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FROM: (Name, org. symbol, Agency/Post) <i>A. P. Brunetti</i>	Room No.—Bldg.
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OPTIONAL FORM 41 (Rev. 7-76)
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FPMR (41 CFR) 101-11.206

FAP 2A3661

SEARLE RESEARCH AND DEVELOPMENT

ASPARTAME FOR USE AS A SWEETENER IN CARBONATED
BEVERAGES

PETITION CONTROL VOLUME 1 of 4

ASPARTAME IN CARBONATED BEVERAGES

I. INTRODUCTION

Aspartame (L-aspartyl-L-phenylalanine methyl ester) is a general purpose food additive that functions as a sweetener and flavor enhancer and was approved on July 24, 1981 (21 CFR 172.804). Aspartame (APM) is now proposed for use as a sweetener in liquid carbonated beverages in quantities necessary to achieve the intended effect. This petition will address the potential consumption and the functionality of APM in liquid food systems.

CONSUMPTION: In estimating APM consumption from the proposed extended use (carbonated beverages), an analysis is presented in Appendix 6 utilizing Market Research Corporation of America (MRCA) and US Department of Agriculture (USDA) 1977-78 data.

These estimates were derived in a manner similar to the March 1976 General Foods Corporation analyses of potential APM consumption that was submitted to the Hearing Clerk Docket No. 75-0355 Volume 103 and used by the Commissioner in his decision for the approval of APM.

Both analyses were based on MRCA data collected from actual dietary records kept by 4,000 households over a 2 week period staggered throughout the year and serving sizes based on food intake data from USDA Nationwide Food Survey. The data are presented by age groups and reported as percentiles to account for both the average and heavy user.

The projected consumption was calculated for all presently approved APM uses (21 CFR 172.804), for carbonated beverages alone, non-carbonated beverages and combinations of all categories with the assumption that all individuals would replace ALL of their present sweeteners and sweetened products with APM-containing products, and that ALL eatings in a particular food category would contain APM. As a result this assumption obviously greatly overstates the potential APM consumption.

If APM were to replace ALL sugar and saccharin in the several hundred products comprising the currently approved food categories, the mean potential exposure would range from 1.0 to 6.6 mg/kg/day, depending on age (the mean for all ages being 1.9 mg/kg/day), (Table 1, pg 10, Appendix 6). Heavy users of these foods (90th percentile of intake) might consume between 2.9 and 17 mg/kg/day (the level for all ages combined being 4.8 mg/kg/day), and the intake of very heavy users, consuming at the 99th percentile, might be between 6.5 and 38 mg/kg/day (the level for all ages being 17 mg/kg/day). The highest levels in relation to body weight are seen in the 2-4 years age-group, as is generally the case with any food.

If APM were also approved for use in carbonated beverages and if ALL sugar and ALL saccharin in these drinks were to be replaced by APM, such uses would add 0.95 mg/kg to the daily mean consumption of APM in the lowest intake age group (18 years +), and 3.3 mg/kg in the highest intake age group (2-4 years). In the heavy users (90th percentile) it would increase by 2.2 mg and 6 mg/kg respectively.

APM Consumption at 90th percentile

mg/kg/day

Age Group	currently approved uses	carbonated beverages plus currently approved uses
0-23 mos	11	15
2-4 yrs	17	23
5-6 yrs	13	17
7-8 yrs	11	15
9-12 yrs	7.5	11
13-17 yrs	4.9	8.0
18 yrs +	2.9	5.1
All ages	4.8	8.1

The very heavy user level (99th percentile) would increase by 3.5 mg/kg in the 18 years + group and by 6 mg/kg in the 2-4 years group (Table 1, pg 11, Appendix 6).

Although the projected amount of APM consumed by the heavy user exceeds the acceptable daily intake determined in 1973, data from human beings previously reviewed by the Agency and the Commissioner document that even at the projected unrealistically high intake levels, APM is safe. It has been established by clinical studies (L.D. Stegink et al, J. Nutr. 110 (1980) 2216) that even at abuse levels of 200 mg/kg, acute ingestion of APM results in blood levels of aspartate plus glutamate well below those (100 umol/dl) found acceptable by the Agency (FDA communication to Searle July 14, 1982) and "the remarkably low amount of amino acid intake which would result, from even the 99th percentile of estimated aspartame consumption, in relation to the prevalence of these same amino acids in common protein foods," (46FR 142:38287, July 24, 1981).

2 developed
Cancer
during
study

In chronic studies in normal adults and children, diabetics, obese, and PKU heterozygote adults, 1.8 gm APM/day were consumed for 13-21 weeks with no evidence of adverse effects. No clinically significant differences were noted in the clinical parameters measured: liver function, renal function, hematologic status including serum glucose and insulin or plasma levels of phenylalanine and tyrosine. No discernible effects of APM alone or in comparison to sucrose and/or placebo were reported from the 322 adults and children ingesting APM on a chronic basis (FAP 3A2885, Volumes E-60, 61, 64, 65 and 67).

No

Because many food additives have not been clinically studied prior to approval, the FDA has established a 100 fold safety factor below the "no harm" level in animals for projecting an acceptable intake by human beings (21 CFR 170.22).

The data from clinical studies of APM make the need for a 100 fold safety factor based on toxicity tests in animals less relevant. However, projected consumption of APM still falls within the 100 fold safety factor even at the overstated estimates at the 90th percentile of use.

dog
"Conservatively we have taken the 2gm/kg test level in rat and dog as a 'no effect' level. However, APM at levels of 4 and 8gm/kg were fed to rats and up to 4gm/kg to dogs. The effects seen at these higher levels can be considered minimal..." (memorandum Dr. C. J. Kokoski, April 11, 1974 p.12). Additionally, the long-term animal studies of diketopiperazine were reviewed by the Bureau of Foods in 1975 and no-effect levels of 3 gm/kg (rat) and 1 gm/kg (mouse) were established. me

As recognized by the Bureau of Foods Toxicology opinion the effects at 4 gm/kg/day in animal studies were minimal and without harm. This conclusion was arrived at independently by both the Joint FAO/WHO Expert Committee (JECFA) and the Canadian Health Protection Branch (HPB) in their reviews.

JECFA in its review of Searle's safety data assigned an acceptable daily intake level of 40 mg/kg based upon the two 104 week rat studies and the 110 week mouse study. This level was also accepted by the HPB which in its letter of intent to approve aspartame stated that "Based on the safety data available at that time an acceptable daily intake of 40 mg/kg body weight per day was established. This would permit all of the requested uses [including carbonated beverages] for which the Health Protection Branch had received a submission," (HPB I.L. 602, July 31, 1981) and "The data on the safety of Aspartame are the most comprehensive ever received by the Health Protection Branch in support of a food additive," (HPB I.L. 564, September 12, 1979). ma

In his decision on APM, the Commissioner, based on his review of the data, stated "Aspartame is being approved only because the available data establish that the maximum projected consumption of aspartame [34 mg/kg] is still far, far below any level even suspected of being toxic." (46 FR 142:38303, first column, 3rd paragraph).

Therefore, the expansion of APM uses to liquid food systems will not compromise the well-established safety margin as documented by human and animal studies.

Under conditions of normal use within the beverage industry, APM is and will be a functional sweetener.

Data from beverage industry sources indicate that a typical carbonated beverage sweetened with either sucrose or saccharin is consumed within three months of manufacture. Typically, the unsweetened beverage concentrate is prepared by a supplier. The bottling company carbonates, adds the sweetener and packages in one day. Normal warehouse inventory is turned over every two weeks with delivery to the retail stores weekly. Storage and delivery are conducted at ambient temperatures.

Fountain syrups are formulated with the basic beverage base and the sweetener at syrup branches and packaged immediately for distribution. All storage and delivery are performed at ambient temperatures. Ultimate consumption usually occurs within two to three months of manufacture.

As described below, APM-sweetened beverages remain acceptable over a range of APM concentrations and storage conditions.

II. APM STABILITY - SENSORY EVALUATION

To
methanol
The satisfactory stability of APM (as the neat chemical and in dry food systems) has been documented (volume A-2 of FAP 3A2885). When added to liquid systems, APM undergoes hydrolysis and cyclization at a rate that is dependent on pH and temperature.

To evaluate the rate of APM degradation and its effect on functionality the following studies were conducted in 1981-2: 1) a sensory evaluation and chemical stability study of APM in carbonated beverages and 2) a chemical stability study of APM in syrups. These studies are summarized below and the full reports are contained in the Appendices. In 1975 a sensory evaluation of the acceptance of varying concentrations of APM was performed and is summarized in Part III. Concomitant chemical stability analyses were not conducted.

1.a. CHEMICAL STABILITY METHODS

CARBONATED BEVERAGES: Four different flavors of ready-to-drink carbonated beverages sweetened only with APM and one with both APM and saccharin were studied. The beverages contained the following APM and saccharin concentrations at the start of the study:

Flavor	APM (mg/100 ml)	12oz Serving (mg)	Saccharin (mg/100 ml)	pH
Cola	57.7	197 mg	-	3.05
Lemon-Lime	50.1	171 mg	-	3.72
Orange	92.6	316 mg	-	3.49
Root Beer	60.5	200 mg	-	4.59
Cola	13.7	46 mg	14.5	2.83

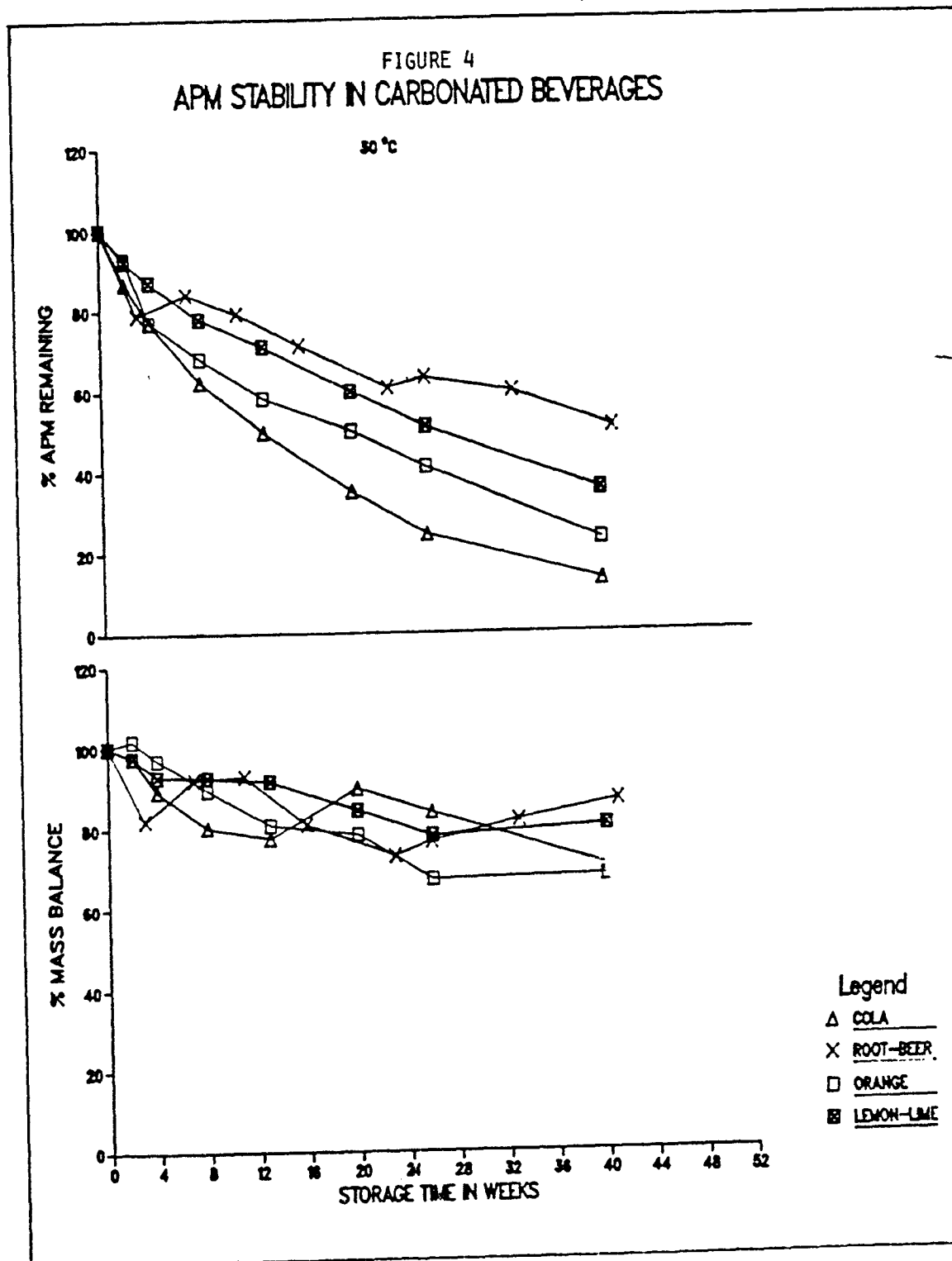
These levels were chosen through the use of sensory screening panels and were determined as having acceptable sweetness. APM or APM plus saccharin was added by commercial bottling firms to the flavor formulations in lieu of sucrose. The beverages were packaged in standard glass bottles with either crown or screw caps.

Bottles of each carbonated flavor were stored at 55°, 40°, 30°, 20° and 5°C with the exception of the cola containing APM plus saccharin which was stored at 55°, 40° and 20°C.

Samples for chemical stability were analyzed at the same time points as specified in the sensory evaluation protocols.

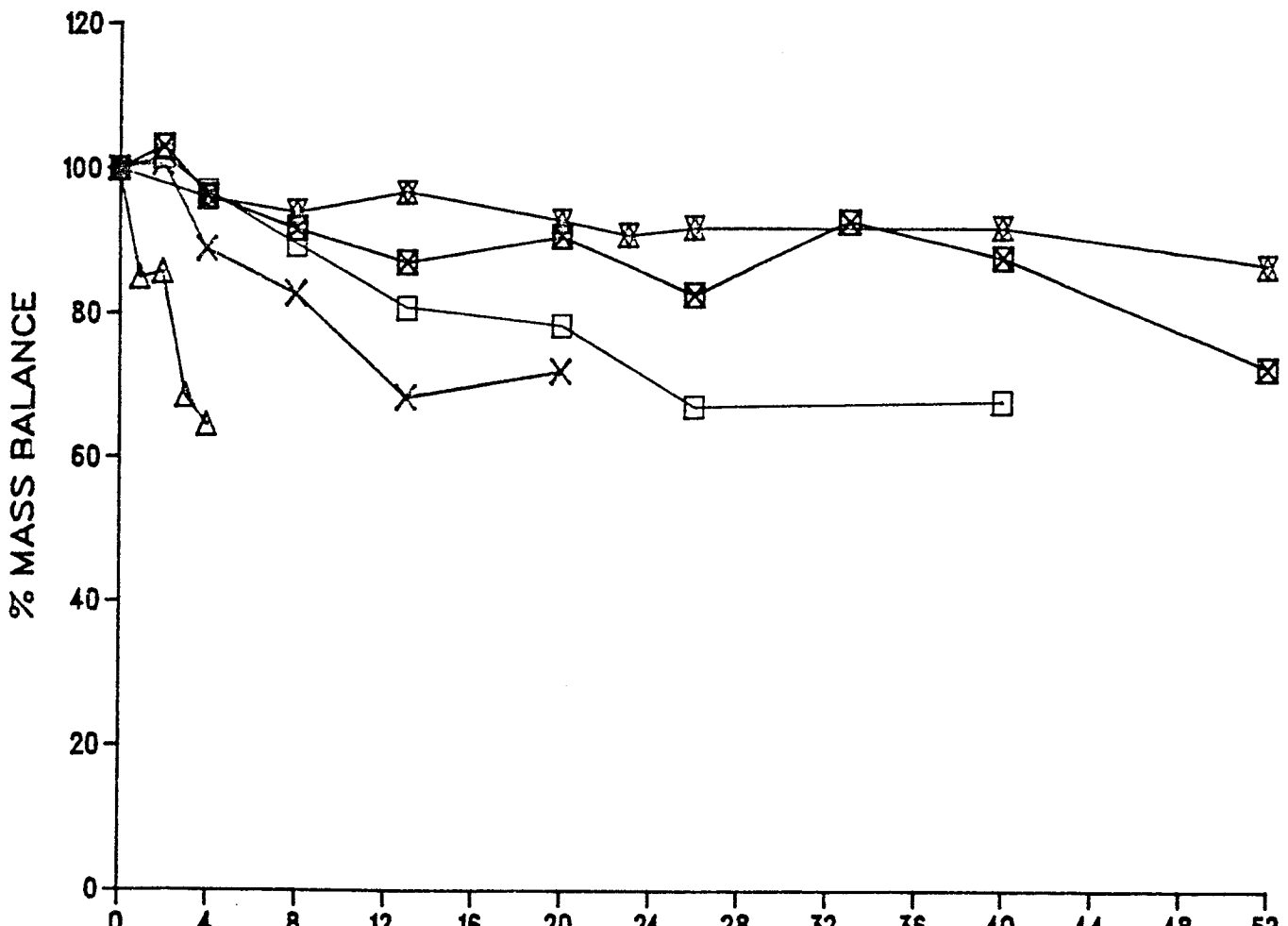
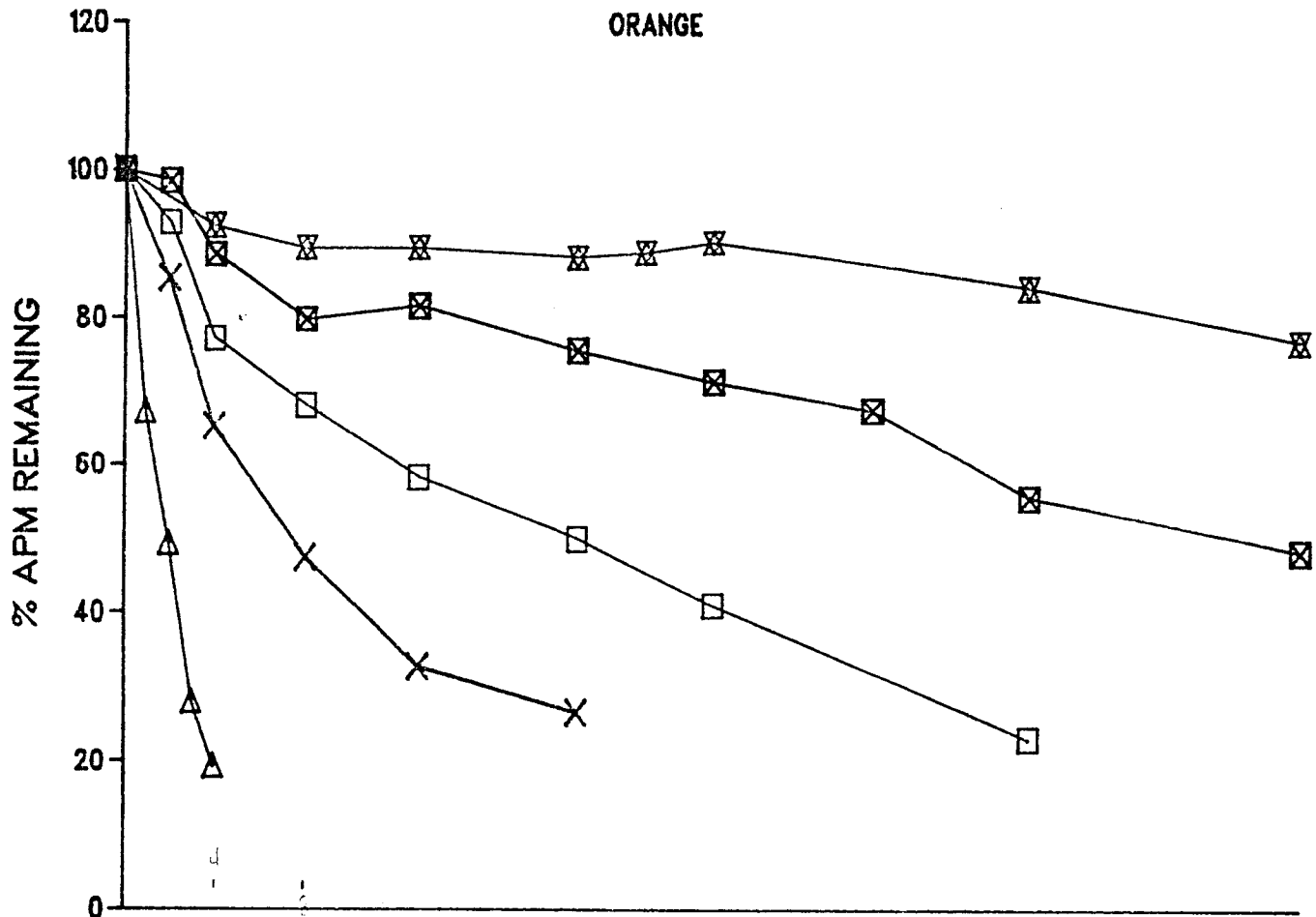
The 55° and 40°C temperature samples were utilized for identification of degradation products and were not included in the sensory evaluation protocol. For products stored at 30°C, analyses were performed through 20 weeks for orange, lemon-lime, and cola and through 23 weeks for the root beer. Chemical analyses were conducted through 40 weeks for orange and lemon-lime, 41 weeks for root beer and 52 weeks for cola beverages stored at 20° and 50C.

With the exception of the APM plus saccharin sweetened cola, the mass balance was calculated at each study point as a percentage of the initial quantity of APM. Since PM and beta-APM were not identified and therefore not quantified until later in the study, the percent recovery in some cases is lower for the early time periods. The percent recovery in relation to the percent of APM remaining for all four carbonated beverages at 30°C storage temperature is illustrated in Figure 4.



APM STABILITY IN CARBONATED BEVERAGES

ORANGE

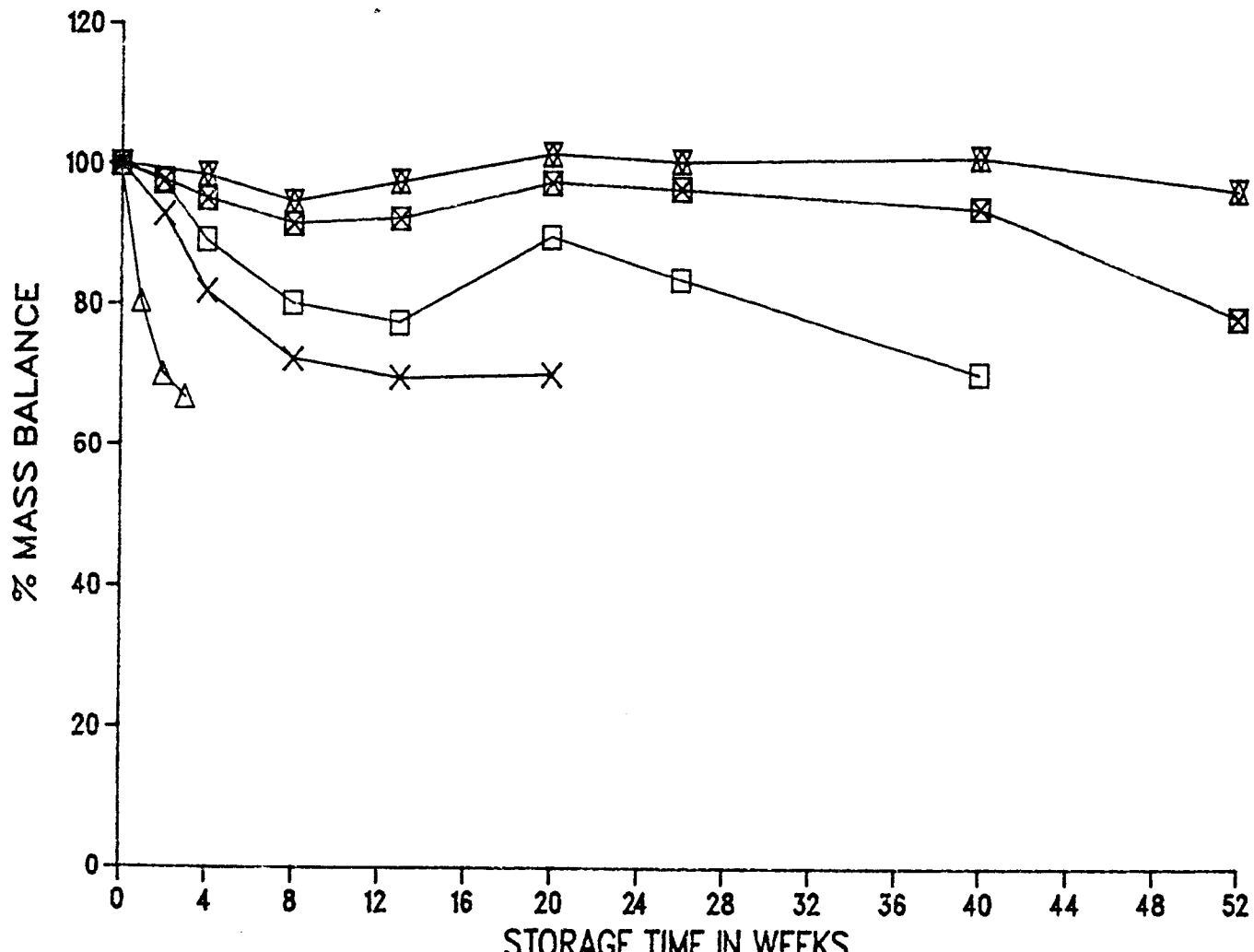
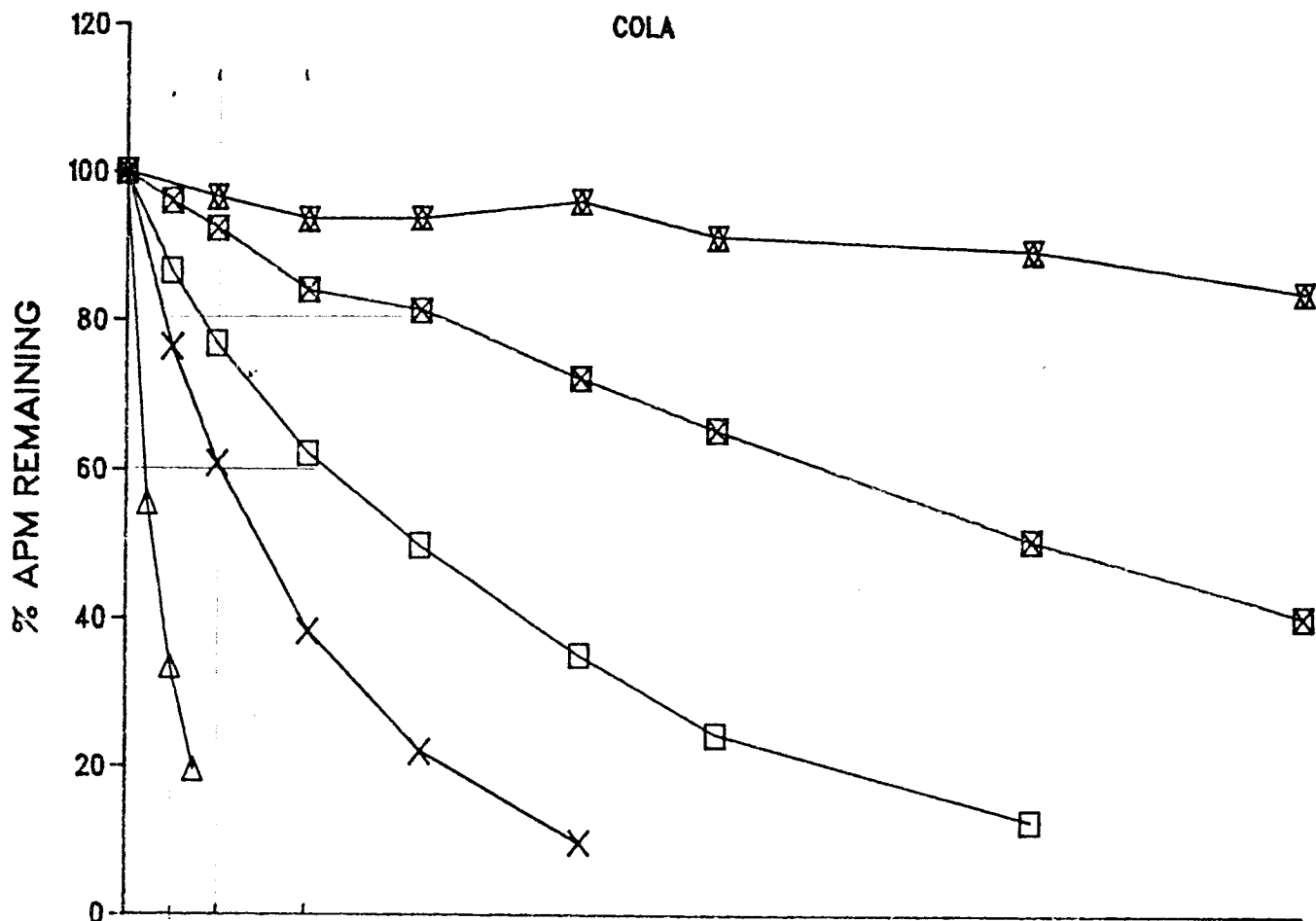


Legend

- △ 55
- × 40
- 30
- ⊠ 20
- ⊠• 5

APM STABILITY IN CARBONATED BEVERAGES

COLA



- Legend
- △ 55
 - × 40
 - 30
 - ⊠ 20
 - ⊞ 50