EVALUATION OF THE HEALTH ASPECTS OF CARAMEL

AS A FOOD INGREDIENT

JANUARY 1973

Prepared for

Bureau of Foods
Food and Drug Administration
Department of Health, Education, and Welfare
Washington, D.C.

(This report has not been approved for public release.)

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Life Sciences Research Office
Federation of American Societies for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014
This report is one of a series of evaluations of the health aspects of the Generally Recognized as Safe (GRAS) food substances that are being made by the Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (FASEB) under contract with the Food and Drug Administration of the U.S. Department of Health, Education, and Welfare. The Federation recognizes that the safety of GRAS substances is of national significance, and its resources are particularly suited to marshalling the opinions of knowledgeable scientists to assist in these evaluations. The Life Sciences Research Office, established in 1962 to make scientific assessments in the biomedical sciences, is conducting these studies.

Qualified scientists were selected as consultants to make a continuing review, analysis, and evaluation of the available information on each of the GRAS substances. These scientists, designated the Select Committee on GRAS Substances, were chosen for their competence and judgment with due consideration for balance and breadth in the appropriate professional disciplines. Members of the Select Committee on GRAS Substances who have contributed to this report are named in Section VII. The Select Committee's evaluations are being made independently of FDA or any other governmental or nongovernmental group.

These reports are approved by the Select Committee prior to submission to FDA. Although most LSRO consultants are members of FASEB constituent societies, the reports do not necessarily reflect the views of the Federation as a corporate body or carry the endorsement of the members of its constituent societies.

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Life Sciences Research Office
FASEB
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I. INTRODUCTION

Under terms of FDA Contract 72-85, FASEB's Life Sciences Research Office was requested to evaluate the health aspects of using caramel as a food ingredient, primarily on the basis of information contained in a monograph furnished by FDA (1), summarizing the world's scientific literature from 1920 through 1970, and in certain supplemental documents available as of January 1973. Caramel is one of the food substances that has been generally recognized as safe (GRAS) under the provisions of Section 121.101 of the Code of Federal Regulations (21 CFR 121.101, revised January 1, 1972).

As indicated in the Food, Drug and Cosmetic Act [21 USC 321(s)], GRAS substances are exempt from the requirement of premarking clearance for food additives. It is stated in 21 CFR 121.1 that GRAS means general recognition of safety by experts qualified by scientific training and experience to evaluate the safety of substances on the basis of scientific data derived from published literature. This section of the Code also indicates that expert judgment is to be based on the evaluation of results of credible toxicological testing, or for those substances used in food prior to January 1, 1958, on a reasoned judgment founded in experience with common food use, and is to take into account reasonably anticipated patterns of consumption, cumulative effects in the diet, and safety factors appropriate for the utilization of animal experimentation data. It is recognized further (21 CFR 121.3) that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

The Select Committee on GRAS Substances of LSRO is making its evaluations of these substances in full recognition of the foregoing provisions. In reaching its decisions the Select Committee, with the concurrence of FDA, is relying primarily on the absence of substantive evidence indicating the existence of a significant risk to the public health, and realizes that a decision, based on reasoned judgment, is expected even in instances where the available information is qualitatively or quantitatively limited.

In this context, the LSRO Select Committee on GRAS Substances has reviewed the available information on caramel and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of caramel under the Federal Food, Drug and Cosmetic Act.
II. BACKGROUND INFORMATION

As manufactured and used commercially, caramel (also known as caramel color) is the amorphous dark brown material, either powdered or liquid, resulting from the controlled heating of various food grade carbohydrates with various acids, bases or salts. Caramel is used commercially to impart a brown color to certain foods and beverages. It does not occur naturally, but is formed in many foods as a consequence of cooking or sterilization (1,2). Caramel flavoring, produced commercially in the home, owes its color to the caramelization of sugar during the heating process.

Caramel is a mixture of carbohydrate polymers whose structures have not been elucidated. The composition and physical properties of caramel vary with the nature of the manufacturing process (1) and upon storage (16). Specifications for the production and composition of food grade caramel, as given in the Code of Federal Regulations (3), include limitations on lead, arsenic and mercury content of 10, 3, and 0.1 ppm, respectively. The carbohydrates that can be used for production of caramel color are dextrose, invert sugar, lactose, malt syrup, molasses, starch hydrolysates and fractions thereof, and sucrose. The Code of Federal Regulations also limits the use of added caramel to foods for which standards of identity have not been promulgated, unless added color is authorized by such standards.

Caramel color is currently used in the following food categories, in amounts ranging from 54.3 to 0.0002 percent, arranged in decreasing order of caramel content: gravies, reconstituted vegetables (4.8-2.1%), seasoning and flavors, condiments and relishes (1%), baked goods (0.43-0.23%), processed vegetables, frostings, soft candy, sweet sauce, snack foods, alcoholic beverages, meat products, poultry, nonalcoholic beverages (0.17-0.15%), soups, frozen dairy products, gelatins and puddings, breakfast cereals (0.12%), other grain products, fats and oils, processed fruit, fish products, hard candy, instant coffee or tea (0.02-0.005%), nut products, and cheese (4). The Select Committee has no information to indicate whether the percentage of caramel in the foregoing food categories has changed significantly in recent years.

The total amount of caramel used in foods did not increase significantly between 1960 and 1970 (4).

III. CONSUMER EXPOSURE DATA

A comprehensive survey by a National Research Council (NRC) subcommittee has provided information on the possible daily human intake of caramel in the total diet, as shown in the following table for individuals in
various age groups (4). The Select Committee has converted these figures to possible intake per kilogram of body weight.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Possible daily intake</th>
<th>Per kilogram of body weight*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Average mg</td>
<td>Maximum mg</td>
</tr>
<tr>
<td>0-5 mos.</td>
<td>82 mg</td>
<td>229 mg</td>
</tr>
<tr>
<td>6-11 mos.</td>
<td>1,111 mg</td>
<td>3,028 mg</td>
</tr>
<tr>
<td>12-23 mos.</td>
<td>2,580 mg</td>
<td>6,812 mg</td>
</tr>
<tr>
<td>2-65+ yrs.</td>
<td>5,838 mg</td>
<td>14,149 mg</td>
</tr>
</tbody>
</table>

*Calculations based on an average weight of 60 kg for an adult (5) and the following estimated weights of infants by age groups: 0-5 mos., 5 kg; 6-11 mos., 8 kg; and 12-23 mos., 11 kg (6).

It is recognized that the figures calculated for the daily intake of caramel per kg of body weight in the age group 2-65+ years could be deceptively low, since the majority of individuals from age 2 to maturity will probably weigh less than 60 kg. Thus the daily intake of caramel for children could be significantly higher than the figures indicated. For example, a child weighing 20 kg could consume, on the average, 292 mg per kg per day rather than 97 mg, and at a maximum, 707 mg per kg per day rather than 236 mg.

However, such deviations from the figures in the table must also be considered in respect to total production and use of caramel. The data developed by the National Research Council subcommittee are based on (a) a survey of the frequency of eating various food products, (b) a determination of the portion size of these food products, and (c) a survey of food producers to determine the percentage use of caramel in these food products (4). The NRC subcommittee has pointed out that its calculations of intakes in most cases are overstated, often by considerable margins.* That this is true in the case of caramel is borne out by

*An explanation for such overstatements is detailed in Section XI, "Significance and Use of Data in Safety Evaluations," of the NRC subcommittee's report (4). The Select Committee finds this explanation reasonable, and concurs in the first recommendation in Section XII of the same report, that "In order to conduct a more accurate survey on the intake of substances used in food processing, food consumption data collected specifically for this purpose are needed."
the following calculation: Other NRC data show that in 1970 the use of caramel for food purposes in the United States was 37,179,574 pounds (16,899,806 kg) (4). It is stated that these reported figures comprise between 60 and 70 percent of the total actual poundage used in food. On the basis of 60 percent adjusted to 100 percent (28,166,343 kg) and a U. S. population of 200 million, the per capita per day average intake would be 386 mg of caramel. This means that not nearly enough caramel is used by the food industry to permit daily human intakes as high as is indicated in the table above. For example, the average per capita daily intake of 5,838 mg of caramel indicated in the table would require the use of 426 million kg (937 million pounds) of caramel annually.

In the light of these considerations, the Select Committee regards the figures given in the table as levels that are highly unlikely to be achieved by any of the age groups, but are more likely to be generous overestimates of the caramel content of the human diet.

The Joint FAO/WHO Expert Committee on Food Additives has established a temporary acceptable daily intake level of caramel colors made by the ammonia process as 0 to 100 mg per kg body weight (20).

IV. BIOLOGICAL STUDIES

The inherent compositional variability of commercial food grade caramels, made, as they can be, from a variety of sugar sources by use of a variety of catalysts and under variable conditions of temperature and duration of heating, must be recognized in evaluating the biological and potential toxic effects reported in the literature. Careful control of processing is exercised to achieve color consistency, and some caramel manufacturers emphasize the necessity of using pure grades of carbohydrate in preparing the product (7). Freedom of food grade caramel from certain nitrogenous compounds could be significant, since some ammoniated feed supplements for cattle, prepared by a process similar to that used in the ammonia process of caramel manufacture, have been reported to produce toxic effects due principally to the presence of 4-methylimidazole (8,9). This compound has been found to occur in some food caramels at a level of 0.002 to 0.02 percent (10). Based on other published work on the toxicity of methylimidazoles (21), these levels appear to be insignificant with regard to the possible toxicity of food grade caramel. The Joint FAO/WHO Expert Committee on Food Additives (20) has expressed the need for more precise information on the trace amounts of nitrogen-containing heterocyclic compounds in caramel colors made by the ammonia process, and indicates that it has prepared a revised specification for publication in due course. A copy of this proposed revised specification sent in response to a request to FAO, indicates limitations of not more than 0.5 percent ammoniacal nitrogen and not more than 200 mg per kg of 4-methylimidazole in caramel color made by the ammonia process.
There is very little information on the absorption, metabolism, and excretion of caramel color by animals or man. Observations on rats suggest that only about one-third of the color-yielding components of caramel fed at levels of 3.3 to 6.6 g per day for 100 days are absorbed from the gastrointestinal tract (11). The caramels used were commercial products derived from starch hydrolysate using ammonium hydroxide and sulfuric acid as catalysts. Caramel was tried as a sugar substitute in diabetics in 1914, and has been studied in man as a substitute carbohydrate (12). Bahrs has reviewed this study and also has noted that doses greater than 100 g per day induce diarrhea and reduce absorption of caramel. The absorbed portion of caramel is at least partially metabolized as utilizable carbohydrate; the non-utilized portions which are absorbed are excreted to a large extent in the urine (13).

The following short-term animal feeding studies (conducted for less than half of the life span of the species) are relevant.

Acute toxicity levels for caramel have not been established. In one report, male and female Sprague-Dawley albino rats were fed a single dose by intubation of solutions of three commercial types of caramel coloring made from starch hydrolysate or molasses (15). Doses ranged from 13 to 20 g per kg and the animals were observed during 14 days following administration. It was concluded that the LD₅₀ for rats exceeded 20 g per kg for each of these three types of caramel.

Male and female Sprague-Dawley rats were fed daily, by intubation, the equivalent of 500 to 800 mg of caramel as commercial caramel solutions (17). Dosing continued for 21 days followed by two weeks of observation. The seven different caramels were made from starch hydrolysate using a variety of catalysts. No significant adverse effects were noted in gross or microscopic pathological examination of the rats.

Male and female Sprague-Dawley weanling rats were fed 10 g per kg of each of three commercial caramel colors daily for 90 days (18). The caramels were made from starch hydrolysate or molasses using several catalysts. No gross or microscopic pathology was observed. Cumulative feed efficiency was lower in animals fed caramel (76 to 81 percent of the controls).

Male and female weanling Sprague-Dawley rats were fed two commercial caramels derived from starch hydrolysate using ammonium hydroxide, sulfuric acid and bisulfite salts as catalysts (19). Dosages were 5 and 10 g per kg daily for 90 days. No abnormalities were noted in comparing the experimental animals with the controls.

Male and female adult beagles were fed a commercial "single-strength acid-fast" caramel at levels of 6, 12.5, and 25 percent by weight (as high as 55 g per kg per week) in lab chow for 90 days (14). No abnormalities were noted in the urine, blood, liver and kidney function, organ weights, or in gross examination of organs and glands.
Feeding studies designed to elicit evidence of carcinogenicity, mutagenicity or teratogenicity, or adverse effects on lactation, vital enzymes, or metabolic mechanisms have not been reported.

One long-term animal study has been reported (11). Wistar rats, fed as much as 12.5 g per kg per day of six different commercial caramels for 300 days, remained unaffected and exhibited normal reproduction. Second generation animals, fed about the same amount for 100 days, exhibited no abnormalities (11).

One study on man has been reported, wherein a single subject consumed from 60 to 120 g of caramel per day (up to 1.4 g per kg) over a 20 day period (13). No untoward effects were observed.

V. OPINION

Interpolation of data from long-term feeding studies in the rat and from consumer exposure data indicates that the highest no-effect level reported in laboratory animal feeding of caramel is approximately 130-fold the usual level of man's daily intake. The highest no-effect level reported in laboratory animal feeding is approximately 50-fold the intake level if an individual's diet were to consist only of those foods containing the greatest amounts of caramel. Based on the one published experiment in man, the corresponding figures are approximately 15-fold and 6-fold.

The Select Committee believes that the level of heterocyclic nitrogen-containing compounds in caramel colors should not be left to chance. While all available information indicates that the levels of nitrogen-containing heterocyclic compounds in commercial caramel colors as currently used is well below that which could be toxic to the consumer, a limitation with respect to nitrogen-containing compounds in the specification for food grade caramel would avoid possible future problems in this regard.

The Select Committee has weighed the foregoing and concludes that:

There is no evidence in the available information to show that caramel as a food ingredient constitutes a hazard to the general public when used at levels that are now current or might reasonably be expected in future.
VI. REFERENCES CITED


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18. Chacharonis, P. 1963. Subacute oral toxicity study in rats on caramel colorings (25A-1, 30B-0, and 30F-1). Report prepared for Union Starch and Refining Co., Granite City, Ill. [33 pp.] (Copy supplied with ref. no. 1.)


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March 16, 1973

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