained from historical control data (53 FR 28379 at 28381, see also Ref. 21).

With respect to the use of historical control data, the agency notes that, as in its objections to the dry uses final rule, CSPI mischaracterizes the information on historical controls and fails to acknowledge the detailed information on this point that FDA has evaluated. In its response to CSPI's objections, the agency noted that the historical control data were from the same type of studies conducted in the same laboratory, with the same strain of rat, under similar conditions, with continuity of pathological standards, and, furthermore, were from the same time period as the long-term studies evaluated in FDA's original review (57 FR 6667 at 6672 and Ref. 8 of that document). CSPI has presented no new information to support its allegation that FDA made inappropriate use of the relevant historical control data.

In summary, CSPI has presented no new evidence that would change the agency's previous conclusion that the occurrence of mammary gland neoplasms was not associated with treatment with ACK, and FDA incorporates its earlier discussion of the results of the second rat study, in full, into the safety determination on the present petition. Because CSPI has presented no new evidence to support its opinion nor identified evidence that the agency overlooked in its previous evaluations, FDA reaffirms its earlier determination that the data from the second rat study do not establish an association between the occurrence of neoplasms and treatment with ACK (53 FR 28379 at 28380 and 28381).

ii. *Issues not raised previously—(1) Incidence of respiratory disease.* In its NTP nomination package, CSPI claims that the incidence of respiratory disease in the animals used in the second rat study was too high[32] and questioned whether this study or the other long-term studies of ACK in rodents were adequate: ''The poor health of the animals used in the Hoechst studies raises the question as to whether any of the test results in the subchronic and chronic studies were good enough to be used.'' However, CSPI's submission neither identifies nor contains any data or other evidence that establish that the second rat study was, in fact, rendered inadequate for an assessment of ACK's carcinogenic potential by the incidence of respiratory disease in the test animals.

In its original evaluation of the safety of ACK, FDA carefully considered all of the data and information relevant to an evaluation of the long-term testing of ACK, including the general health of, and the incidence of respiratory disease in, test animals. In the case of the second rat study, FDA determined that the mortality rate was low in all dose groups and the signs of chronic respiratory disease randomly distributed (Refs. 21 and 23). Only in the case of the first rat study did FDA conclude that the incidence of respiratory disease in test animals confounded the test results to such an extent that such incidence contributed to a finding that the study was inadequate for assessing the safety of ACK (53 FR 28379 at 28380, see also Ref. 24). Because CSPI has not presented any new evidence to support its allegation nor has the organization identified evidence that the agency overlooked in its previous evaluations, FDA reaffirms its earlier determination that the second rat study was adequate for an assessment of the carcinogenic potential of acesulfame potassium.

(2) Assignment of animals to test groups. CSPI's NTP nomination package also raises a question regarding the procedure used to assign animals to the various test groups in the second rat study. CSPI implies that improper assignment procedures were used, which confounded the results of the second rat study. CSPI does not, however, provide any data or other information to support its speculation.[33]

In its original evaluation of the safety of ACK, FDA carefully considered all of the data and information relevant to an evaluation of the long-term testing of ACK, including the question of whether the assignment procedures or other aspects of the study designs compromised the suitability of the studies for an assessment of ACK's carcinogenic potential (Ref. 23). FDA concluded that the second rat study was adequate for an assessment of ACK's carcinogenic potential (Ref. 24, see also 53 FR 28379, 28380, and 57 FR 6667 at 6669). Because CSPI, in support of its allegations, has neither presented evidence that has not already been evaluated by the agency nor identified evidence that the agency overlooked in its previous evaluations, FDA reaffirms its earlier conclusion that the second rat study was adequate for an assessment of ACK's carcinogenic potential.

b. *The mouse study.* In concluding that ACK had been shown to be safe, FDA reviewed a long-term study conducted in Swiss mice in which ACK was administered at 0, 0.3, 1.0, or 3.0 percent in the test diet (''the mouse study''). FDA concluded that the results of this study showed no association between neoplastic disease and treatment with ACK (53 FR 28379 at 28380). In the preamble to the dry uses final rule, the agency explicitly discussed the adequacy of the mouse study with respect to study duration. FDA concluded that the length of the study was adequate because it had been conducted for the majority of the animals' lifespan (53 FR 28379 at 28380; see also 57 FR 6669 at 6670). Implicit in FDA's determination of the mouse study's adequacy was that the dosing levels in this study were appropriate (57 FR 6667).

i. *Issues raised previously—(1) Adequacy of the study length.* In its NTP nomination package, CSPI asserts that the mouse study was inadequate because the study was too short. To support its assertion, CSPI again refers to NTP ''requirements'': ''NTP generally requires that long-term studies on rats and mice be carried out for a 104-week period. Hoechst's study in mice lasted only 80 weeks.'' CSPI also presents some figures for survival levels in the various test groups (apparently derived from information in the final report for the mouse study, a document not included in CSPI's NTP nomination package) and remarks that ''survival of the mice was very high at 80 weeks.'' CSPI implies that the survival statistics suggest that the study was not conducted for the majority of the animals' lifespan. However, CSPI provides no data or other evidence to support its view.

FDA disagrees with CSPI's comments regarding the length of the mouse study. First, as previously noted in this document, the NTP document cited by CSPI does not establish either scientific or regulatory requirements. Second, in its original evaluation of the safety of ACK, FDA carefully considered all of the data and information relevant to an

[32] CSPI presents some figures for the incidence of pneumonia in the rats in the second study that are apparently derived from information in the final report for this study, a document not included in CSPI's NTP nomination package.

[33] In its NTP nomination package, CSPI remarks: ''* * * the likelihood that animals were of different ages when exposure to the test agent began, and that female animals may have been considerably older than males, makes it difficult to know what to make of the data.'' While CSPI speculates, at length, on the ages of the animals in the subchronic study, CSPI does not provide any substantive information to support its claims regarding the long-term study, nor does the organization provide an explanation of the significance of its allegations.

evaluation of the long-term testing of ACK, including the duration of, and survival data from, the mouse study. As previously noted, FDA concluded that length of the study was adequate because it had been conducted for the majority of the animals' lifespan (see 53 FR 28379 at 28380, see also Ref. 24.) Specifically, the agency found that at the time the study was conducted, survival of the Swiss strain of mice tended to decline severely between 18 and 24 months of age; thus, at that time, 80 weeks was representative of a time period corresponding to the majority of the animals' lifespan (Ref. 24).

CSPI previously raised this issue in its objections to the dry uses final rule, and the agency previously discussed this issue in responding to CSPI's objections (57 FR 6667). FDA incorporates that discussion, in full, into the safety determination on the present petition. Because CSPI has not identified any evidence that the agency overlooked in its previous evaluations, FDA reaffirms its earlier determination that the mouse study was of adequate duration for an assessment of the carcinogenic potential of ACK.

(2) Appropriateness of dosing. CSPI, in its NTP nomination package, comments on the appropriateness of the dosing in the mouse study: ''* * * the high survival at 80 weeks of mice fed 3% acesulfame potassium in the diet suggests that a higher dose might have been more in keeping with NTP recommendations.'' CSPI provides no other further explanation of the significance of its remarks, nor does it provide any data or other information that would establish that the dosing in the mouse study was too low to permit an assessment of ACK's carcinogenic potential. CSPI previously questioned the adequacy of the dosing in the mouse study in its objections to the dry uses final rule, and the agency previously discussed this issue in responding to CSPI's objections (57 FR 6667). FDA incorporates that discussion, in full, into the safety determination on the present petition. Because CSPI has presented no new evidence to support its opinion nor identified evidence that FDA overlooked in its previous evaluations, FDA reaffirms its earlier determination that the dosing in the mouse study was appropriate for an assessment of the carcinogenic potential of acesulfame potassium (see 57 FR 6667 at 6669).

ii. *Issues not raised previously—(1) Incidence of respiratory disease.* In its NTP nomination package, CSPI notes that respiratory infections occurred in the mice, but offers no specific supporting information.[34] In particular, CSPI neither identifies nor provides any data or other evidence regarding the actual incidence of respiratory infections in the mice, nor does it provide any information that would establish that the mouse study was rendered inadequate for an assessment of ACK's carcinogenic potential by the alleged incidence of respiratory disease in the test animals.

FDA notes that, in its original evaluation of the safety of ACK, the agency carefully considered all of the data and information relevant to an evaluation of the long-term testing of ACK, including the health of the test animals (Ref. 23). CSPI has presented no evidence to support its claim that has not already been evaluated by the agency nor identified evidence that the agency overlooked in its previous evaluations. Thus, FDA reaffirms its earlier conclusion that the mouse study was suitable for an assessment of ACK's carcinogenic potential (see 53 FR 28379 at 28380, and 57 FR 6667 at 6669).

(2) Histopathology data. CSPI also criticizes aspects of the histopathological examinations in the mouse study. CSPI specifically compares the extent of the histopathology review of tissues from animals from the low and mid-dose test groups with ''NTP requirements.'' CSPI implies that the histopathology review was not extensive enough and, thus, obscured the results of the mouse study. CSPI does not, however, provide any data or other information that would establish that the histopathological examinations of tissues from the animals in the mouse study were inadequate for an assessment of ACK's carcinogenic potential.

FDA notes that, in its original evaluation of the safety of ACK, the agency carefully considered all of the data and information relevant to an evaluation of the long-term testing of ACK, including the histopathology data from the mouse study. FDA concluded both that the mouse study was adequate for an assessment of ACK's carcinogenic potential and that the results of the study showed no association between neoplastic disease and treatment with ACK (53 FR 28379 at 28380 and 57 FR 6667 at 6669, see also Ref. 24). Again, because CSPI has presented no evidence to support its assertions that has not already been evaluated by the agency nor has CSPI identified evidence that the agency overlooked in its previous evaluations, FDA reaffirms its prior conclusion that the mouse study was suitable for an assessment of ACK's carcinogenic potential.

(3) Time-to-tumor. In its NTP nomination package, CSPI also claims that the data in the mouse study showed that ACK caused tumors: ''[i]n the mouse study, there was an early time-to-tumor reported for first tumors in treated animals relative to first tumors in controls.'' However, CSPI provides no additional data or other information to support this claim, nor does it provide further explanation of the significance of this alleged time-to-tumor differential.

In the original safety evaluation of ACK, FDA carefully considered all of the data in the mouse study, including data in the study report that showed an apparent ACK-related decreased time-to-tumor for first tumors. After an interim review of all the data, the agency concluded that the only finding of possible significance was an increase in lymphocytic leukemia in female mice in the highest dose group (Ref. 25). After detailed consideration of this reported finding, FDA concluded that this finding was not treatment-related and that no increase in neoplastic disease of the lymphoreticular system could be attributed to ACK (Ref. 24).

Because CSPI has presented no new evidence to support its opinion nor identified evidence that the agency overlooked in its previous evaluations, it has provided no basis for FDA to change its previous conclusions regarding the results of the mouse study. Thus, FDA reaffirms its earlier determination that the data from the mouse study do not establish an association between neoplasia and treatment with ACK (see 53 FR 28379 at 28380 and 57 FR 6667 at 6669).

c. *The first rat study.* In its evaluation of the original petition for the use of ACK, the agency reviewed a long-term study conducted in CIVO-bred Wistar rats in which ACK was administered at 0, 0.3, 1.0, or 3.0 percent in the diet (the ''first rat study''). In the preamble to the dry uses final rule, the agency concluded that the data from this study did not establish a carcinogenic effect of ACK (53 FR 28379 at 28380). However, the agency further concluded, because of deficiencies and confounding factors in this study (e.g., a high incidence of respiratory disease in the test animals), that it was ''inadequate for assessing the carcinogenic potential of the test compound or for any other purposes of

[34] As noted previously in this document, CSPI questions, in its NTP nomination package, the health of the test animals in all of the long-term studies of ACK in rodents. However, CSPI also cites the high survival rates of the test animals in the mouse study in support of some of the organization's criticisms of this study. The agency notes that CSPI's positions regarding animal health and survival rates in the mouse study are not entirely consistent.

a safety evaluation'' (53 FR 28379 at 28381).

Issues raised previously. In its NTP nomination package, CSPI asserts that, despite the prevalence of chronic respiratory disease in the test animals in the first rat study, the test results were suggestive of a carcinogenic effect of ACK.[35] Specifically, CSPI claims that the data in the first rat study showed a dose-dependent effect on incidence of lymphoreticular cancers of pulmonary origin and on time-to-tumor. In support of its claims, CSPI cites a single FDA interim review memorandum (Ref. 23). CSPI also asserts that the agency made inappropriate use of historical control data in evaluating the results of the first rat study.[36] With respect to the use of historical control data, CSPI merely expresses its opinion that more information on ''animals and test conditions'' (e.g., diets and animal husbandry) should have been obtained by FDA before using the data from ''previous studies'' conducted at the testing laboratory where the long-term studies of ACK were conducted.

The agency notes that the issue of a possible dose-dependent effect of ACK on the incidence of lymphoreticular tumors and on time-to-tumor was raised by CSPI in its letter to FDA dated September 23, 1987, and this issue was addressed by the agency in the preamble to the dry uses final rule (53 FR 28379). Specifically, the agency noted that, in the first rat study, there was a slightly higher incidence, and earlier appearance, of lymphoreticular tumors in dosed rats than in the concurrent control group. However, the agency concluded that under the circumstances of severe chronic respiratory disease, sampling limitations, and the very high rate of spontaneously-occurring lung tumors in this strain of rat, no conclusions could be made regarding any effect of ACK on the lungs (53 FR 28379 at 28380; see also Ref. 24).[37] FDA also notes that CSPI previously raised this particular issue in its objections to FDA's original approval decision on ACK, and the agency discussed these issues, at length, in responding to CSPI's objections (57 FR 6667 at 6671 and 6672). FDA incorporates those discussions, in full, into the safety determination on the present petition. Because CSPI has presented no new evidence to support its opinion nor identified evidence that the agency overlooked in its previous evaluations that would change the outcome of those evaluations, FDA reaffirms its earlier determination that the data from the first rat study do not establish a carcinogenic effect of ACK.

C. Summary of FDA's Response to Comments

In determining that ACK is safe for use in nonalcoholic beverages, FDA carefully considered all of the data and information in the present petition, as well as other information in its files, including relevant information from previous petitions for ACK. FDA has also carefully considered all of the issues raised in the comments on the present petition.

As previously noted in this document, many of the specific issues raised in the comments on the present petition are the same as those raised in earlier objections to the dry uses final rule, and the agency has previously considered and responded to these issues in detail (see 57 FR 6667). Also as noted, the comments supply no new information that would change any of the agency's prior conclusions on any of the issues previously raised. Likewise, with respect to specific issues raised in the comments on the present petition that have not been raised previously, the comments neither provide new evidence nor identify evidence that FDA has overlooked that would change the agency's conclusion that the use of ACK in nonalcoholic beverages is safe.

Because no outstanding issues in the comments undermine FDA's determination of safety, FDA is denying the requests that: (1) The petitioner be required to conduct additional testing of ACK or AAA, (2) the present petition be denied, and (3) all existing regulations permitting the use of ACK in food be revoked.

V. Conclusion of Safety

FDA has evaluated the data in the petition, published scientific literature, and other relevant material from its files and concludes that the use of ACK in nonalcoholic beverages is safe. Therefore, the agency concludes that § 172.800 should be amended as set forth below.

In accordance with § 171.1(h) (21 CFR 171.1(h)), the petition and the documents that FDA considered and relied upon in reaching its decision to approve the petition are available for inspection at the Center for Food Safety and Applied Nutrition by appointment with the information contact person listed above. As provided in § 171.1(h), the agency will delete from the documents any materials that are not available for public disclosure before making the documents available for inspection.

VI. Environmental Impact

The agency has carefully considered the potential environmental effects of this action. FDA has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

VII. Paperwork Reduction Act

This final rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VIII. Objections

Any person who will be adversely affected by this regulation may at any time on or before August 5, 1998, file with the Dockets Management Branch (address above) written objections thereto. Each objection shall be separately numbered, and each numbered objection shall specify with particularity the provisions of the regulation to which objection is made and the grounds for the objection. Each numbered objection on which a hearing is requested shall specifically so state. Failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held. Failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the

[35] Several of CSPI's ten consultants made similar remarks. None of these individuals, however, provided any substantive information in support of their remarks.

[36] Importantly, as in its objections to the dry uses final rule, CSPI mischaracterizes the information on historical controls and fails to acknowledge the information on this point that FDA evaluated. The agency has previously discussed, in detail, its use of historical control data in the evaluation of the first rat study in responding to CSPI's objections to the dry uses final rule. In its response to CSPI's objections, the agency noted that the historical control data were from the same type of studies conducted in the same laboratory, with the same strain of rat, under similar conditions, with continuity of pathological standards, and, furthermore, were from the same time period as the first rat study (57 FR 6667 at 6672).

[37] Because the first rat study was inadequate for use in assessing the carcinogenic potential of ACK, the petitioner conducted a second long-term study in a different strain of rat. This second rat study did not show lymphoreticular tumors in the lungs (53 FR 28379 at 28380).

objection. Three copies of all documents shall be submitted and shall be identified with the docket number found in brackets in the heading of this document. Any objections received in response to the regulation may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

IX. References

The following sources are referred to in this document. References marked with an asterisk (*) have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. References without an asterisk are not on display; they are available as published articles, books, and reports.

*1. Memorandum, from M. DiNovi, Chemistry Review Branch, to P. Hansen, Biotechnology Policy Branch, dated April 28, 1994.

*2. Memorandum to the file FAP 0A4212, from M. DiNovi, K. Ekelman, and P. Hansen, dated June 3, 1998.

*3. Memorandum, from M. DiNovi, Chemistry Review Branch, to P. Hansen, Biotechnology Policy Branch, dated November 9, 1994.

*4. Memorandum, from K. Ekelman, Division of Health Effects Evaluation, to P. Hansen, Regulatory Policy Branch, dated June 2, 1998.

5. Green, W. L., ''Mechanisms of Action of Antithyroid Compounds,'' pp. 77–87 in: *The Thyroid*, edited by S. C. Werner and S. H. Ingbar, Harper & Row, New York, 1978.

6. Hill, R. N. et al., ''Thyroid Follicular Cell Carcinogenesis,'' *Fundamental and Applied Toxicology*, 12:629–697, 1989.

*7. Report, Borzelleca, J. F., C. C. Capen, M. S. Christian, and B. N. LaDu, ''Summary and Consensus of the Acesulfame K Scientific Expert Panel on the Safety of Acetoacetamide-N-Sulfonic Acid and Acetoacetamide,'' dated October 13, 1992.

*8. Letter, from C.C. Capen, Ohio State University, to J. Simplicio, Hoechst-Celanese Corp., dated December 6, 1991.

9. Gaylor, D. W., and R. L. Kodell, ''Linear Interpolation Algorithm for Low Dose Assessment of Toxic Substances,'' *Journal of Environmental Pathology and Toxicology*, 4:305–315, 1980.

10. National Academy of Sciences/National Research Council, ''Risk Assessment in the Federal Government: Managing the Process,'' Washington, DC, 1983.

11. Lorentzen, R. J., ''FDA Procedures for Carcinogenic Risk Assessment,'' *Food Technology*, pp. 108–111, 1984.

12. Gold, L.S. et al., ''Target Organs in Chronic Bioassays of 533 Chemical Carcinogens,'' *Environmental Health Perspectives*, 93:233–246, 1991.

13. McConnell, E. E., ''Thyroid Follicular Cell Carcinogenesis: Results from 343 2–Year Carcinogenicity Studies Conducted by the NCI/NTP,'' *Regulatory Toxicology and Pharmacology*, 16:177–188, 1992.

14. IRIS (1995), Cincinnati: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, EPA.

15. Curran, P. G., and L. J. DeGroot, ''The Effect of Hepatic Enzyme-Inducing Drugs on Thyroid Hormones and the Thyroid Gland,'' *Endocrine Reviews*, 12(2):135–150, 1991.

16. Donaich, I., ''Aetiological Considerations of Thyroid Carcinoma,'' vol. 6, pp. 55–72, in: *Tumors of the Thyroid Gland*, edited by D. Smithers, E & S Livingstone, Edinburgh, 1970.

17. Capen, C. C. and S. L. Martin, ''Mechanisms that Lead to Disease in the Endocrine System in Animals,'' *Toxicologic Pathology*, 17:234–249, 1989.

18. *Handbook of Carcinogenic Potency and Genotoxicity Databases*, edited by L. S. Gold and E. Zeiger, CRC Press, Boca Raton, FL, 1997.

19. Goddard, M. J., D. J. Murdoch, and D. Krewski, ''Temporal Aspects of Risk Characterization,'' *Inhalation Toxicology*, 7:1005–1018, 1995.

20. Kodell, R. L., D. W. Gaylor, and J. J. Chen, ''Using Average Lifetime Dose Rate for Intermittent Exposures to Carcinogens,'' *Risk Analysis*, 7:339–345, 1987.

*21. Memorandum, from F. Hines, Diagnostic Pathology Branch, to L. Taylor, Additives Evaluation Branch, dated June 6, 1986.

22. ''Health Effects Test Guidelines,'' U.S. EPA, June, 1996.

*23. Memorandum, from L. Taylor, Additives Evaluation Branch, to P. McLaughlin, Petitions Control Branch, dated November 17, 1982.

*24. Memorandum, Cancer Assessment Committee (CAC) (covers conferences of November 21, 1983, February 21, 1985, December 12, 1985, and June 17, 1986, and information in Ref. 25 of this document).

*25. Memorandum, from L. Taylor, Additives Evaluation Branch, to Cancer Assessment Committee, dated June 19, 1986.

List of Subjects in 21 CFR 172

Food additives, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 172 is amended as follows:

PART 172—FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION

1. The authority citation for 21 CFR part 172 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 342, 348, 371, 379e.

2. Section 172.800 is amended by adding paragraph (c)(13) to read as follows:

§ 172.800 Acesulfame potassium.

* * * * *

(c) * * *

(13) Nonalcoholic beverages, including beverage bases.

* * * * *

Dated: June 29, 1998.

Michael A. Friedman,

Acting Commissioner of Food and Drugs.

[FR Doc. 98–17700 Filed 6–30–98; 10:34 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 172

[Docket No. 93F–0286]

Food Additives Permitted for Direct Addition to Foods for Human Consumption; Acesulfame Potassium

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule; response to objection, confirmation of effective date.

SUMMARY: The Food and Drug Administration (FDA) is overruling the objection that it has received on the final rule that amended the food additive regulations to provide for the safe use of acesulfame potassium (ACK) as a nonnutritive sweetener in alcoholic beverages. After reviewing the objection to the final rule, the agency has concluded that the objection does not provide a basis for revoking the amendment to the regulation. Therefore, FDA is confirming the effective date for the final rule. The final rule was issued in response to a food additive petition filed by Hoechst Celanese Corp.

DATES: The effective date of the final rule published at 60 FR 21700 is confirmed as May 3, 1995.

FOR FURTHER INFORMATION CONTACT: Patricia A. Hansen, Center for Food Safety and Applied Nutrition (HFS–206), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–418–3093.

SUPPLEMENTARY INFORMATION:

I. Introduction

In the **Federal Register** of May 3, 1995 (60 FR 21700), FDA issued a final rule amending its regulations to permit the use of acesulfame potassium (ACK) as a nonnutritive sweetener in alcoholic beverages (the ''alcoholic beverages final rule''). This amendment of the regulation, codified at 21 CFR 172.800(c)(12), was issued in response to a food additive petition (FAP No. 3A4391) filed by Hoechst Celanese Corp. FDA based its decision to permit the use of ACK in alcoholic beverages on the data in this petition and other relevant information in its files, including data and information from