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Investigation of Synergism in Binary Mixtures of Sweeteners

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ABSTRACT: The purpose of the present study was to determine the presence and degree of synergism among all binary mixtures of 14 sweeteners varying in chemical structure. A trained panel evaluated binary combinations of the following sweeteners: three sugars (fructose, glucose, sucrose), two polyhydric alcohols (mannitol, sorbitol), two diterpenoid glycosides (rebaudioside-A, stevioside), two dipeptide derivatives (alitame, aspartame), one sulfamate (sodium cyclamate), one protein (thaumatin), two *N*-sulfonyl amides (acesulfame-K, sodium saccharin), and one dihydrochalcone (neohesperidin dihydrochalcone). Each sweetener was tested at three concentrations that were isosweet with 3%, 5%, and 7% sucrose. Two methods of analysis were performed to determine synergistic effects. In Method I, an ANOVA was performed for each intensity level to determine if the mean sweetness intensity ratings of each binary mixture were equal to nominal sweetness (i.e., additivity) or not equal to nominal sweetness (i.e., synergism or suppression). In Method II, an additional ANOVA was performed to determine if the sweetness intensity ratings of any given mixture were equal to or greater than the average of the sweetness ratings of the two pure components in that blend.

KEY WORDS: Taste, Sweeteners, Synergism, Psychophysics, Mixtures.

INTRODUCTION

Sweeteners are often used in combination to provide certain sensory properties and to take advantage of the synergism that occurs with certain sweetener combinations [1–3,5,8,11–13,15,19,22,24,25,27,29–31,33,39,40,50,56,57,59–62]. Mixtures of certain sweeteners have been reported to produce a total sweetness intensity that is greater than the theoretical sum of the sweetening effects of the individual components of the mixture [5,6,10,14,16,22,34–36,49,54,58]. That is, when one sweetener is combined with another sweetener(s), it may produce a synergistic sweetening effect. Table 1 provides a summary of some of the previously reported synergistic effects among high potency sweeteners. Although most reports on synergy have focused on binary mixtures that contain at least one high-potency sweetener, combinations of sugars such as fructose and sucrose [7,34] have also been reported to be synergistic.

Two methods of calculation have been used to determine if mixtures of two sweeteners are synergistic. In the first and most common method, the perceived sweetness of the mixture is compared with the sum of the intensities of the unmixed components. For example, if aspartame (equivalent in sweetness to 3% sucrose) is mixed with Na saccharin (equivalent in sweetness to 3% sucrose), the theoretical sum of the mixture is presumed to have a sweetness intensity of 6% sucrose. If the sweetness intensity of the mixture is significantly greater than 6% sucrose, then the mixture is labeled synergistic. If the sweetness intensity of the mixture is equal to 6% sucrose, then the mixture is labeled additive. If the sweetness intensity of the mixture is significantly less than 6% sucrose, then the mixture produces suppression.

The second method of determining synergistic effects of mixtures compares the sweetness intensity of the blend with that of the average of the self-mixtures of the two single components in the blend. This definition arose from the work of Frank et al. [22] who described the concept of superadditivity. It is possible for the sum of the intensities of two sweeteners to be significantly greater than the perceived intensity mixture and yet not be synergistic. This could occur when the component psychophysical functions that relate perceived sweetness and concentration are sigmoidal in shape, i.e., vary from > 1.0 to 1.0 to < 1.0. When the slopes of the psychophysical functions are positively accelerating (> 1.0), superadditivity without actual synergism could occur. Thus, Frank et al. [22] emphasized the importance of assessing the behavior of self-mixtures (mixtures of each individual component with itself) to compare with the intensity of binary mixtures to confirm synergy of sweetener mixtures. Ayya and Lawless [5] have extended Frank et al.'s [22] approach into the time domain.

The purpose of the present study was to examine these two definitions of synergy, one that simply compares the perceived sweetness of a binary mixture with the sum of the intensities of the unmixed components and a second that compares the sweetness of binary blends to the average of the two pure components of the blend. The degree of synergism among all binary mixtures

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TABLE 1

SWEETENER COMBINATIONS PREVIOUSLY SUMMARIZED BY WELLS [58] TO EXHIBIT SYNERGY

Acesulfame-K	Alitame, aspartame, cyclamate, thaumatin, stevioside, sucralose
Alitame	Acesulfame-K, cyclamate
Aspartame	Acesulfame-K, saccharin, cyclamate, stevioside
Cyclamate	Alitame, aspartame, acesulfame-K, saccharin, stevioside, sucralose
Neohesperidin dihydrochalcone	Saccharin
Saccharin	Aspartame, cyclamate, neohesperidin, dihydrochalcone, thaumatin
Stevioside	Aspartame, acesulfame-K, cyclamate, thaumatin
Sucralose	Acesulfame-K, cyclamate
Thaumatin	Acesulfame-K, saccharin, stevioside

of 14 sweeteners varying widely in chemical structure was assessed using a trained panel.

METHOD

Subjects

A trained panel of 15 subjects, 8 males and 7 females, participated in the study. The maximum number of subjects who participated in each tasting session was 15 and the minimum number was 8. All subjects were affiliated with Duke University. Their mean age was 44 ± 15 years. All subjects were paid for their participation.

Stimuli

Fourteen sweeteners were tested: three sugars (fructose, glucose, sucrose), two polyhydric alcohols (mannitol, sorbitol), two diterpenoid glycosides (rebaudioside-A, stevioside), two dipeptide derivatives (alitame, aspartame), one sulfamate (sodium cyclamate), one protein (thaumatin), two *N*-sulfonyl amides (acesulfame-K, sodium saccharin), and one dihydrochalcone (neohesperidin dihydrochalcone or Neo-DHC).

Procedure

Fourteen sweeteners were tested with the trained panel at concentrations isosweet with 3%, 5%, and 7% sucrose, according to formulae determined by DuBois et al. [18]. These concentrations may be found in Table 2. All 14 sweeteners were assessed in binary combinations with the same 14 sweeteners at the same sucrose sweetness intensity level (either 3%, 5%, or 7%). For example, the concentration of aspartame equivalent to 3% sucrose was mixed with the concentration of sodium saccharin equivalent to 3% sucrose.

Before evaluating the binary mixtures, the trained panelists tasted sweet taste references according to the method used by DuBois et al. [18]: 2 sweet (2% sucrose), 5 sweet (5% sucrose), 7.5 sweet (7.5% sucrose), 10 sweet (10% sucrose), 12 sweet (12% sucrose), and 15 sweet (16% sucrose). Subjects also tasted bitter references labeled 2.2 bitter (0.02% caffeine) and 4 bitter (0.03% caffeine) and sour references labeled 2.1 sour (0.01% citric acid) and 7.4 sour (0.08% citric acid). These references were based on previous evaluations by the present panelists, as well as other trained panels.

At a given taste panel, subjects gave sweetness intensity ratings, as well as other flavor profile notes, of five binary mixtures. Each of the five mixtures tested on one day contained one common sweetener isosweet to 3%, 5%, or 7% sucrose mixed with five other sweeteners equivalent to the same sucrose sweetness intensity level. Because each of the 14 sweeteners was mixed with all of the same 14 sweeteners, including itself, each binary mixture was evaluated twice.

Trained panelists received 15 ml of each binary mixture in 30 ml plastic medicine cups. Each mixture was assigned a random three-digit number, and cups containing that mixture were labeled with that number. After sampling the references, subjects were instructed to swirl each mixture around in their mouths, and then expectorate. Panelists would then make a full flavor profile evaluation of the sample, which included all tastes, feeling factors, and aromatics. In making an evaluation, subjects would make a mark on a 15-cm line scale that was anchored at 0, 5, 10, and 15 cm, and would then measure the length of the mark with a ruler. The marks would reflect the intensity perceived of each

TABLE 2

CONCENTRATIONS (IN PERCENT W/V AND MOLARITY) OF THE 14 SWEETENERS ESTIMATED TO BE ISOSWEET WITH 3%, 5%, AND 7% SUCROSE

Sweetener	Concentrations Tested		
	3% Equivalent	5% Equivalent	7% Equivalent
Acesulfame-K	0.016% (0.795 mM)	0.036% (1.79 mM)	0.072% (3.58 mM)
Alitame	0.00072% (21.72 μM)	0.0015% (45.26 μM)	0.0026% (78.45 μM)
Aspartame	0.013% (0.442 mM)	0.025% (0.849 mM)	0.044% (1.495 mM)
Fructose	2.33% (0.129 M)	3.910% (0.217 M)	5.480% (0.304 M)
Glucose	5.03% (0.279 M)	8.37% (0.464 M)	11.7% (0.649 M)
Mannitol	5.065% (0.278 M)	7.871% (0.432 M)	10.677% (0.586 M)
Neohesperidin dihydrochalcone	0.002% (32.65 μM)	0.006% (97.94 μM)	0.013% (0.212 mM)
Rebaudioside-A	0.009% (88.60 μM)	0.020% (0.197 mM)	0.047% (0.463 mM)
Sodium cyclamate	0.102% (5.070 mM)	0.158% (7.853 mM)	0.236% (11.730 mM)
Sodium saccharin	0.006% (0.249 mM)	0.011% (0.456 mM)	0.023% (0.954 mM)
Sorbitol	6.249% (0.343 M)	8.618% (0.473 M)	11.223% (0.616 M)
Stevioside	0.018% (0.224 mM)	0.042% (0.522 mM)	0.099% (1.230 mM)
Sucrose	3.000% (0.088 M)	5.000% (0.146 M)	7.000% (0.204 M)
Thaumatin	0.00015% (67.41 nM)	0.00035% (0.157 μM)	0.00081% (0.364 μM)

flavor note by the subject. Subjects also indicated the time of maximum sweetness intensity by circling either early, middle, or late. Between tasting the five samples on any given test day, the trained panelists would rinse their mouths thoroughly with distilled, deionized water and would eat unsalted top crackers to eliminate any lingering tastes in their mouths. Subjects also refrained from smoking, eating, or drinking anything but water for 30 min prior to each tasting session.

RESULTS

Two methods of analysis were applied to the data. In Method I, an analysis of variance was performed for each binary mixture at each sweetness equivalency level to determine if the mean sweetness intensity ratings of each mixture were equal to nominal sweetness (i.e., additivity) or not equal to nominal sweetness (i.e., synergism or suppression). Ninety-five percent two-sided confidence intervals were constructed using the individual least square means and the standard errors from the ANOVA. For any given binary mixture, if the lower confidence limit (LCL) of a given binary mixture fell above the nominal sweetness value, then it was concluded that significant synergism of sweet taste had occurred. Conversely, if the upper confidence limit (UCL) was less than the nominal sweetness level (i.e., 6, 10, or 14 sweetness intensity), then it was concluded that significant suppression of sweet taste had occurred. If the nominal sweetness value fell between the UCL and the LCL of a given binary mixture, then the assumption of additivity was not rejected.

Table 3 gives the mean sweetness intensity response as well as the UCL and LCL of each binary mixture at intensities equivalent to 3% sucrose. When sweeteners in a mixture were equivalent to 3% sucrose, 41.9% of mixtures were determined to be additive in sweetness intensity responses, 50.5% were determined to be synergistic, and 7.6% were considered to be suppressed. The greatest number of synergistic responses occurred with all 14 sweeteners mixed with Neo-DHC. Additionally, synergism occurred in 12 of the mixtures containing stevioside and 11 of the mixtures containing sodium cyclamate and containing sorbitol. The greatest degree of synergism occurred with the thaumatin-Neo-DHC mixture, which had a mean sweet response of 10.19 (LCL = 9.32, UCL = 11.06). The greatest degree of suppression occurred with the sodium saccharin-sodium saccharin mixture, which had a mean sweet response of 3.90 (LCL = 2.72, UCL = 5.08). Additivity would predict a mean sweet response of 6.00.

Table 4 gives the mean sweetness intensity response, UCL and LCL of each binary mixture at intensities equivalent to 5% sucrose. When the sweeteners of a binary mixture were equivalent to 5% sucrose in sweetness intensity, 65.7% were considered to be additive, 12.4% were considered synergistic, and 21.9% were determined to be suppressed in ratings of sweetness intensity. The greatest degree of synergism occurred with the acesulfame-K-aspartame mixture, which had a mean sweet response of 12.35 (LCL = 11.33, UCL = 13.36). The greatest degree of suppression occurred again with the sodium saccharin-sodium saccharin mixture, which had a mean response of 6.29 (LCL = 4.83, UCL = 7.75). Additivity would predict a mean sweet response of 10.00.

Table 5 gives the mean sweetness intensity response as well as the UCL and LCL of each binary mixture at intensities equivalent to 7% sucrose. When the sweeteners of each mixture were equivalent in sweetness intensity with 7% sucrose, 24.0% were considered to be additive and 76.0% were considered to be suppressed. No sweetener combinations were synergistic at intensities equivalent with the 7% sucrose level. The greatest number of additive responses occurred with the sugars (fructose with 6 additive responses, glucose with 10 additive responses, and sucrose with 5 additive responses) and with Neo-DHC, which had 5 additive responses. The greatest number of suppressed responses occurred with alitame and thaumatin, in which all mixtures were suppressed and with sodium saccharin and stevioside, in which 13 of the mixtures were suppressed. The greatest degree of suppression occurred with the acesulfame-K-acesulfame-K mixture, which had a mean sweet response of 6.47 (LCL = 5.13, UCL = 7.81). Additivity would predict a mean sweet response of 14.00.

An additional analysis of variance (Method II) was performed that determined if the sweetness of any given binary blend was equal to or greater than the average of the sweetness ratings of the two pure components of the mixture. For example, are the sweet ratings of the 3% aspartame-sucrose blend equal to or greater than the average of the sweet ratings of the 3% aspartame-aspartame blend plus the 3% sucrose-sucrose blend? Table 6 gives the results of this analysis for each of the three sweetness intensity levels. Using this analysis, synergy may be defined as the mixture being significantly sweeter than the average of the two pure components at the $\alpha = 0.05$ level. Additionally, one may define superadditivity as a binary mixture being significantly sweeter than the average of the two pure components at the $\alpha = 0.15$ level. Using these definitions, it appears that the sugar alcohols (mannitol, sorbitol), two of the sugars (glucose, sucrose), and the protein (thaumatin) are the least often superadditive or synergistic. Conversely, the *N*-sulfonyl amides (acesulfame-K, sodium saccharin), the diterpenoid glycosides (rebaudioside-A, stevioside), the sulfamate (sodium cyclamate), and the dihydrochalcone (neohesperidin dihydrochalcone) appear to be the most frequently superadditive or synergistic.

Figure 1a–i graphically depicts the mean sweetness intensity ratings and the UCL of the mixtures containing all three sugars (fructose, glucose, and sucrose) at all three concentration levels isosweet to 3%, 5%, and 7% sucrose. Figure 2a–f shows the mean sweetness intensity ratings (plus UCL) of both of the sugar alcohols (mannitol and sorbitol) at each intensity level. Figure 3a–f gives the ratings for the two diterpenoid glycosides, rebaudioside-A and stevioside. Figure 4a–f depicts both dipeptide derivatives (alitame and aspartame) at all three levels. Figure 5a–f shows the *N*-sulfonyl amides, acesulfame-K and sodium saccharin. Figure 6a–c depicts the sulfamate, sodium cyclamate. Figure 7a–c gives the mean sweetness intensity responses for the protein, thaumatin, at all three levels. Lastly, Figure 8a–c shows the mean responses for the dihydrochalcone, Neo-DHC. Each graph includes a nominal sweetness line inserted on the graph as a reference.

DISCUSSION

Two different statistical methods were used to assess synergism in this study. Each analysis used a different definition of synergism. Both methods yielded similar results when the two components of a mixture were equivalent in sweetness to 3% sucrose, with the exception of mixtures containing sorbitol. However, different conclusions can be drawn from the two statistical methods for binary mixtures of two components equivalent in sweetness to 5% (or 7%) sucrose. Table 7 gives the number of binary combinations for each of the 14 sweeteners found to be synergistic by the two different computational procedures (Methods I and II) for each sweetener.

Method I

In the first analysis, 95% two-sided confidence intervals were constructed using the individual least square means and standard

TABLE 3

RESULTS OF THE ANOVA WITH THE MEAN SWEETNESS INTENSITY RATINGS AND THE LOWER AND UPPER CONFIDENCE LIMITS FOR ALL SWEETENERS AT SWEETNESS INTENSITIES EQUIVALENT TO 3% SUCROSE

	Acesulfame-K	Alitame	Aspartame	Fructose	Glucose	Mannitol	Na Cyclamate	Na Saccharin	Neo-DHC	Rebaudioside-A	Sorbitol	Stevioside	Sucrose	Thaumatin
Acesulfame-K	additive X=4.75 LCL=3.46 UCL=6.03													
Alitame	suppression X=4.60 LCL=3.69 UCL=5.51	suppression X=4.64 LCL=3.46 UCL=5.82												
Aspartame	synergy X=7.86 LCL=6.98 UCL=8.73	suppression X=4.18 LCL=3.34 UCL=5.02	suppression X=4.70 LCL=3.52 UCL=5.88											
Fructose	synergy X=7.22 LCL=6.26 UCL=8.17	additive X=6.17 LCL=5.34 UCL=7.01	additive X=5.94 LCL=5.02 UCL=6.86	additive X=4.63 LCL=3.22 UCL=6.05										
Glucose	synergy X=7.48 LCL=6.55 UCL=8.41	additive X=5.76 LCL=4.86 UCL=6.67	additive X=6.55 LCL=5.68 UCL=7.43	additive X=6.39 LCL=5.46 UCL=7.32	additive X=6.34 LCL=4.93 UCL=7.76									
Mannitol	synergy X=6.92 LCL=6.01 UCL=7.83	additive X=5.67 LCL=4.72 UCL=6.63	additive X=5.91 LCL=5.06 UCL=6.76	additive X=6.16 LCL=5.25 UCL=7.07	additive X=5.82 LCL=4.88 UCL=6.76	additive X=5.43 LCL=4.20 UCL=6.65								
Na Cyclamate	synergy X=8.17 LCL=7.19 UCL=9.15	additive X=6.70 LCL=5.81 UCL=7.59	synergy X=7.54 LCL=6.61 UCL=8.46	synergy X=8.48 LCL=7.51 UCL=9.46	synergy X=7.42 LCL=6.50 UCL=8.34	additive X=6.08 LCL=5.23 UCL=6.93	additive X=5.62 LCL=4.44 UCL=6.80							
Na Saccharin	suppression X=4.16 LCL=3.29 UCL=5.04	additive X=5.27 LCL=4.38 UCL=6.16	synergy X=7.70 LCL=6.86 UCL=8.53	additive X=6.49 LCL=5.57 UCL=7.41	additive X=6.84 LCL=5.98 UCL=7.70	synergy X=7.11 LCL=6.27 UCL=7.95	synergy X=7.41 LCL=6.50 UCL=8.32	suppression X=3.90 LCL=2.72 UCL=5.08						
Neo-DHC	synergy X=8.50 LCL=7.59 UCL=9.41	synergy X=8.18 LCL=7.30 UCL=9.05	synergy X=7.79 LCL=6.95 UCL=8.63	synergy X=8.57 LCL=7.73 UCL=9.40	synergy X=8.38 LCL=7.47 UCL=9.29	synergy X=7.45 LCL=6.49 UCL=8.40	synergy X=7.54 LCL=6.65 UCL=8.43	synergy X=8.48 LCL=7.59 UCL=9.37	synergy X=8.38 LCL=7.10 UCL=9.66					
Rebaudioside-A	additive X=6.86 LCL=5.88 UCL=7.83	synergy X=7.21 LCL=6.28 UCL=8.14	synergy X=7.43 LCL=6.51 UCL=8.35	additive X=6.01 LCL=5.03 UCL=6.99	additive X=6.77 LCL=5.79 UCL=7.74	additive X=5.62 LCL=4.71 UCL=6.54	synergy X=7.29 LCL=6.39 UCL=8.18	synergy X=7.85 LCL=6.94 UCL=8.76	synergy X=8.62 LCL=7.69 UCL=9.55	suppression X=4.61 LCL=3.26 UCL=5.96				
Sorbitol	synergy X=8.01 LCL=7.08 UCL=8.94	additive X=6.27 LCL=5.42 UCL=7.13	synergy X=7.22 LCL=6.36 UCL=8.07	synergy X=7.27 LCL=6.41 UCL=8.12	synergy X=7.42 LCL=6.53 UCL=8.30	synergy X=7.10 LCL=6.16 UCL=8.03	synergy X=7.38 LCL=6.51 UCL=8.24	synergy X=7.55 LCL=6.65 UCL=8.46	synergy X=8.68 LCL=7.79 UCL=9.57	additive X=6.22 LCL=5.31 UCL=7.13	synergy X=8.43 LCL=7.21 UCL=9.66			
Stevioside	synergy X=7.98 LCL=7.05 UCL=8.91	synergy X=6.98 LCL=6.07 UCL=7.89	synergy X=8.22 LCL=7.35 UCL=9.09	synergy X=7.27 LCL=6.34 UCL=8.20	synergy X=8.03 LCL=7.02 UCL=9.03	synergy X=7.06 LCL=6.12 UCL=8.00	synergy X=7.93 LCL=7.01 UCL=8.85	synergy X=8.59 LCL=7.73 UCL=9.45	synergy X=8.90 LCL=8.00 UCL=9.81	additive X=5.68 LCL=4.71 UCL=6.66	synergy X=7.78 LCL=6.89 UCL=8.67	additive X=5.59 LCL=4.17 UCL=7.01		
Sucrose	additive X=6.38 LCL=5.49 UCL=7.26	additive X=5.52 LCL=4.61 UCL=6.43	additive X=5.73 LCL=4.88 UCL=6.57	additive X=6.46 LCL=5.52 UCL=7.40	synergy X=7.77 LCL=6.89 UCL=8.66	additive X=6.48 LCL=5.61 UCL=7.35	synergy X=7.04 LCL=6.10 UCL=7.98	additive X=6.01 LCL=5.15 UCL=6.86	synergy X=8.50 LCL=7.59 UCL=9.41	synergy X=7.51 LCL=6.57 UCL=8.44	synergy X=7.78 LCL=6.85 UCL=8.70	synergy X=8.12 LCL=7.23 UCL=9.00	additive X=5.81 LCL=4.58 UCL=7.04	
Thaumatin	additive X=6.71 LCL=5.81 UCL=7.60	additive X=6.81 LCL=5.97 UCL=7.64	additive X=5.85 LCL=5.03 UCL=6.67	additive X=5.25 LCL=4.43 UCL=6.07	additive X=5.13 LCL=4.22 UCL=6.03	suppression X=4.40 LCL=3.44 UCL=5.35	synergy X=7.13 LCL=6.25 UCL=8.02	additive X=6.01 LCL=5.14 UCL=6.88	synergy X=10.19 LCL=9.32 UCL=11.06	additive X=6.43 LCL=5.50 UCL=7.36	additive X=6.11 LCL=5.26 UCL=6.97	synergy X=7.67 LCL=6.76 UCL=8.58	additive X=5.63 LCL=4.73 UCL=6.52	synergy X=7.84 LCL=6.66 UCL=9.02

TABLE 4

RESULTS OF THE ANOVA WITH THE MEAN SWEETNESS INTENSITY RATINGS AND THE LOWER AND UPPER CONFIDENCE LIMITS FOR ALL SWEETENERS AT SWEETNESS INTENSITIES EQUIVALENT TO 5% SUCROSE

	Acesulfame-K	Alitame	Aspartame	Fructose	Glucose	Mannitol	Na Cyclamate	Na Saccharin	Neo-DHC	Rebaudioside-A	Sorbitol	Stevioside	Sucrose	Thaumatin
Acesulfame-K	suppression X=6.62 LCL=5.09 UCL=8.16													
Alitame	suppression X=8.06 LCL=7.10 UCL=9.03	suppression X=7.41 LCL=6.13 UCL=8.69												
Aspartame	synergy X=12.35 LCL=11.33 UCL=13.36	suppression X=7.38 LCL=6.46 UCL=8.31	suppression X=6.83 LCL=5.50 UCL=8.15											
Fructose	additive X=10.86 LCL=9.78 UCL=11.95	suppression X=9.00 LCL=8.04 UCL=9.96	additive X=9.91 LCL=8.90 UCL=10.93	additive X=9.16 LCL=7.62 UCL=10.69										
Glucose	additive X=10.66 LCL=9.63 UCL=11.70	additive X=9.18 LCL=8.14 UCL=10.21	additive X=10.47 LCL=9.54 UCL=11.40	additive X=10.28 LCL=9.30 UCL=11.26	additive X=10.43 LCL=9.10 UCL=11.75									
Mannitol	additive X=10.36 LCL=9.34 UCL=11.38	suppression X=8.81 LCL=7.87 UCL=9.76	additive X=9.34 LCL=8.43 UCL=10.24	additive X=10.28 LCL=9.32 UCL=11.24	additive X=10.27 LCL=9.29 UCL=11.26	additive X=10.43 LCL=8.97 UCL=11.89								
Na Cyclamate	synergy X=11.10 LCL=10.09 UCL=12.12	additive X=9.80 LCL=8.83 UCL=10.77	additive X=10.27 LCL=9.36 UCL=11.18	additive X=10.76 LCL=9.80 UCL=11.72	additive X=9.87 LCL=8.91 UCL=10.83	additive X=9.84 LCL=8.83 UCL=10.84	suppression X=8.00 LCL=6.61 UCL=9.39							
Na Saccharin	suppression X=6.69 LCL=5.63 UCL=7.75	suppression X=7.96 LCL=7.05 UCL=8.87	synergy X=11.67 LCL=10.69 UCL=12.66	additive X=10.91 LCL=9.85 UCL=11.97	additive X=10.80 LCL=9.73 UCL=11.87	additive X=9.84 LCL=8.79 UCL=10.89	additive X=11.01 LCL=9.96 UCL=12.06	suppression X=6.29 LCL=4.83 UCL=7.75						
Neo-DHC	additive X=10.75 LCL=9.74 UCL=11.75	synergy X=11.25 LCL=10.31 UCL=12.20	additive X=10.69 LCL=9.73 UCL=11.66	synergy X=11.45 LCL=10.45 UCL=12.46	synergy X=11.11 LCL=10.06 UCL=12.16	additive X=9.69 LCL=8.73 UCL=10.65	additive X=9.72 LCL=8.74 UCL=10.71	additive X=10.48 LCL=9.52 UCL=11.43	suppression X=8.20 LCL=6.81 UCL=9.59					
Rebaudioside-A	additive X=10.46 LCL=9.42 UCL=11.50	additive X=9.72 LCL=8.80 UCL=10.64	additive X=10.12 LCL=9.19 UCL=11.05	additive X=9.90 LCL=8.92 UCL=10.88	additive X=10.34 LCL=9.29 UCL=11.39	additive X=9.38 LCL=8.29 UCL=10.48	additive X=9.68 LCL=8.61 UCL=10.75	synergy X=11.17 LCL=10.10 UCL=12.24	synergy X=11.00 LCL=10.06 UCL=11.94	suppression X=6.93 LCL=5.30 UCL=8.55				
Sorbitol	additive X=10.83 LCL=9.88 UCL=11.77	additive X=9.58 LCL=8.64 UCL=10.52	additive X=9.92 LCL=9.02 UCL=10.83	synergy X=11.00 LCL=10.05 UCL=11.94	synergy X=11.49 LCL=10.44 UCL=12.55	additive X=9.91 LCL=8.95 UCL=10.87	additive X=10.19 LCL=9.20 UCL=11.18	additive X=10.09 LCL=9.20 UCL=10.98	additive X=10.48 LCL=9.50 UCL=11.46	additive X=9.23 LCL=8.29 UCL=10.17	additive X=11.05 LCL=9.66 UCL=12.44			
Stevioside	additive X=10.18 LCL=9.16 UCL=11.20	additive X=9.68 LCL=8.78 UCL=10.58	synergy X=11.21 LCL=10.30 UCL=12.12	additive X=10.09 LCL=9.13 UCL=11.05	additive X=10.26 LCL=9.30 UCL=11.23	additive X=10.25 LCL=9.25 UCL=11.26	synergy X=11.44 LCL=10.46 UCL=12.42	additive X=10.74 LCL=9.68 UCL=11.79	synergy X=11.63 LCL=10.71 UCL=12.55	suppression X=7.28 LCL=6.21 UCL=8.35	additive X=10.62 LCL=9.70 UCL=11.54	suppresion X=6.65 LCL=5.26 UCL=8.03		
Sucrose	suppression X=8.86 LCL=7.81 UCL=9.92	suppression X=7.98 LCL=7.04 UCL=8.92	suppression X=8.91 LCL=7.93 UCL=9.90	additive X=10.56 LCL=9.50 UCL=11.61	additive X=10.88 LCL=9.92 UCL=11.84	additive X=9.89 LCL=8.95 UCL=10.83	additive X=10.53 LCL=9.59 UCL=11.47	additive X=9.46 LCL=8.43 UCL=10.49	additive X=10.96 LCL=9.97 UCL=11.94	additive X=10.39 LCL=9.43 UCL=11.35	additive X=10.56 LCL=9.64 UCL=11.48	additive X=10.28 LCL=9.34 UCL=11.22	additive X=9.12 LCL=7.66 UCL=10.58	
Thaumatin	additive X=9.10 LCL=8.16 UCL=10.05	additive X=9.17 LCL=8.22 UCL=10.11	additive X=9.28 LCL=8.38 UCL=10.19	additive X=9.71 LCL=8.77 UCL=10.65	additive X=8.94 LCL=7.87 UCL=10.01	suppression X=8.04 LCL=7.06 UCL=9.02	additive X=9.47 LCL=8.46 UCL=10.47	suppression X=8.59 LCL=7.70 UCL=9.48	additive X=9.58 LCL=8.60 UCL=10.56	additive X=10.00 LCL=9.04 UCL=10.96	suppression X=8.72 LCL=7.74 UCL=9.70	additive X=9.53 LCL=8.59 UCL=10.48	suppression X=8.05 LCL=7.13 UCL=8.97	suppression X=7.34 LCL=5.95 UCL=8.72

TABLE 5

RESULTS OF THE ANOVA WITH THE MEAN SWEETNESS INTENSITY RATINGS AND THE LOWER AND UPPER CONFIDENCE LIMITS FOR ALL SWEETENERS AT SWEETNESS INTENSITIES EQUIVALENT TO 7% SUCROSE

	Acesulfame-K	Alitame	Aspartame	Fructose	Glucose	Mannitol	Na Cyclamate	Na Saccharin	Neo-DHC	Rebaudioside-A	Sorbitol	Stevioside	Sucrose	Thaumatin
Acesulfame-K	suppression X=6.47 LCL=5.13 UCL=7.81													
Alitame	suppression X=9.15 LCL=8.11 UCL=10.18	suppression X=8.95 LCL=7.60 UCL=10.29												
Aspartame	additive X=13.41 LCL=12.44 UCL=14.38	suppression X=9.03 LCL=8.04 UCL=10.02	suppression X=8.30 LCL=6.90 UCL=9.70											
Fructose	additive X=13.22 LCL=12.20 UCL=14.24	suppression X=11.59 LCL=10.53 UCL=12.65	suppression X=12.75 LCL=11.71 UCL=13.79	suppression X=12.27 LCL=10.74 UCL=13.80										
Glucose	additive X=13.30 LCL=12.29 UCL=14.32	suppression X=12.49 LCL=11.44 UCL=13.54	additive X=13.84 LCL=12.80 UCL=14.88	additive X=13.61 LCL=12.60 UCL=14.62	additive X=14.48 LCL=13.02 UCL=15.94									
Mannitol	suppression X=12.15 LCL=11.12 UCL=13.18	suppression X=11.05 LCL=10.03 UCL=12.07	suppression X=12.29 LCL=11.24 UCL=13.35	additive X=13.00 LCL=11.97 UCL=14.03	additive X=13.18 LCL=12.13 UCL=14.24	not soluble								
Na Cyclamate	suppression X=12.70 LCL=11.67 UCL=13.74	suppression X=12.71 LCL=11.74 UCL=13.68	additive X=13.10 LCL=12.04 UCL=14.15	additive X=13.15 LCL=12.11 UCL=14.18	additive X=13.48 LCL=12.45 UCL=14.51	suppression X=11.75 LCL=10.69 UCL=12.81	suppression X=8.31 LCL=6.85 UCL=9.77							
Na Saccharin	suppression X=6.69 LCL=5.72 UCL=7.66	suppression X=9.59 LCL=8.58 UCL=10.59	suppression X=12.48 LCL=11.49 UCL=13.47	suppression X=12.53 LCL=11.49 UCL=13.57	additive X=13.39 LCL=12.44 UCL=14.35	suppression X=12.67 LCL=11.69 UCL=13.65	suppression X=12.55 LCL=11.57 UCL=13.52	suppression X=7.58 LCL=6.19 UCL=8.98						
Neo-DHC	additive X=12.98 LCL=11.88 UCL=14.09	suppression X=12.45 LCL=11.48 UCL=13.42	suppression X=12.38 LCL=11.32 UCL=13.44	additive X=12.93 LCL=11.80 UCL=14.05	additive X=13.46 LCL=12.37 UCL=14.55	suppression X=12.27 LCL=11.22 UCL=13.33	suppression X=10.86 LCL=9.85 UCL=11.87	suppression X=12.24 LCL=11.17 UCL=13.32	suppression X=10.83 LCL=9.44 UCL=12.23					
Rebaudioside-A	suppression X=12.74 LCL=11.71 UCL=13.77	suppression X=11.80 LCL=10.83 UCL=12.77	additive X=12.96 LCL=11.90 UCL=14.02	suppression X=12.86 LCL=11.83 UCL=13.90	suppression X=12.65 LCL=11.61 UCL=13.68	suppression X=11.84 LCL=10.78 UCL=12.90	suppression X=11.97 LCL=10.94 UCL=13.00	suppression X=11.45 LCL=10.47 UCL=12.42	additive X=13.57 LCL=12.56 UCL=14.58	suppression X=8.62 LCL=7.16 UCL=10.08				
Sorbitol	suppression X=12.60 LCL=11.65 UCL=13.56	suppression X=10.86 LCL=9.89 UCL=11.83	suppression X=11.93 LCL=11.03 UCL=12.83	suppression X=12.29 LCL=11.31 UCL=13.26	additive X=13.12 LCL=12.05 UCL=14.18	suppression X=12.94 LCL=11.90 UCL=13.98	suppression X=12.78 LCL=11.79 UCL=13.77	suppression X=12.48 LCL=11.56 UCL=13.39	additive X=13.07 LCL=12.08 UCL=14.06	suppression X=12.53 LCL=11.54 UCL=13.52	additive X=13.43 LCL=12.03 UCL=14.82			
Stevioside	suppression X=12.71 LCL=11.70 UCL=13.72	suppression X=10.97 LCL=10.00 UCL=11.93	suppression X=12.18 LCL=11.14 UCL=13.21	suppression X=12.34 LCL=11.32 UCL=13.35	suppression X=12.12 LCL=11.11 UCL=13.13	suppression X=12.07 LCL=11.03 UCL=13.10	suppression X=11.88 LCL=10.87 UCL=12.89	suppression X=12.48 LCL=11.53 UCL=13.43	suppression X=12.24 LCL=11.23 UCL=13.25	suppression X=7.25 LCL=6.24 UCL=8.26	suppression X=12.06 LCL=11.07 UCL=13.05	suppression X=8.38 LCL=6.98 UCL=9.77		
Sucrose	suppression X=10.76 LCL=9.77 UCL=11.75	suppression X=10.34 LCL=9.34 UCL=11.34	suppression X=10.64 LCL=9.63 UCL=11.65	additive X=13.12 LCL=12.06 UCL=14.18	additive X=13.72 LCL=12.65 UCL=14.79	additive X=13.00 LCL=11.92 UCL=14.09	suppression X=12.74 LCL=11.65 UCL=13.83	suppression X=11.35 LCL=10.34 UCL=12.36	suppression X=12.41 LCL=11.34 UCL=13.48	additive X=13.01 LCL=11.92 UCL=14.10	suppression X=12.86 LCL=11.95 UCL=13.78	additive X=12.97 LCL=11.90 UCL=14.04	suppression X=12.30 LCL=10.84 UCL=13.76	
Thaumatin	suppression X=10.93 LCL=9.92 UCL=11.94	suppression X=10.74 LCL=9.79 UCL=11.69	suppression X=11.26 LCL=10.30 UCL=12.22	suppression X=10.76 LCL=9.73 UCL=11.80	suppression X=10.77 LCL=9.72 UCL=11.82	suppression X=9.10 LCL=8.08 UCL=10.12	suppression X=10.60 LCL=9.63 UCL=11.57	suppression X=10.07 LCL=9.10 UCL=11.05	suppression X=12.02 LCL=11.05 UCL=12.98	suppression X=11.59 LCL=10.62 UCL=12.56	suppression X=9.61 LCL=8.64 UCL=10.58	suppression X=10.42 LCL=9.45 UCL=11.39	suppression X=10.42 LCL=9.45 UCL=11.40	suppression X=8.22 LCL=6.88 UCL=9.57

TABLE 6

RESULTS OF THE COMPARISONS OF THE SWEETNESS OF BINARY BLENDS OF SWEETENERS TO THE AVERAGE OF THE TWO PURE COMPONENTS OF THE BLENDS (AT THE 3%, 5%, AND 7% NOMINAL SWEETNESS LEVELS, RESPECTIVELY)

	Acesulfame-K	Alitame	Aspartame	Fructose	Glucose	Mannitol	Na Cyclamate	Na Saccharin	Neo-DHC	Rebaudioside-A	Sorbitol	Stevioside	Sucrose	Thaumatin
Acesulfame-K	—	−+*												
Alitame	−+*	—												
Aspartame	***	−−−	—											
Fructose	***	*−−	+**	—										
Glucose	***	−−−	+**	−−	—									
Mannitol	***	−−*	−−−	−−−	−−−	—								
Na Cyclamate	***	***	***	***	*−*	−−*	—							
Na Saccharin	−−−	+++	***	***	***	***	***	—						
Neo-DHC	***	***	***	**+	+*−	−−+	−*+	***	—					
Rebaudioside-A	***	***	***	***	+**	−−*	***	***	***	—				
Sorbitol	***	−−−	++	−−−	−−−	−−−	−−*	***	−−−	−−*	—			
Stevioside	***	***	***	***	**−	***	***	***	***	−−−	−*+	—		
Sucrose	+−+	−−−	−−−	++−	*+−		***	+*+	**−	***	−−−	***	—	
Thaumatin	**	−**	−**	*−	−−−	−−−	**	−**	***	−**	−−−	+**	−−−	—

− Blend is not significantly sweeter than the average of the two pure components.
+ Blend is significantly sweeter than the average of the two pure components ($p < 0.15$).
* Blend is significantly sweeter than the average of the two pure components ($p < 0.05$).

errors from the ANOVA. Synergism was simply defined as occurring when the lower confidence limit (LCL) of the ANOVA was greater than the nominal sweetness level (i.e., 6%, 10%, 14%). Suppression of sweet intensity ratings occurred when the upper confidence limit (UCL) fell below the nominal sweetness level, and additivity occurred when the nominal sweetness level fell between the lower and upper confidence limits. Using these definitions for Method I, synergism occurred most frequently at the lower concentrations, additivity occurred most commonly at middle concentrations, and suppression was most frequent at higher concentrations (see Tables 3–5). That is, two sweeteners equivalent in sweetness intensity to 3% sucrose were more likely to be synergistic than the same two sweeteners equivalent in sweetness intensity to 5% sucrose. No synergism was found for any binary combination of sweeteners equivalent in intensity to 7% sucrose. Each of the 14 sweeteners was synergistic with at least three of the other sweeteners. Neohesperidin dihydrochalcone and stevioside were the two sweeteners most frequently synergistic with another sweetener at both the 3% and 5% levels. Alitame and thaumatin were least frequently synergistic with other sweeteners. Compounds with similar chemical structures (e.g., Na saccharin/acesulfame-K; aspartame/alitame; stevioside/rebaudioside-A) were never synergistic with one another. However, because most of the sweeteners used in this study fail to reach the nominal sweetness level of 14.00, even singularly [18], one might wish to employ a different definition of synergism such as that used in Method II.

Method II

The second definition of synergism incorporates information on the intensity of mixtures of single components into the analysis, as suggested by Frank et al. [22] and Ayya and Lawless [5]. The sweetness intensity ratings of any given binary blend was compared with the average of the sweet ratings of the two pure components in the blend. If the intensity of the mixture was significantly greater than the average intensity of the two self-mixtures in the blend, the mixture was considered synergistic. This second analysis found that the high-potency sweeteners such as the diterpenoid glycosides (rebaudioside-A and stevioside), the *N*-sulfonyl amides (acesulfame-K and Na saccharin), sodium cyclamate, neohesperidin dihydrochalcone, and the dipeptide derivative aspartame were most commonly synergistic. The sugars, the sugar alcohols, as well as the protein thaumatin and the dipeptide derivative alitame, were the least likely to be synergistic. Defining synergism in this manner may be more practical, especially at elevated concentrations.

Comparison of Methods I and II

Two striking differences were found between the conclusions drawn by the two methods of analysis. First, binary combinations containing sorbitol were only found to be synergistic in two combinations by Method II and in 11 combinations by Method I. The probable reason for this finding is that psychophysical function for sorbitol tends to be sigmoidal in shape [44] and is positively accelerating (> 1.0) at low concentrations. Thus, the synergism found by Method I may be an artifact of the psychophysical function. Another difference is that far more binary combinations were found to be synergistic by Method II. The reason for this is that the psychophysical functions for most of the sweeteners tested are negatively accelerating [18]. Thus, the average of the two pure components of blends at 3%, 5%, and 7% nominal sweetness are less than 6%, 10%, and 14%, respectively.

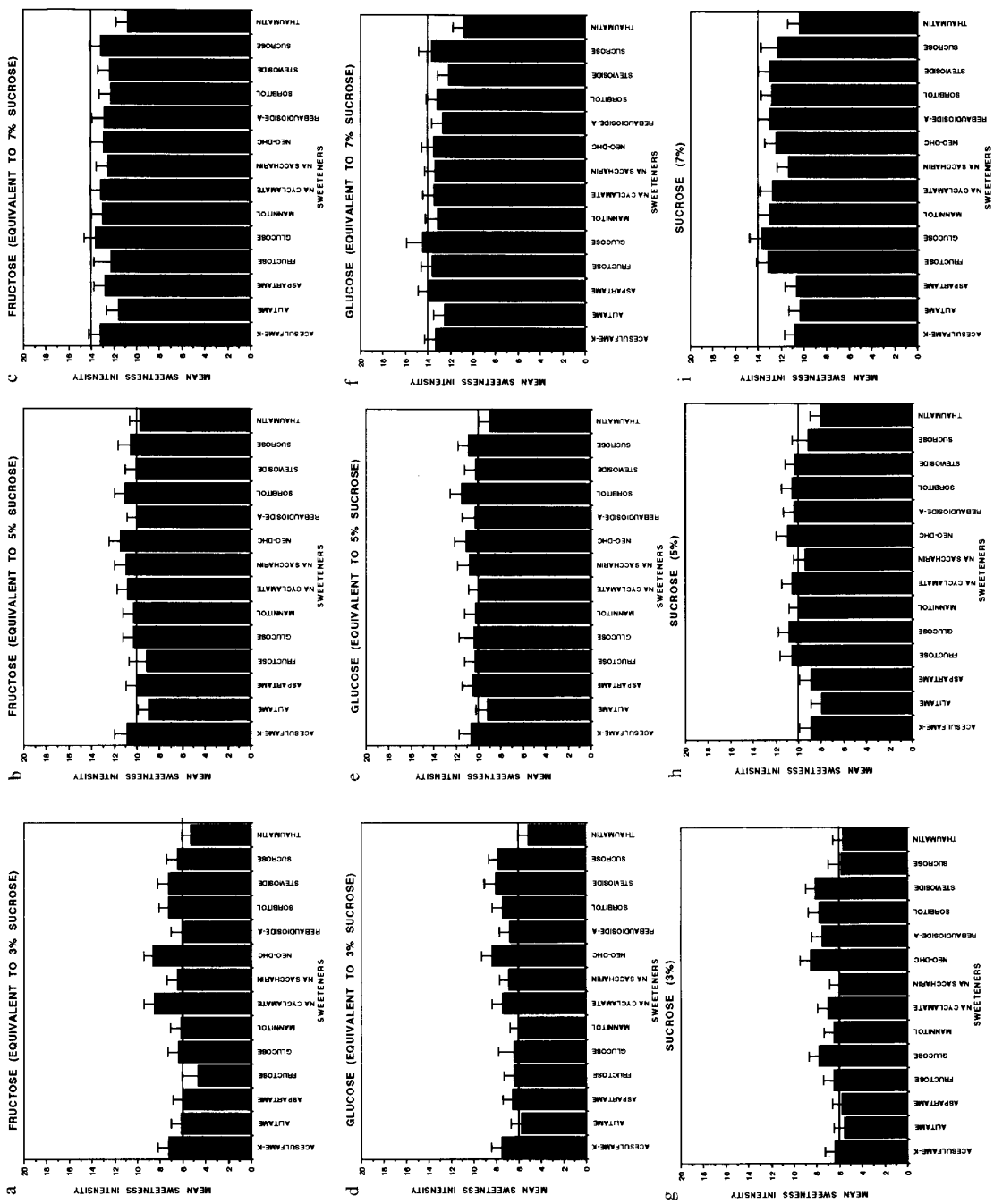

FIG. 1. (a–i) Mean sweetness intensity ratings and the upper confidence limit (UCL) of mixtures containing fructose, glucose, and sucrose at three concentration levels isosweet with 3%, 5%, and 7% sucrose. Figures a–c represent mixtures containing fructose at 3%, 5%, and 7%, respectively. Figures d–f represent mixtures containing glucose at these three levels, respectively. Figures g–i represent mixtures containing sucrose at these three levels, respectively. The lines on each graph indicate the nominal sweetness level.

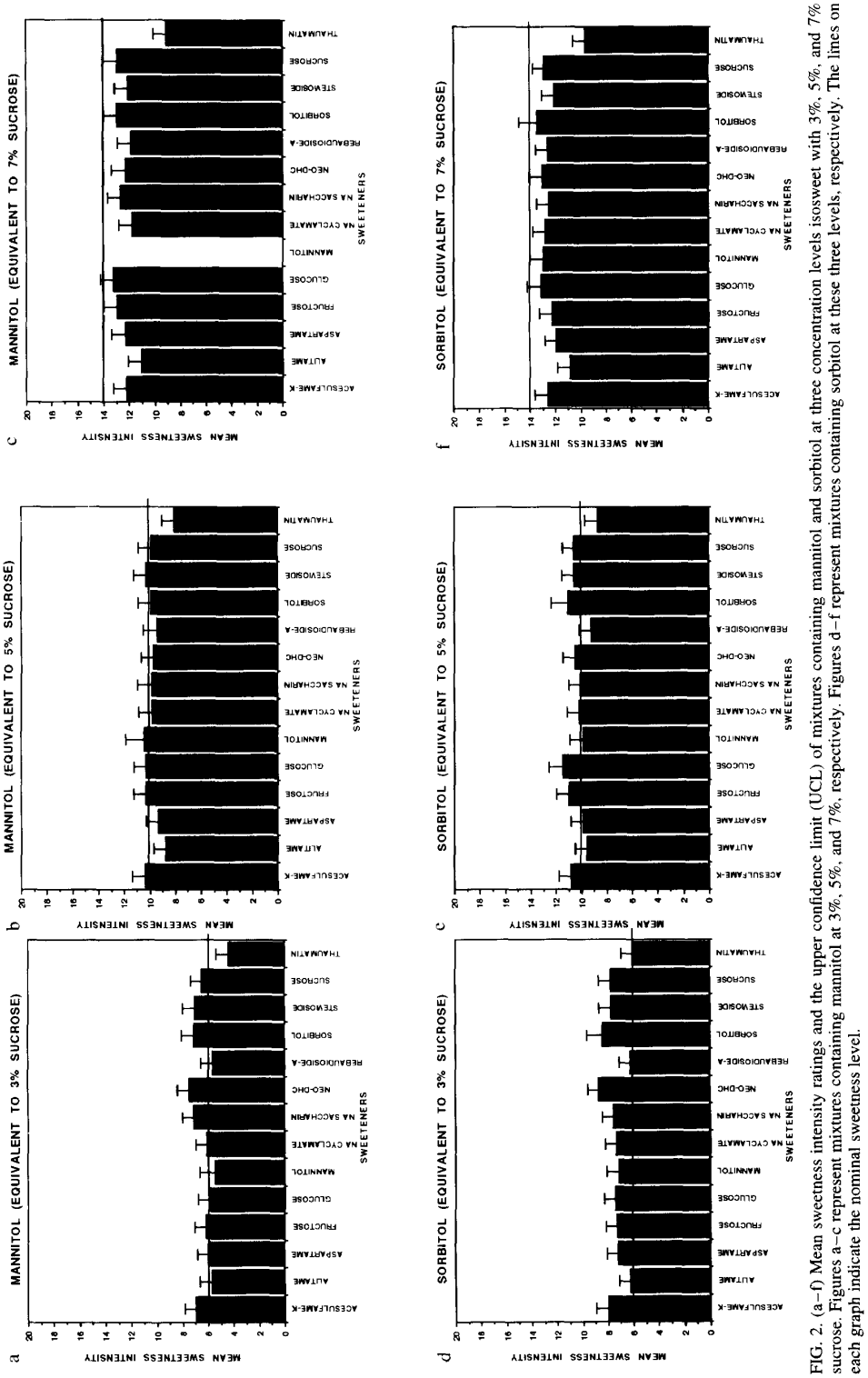

FIG. 2. (a–f) Mean sweetness intensity ratings and the upper confidence limit (UCL) of mixtures containing mannitol and sorbitol at three concentration levels isosweet with 3%, 5%, and 7% sucrose. Figures a–c represent mixtures containing mannitol at 3%, 5%, and 7%, respectively. Figures d–f represent mixtures containing sorbitol at these three levels, respectively. The lines on each graph indicate the nominal sweetness level.

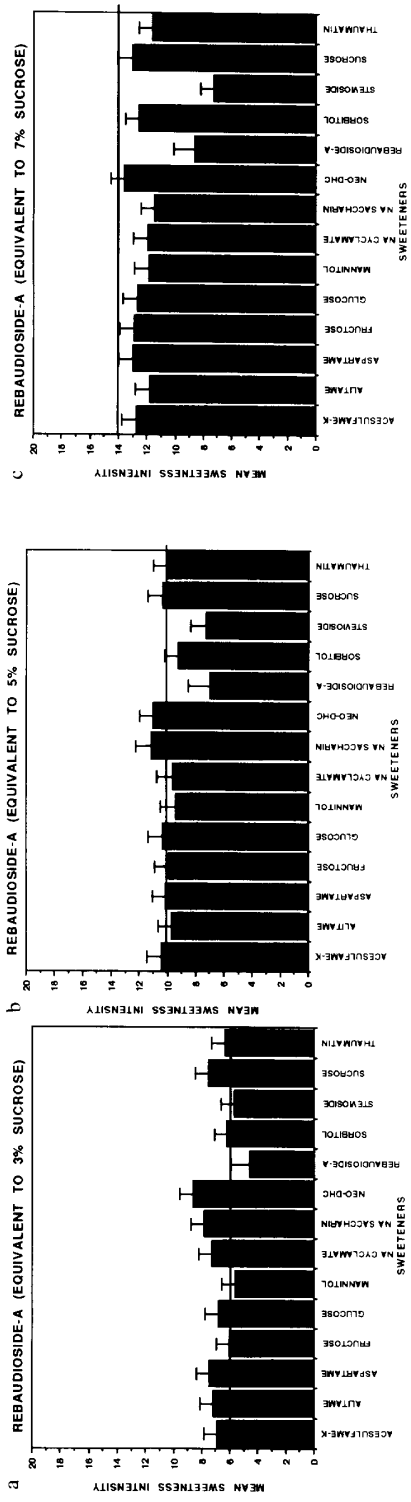

FIG. 3. (a–f) Mean sweetness intensity ratings and the upper confidence limit (UCL) of mixtures containing rebaudioside-A and stevioside at three concentration levels isosweet with 3%, 5%, and 7% sucrose. Figures a–c represent mixtures containing rebaudioside-A at 3%, 5%, and 7%, respectively. Figures d–f represent mixtures containing stevioside at these three levels, respectively. The lines on each graph indicate the nominal sweetness level.

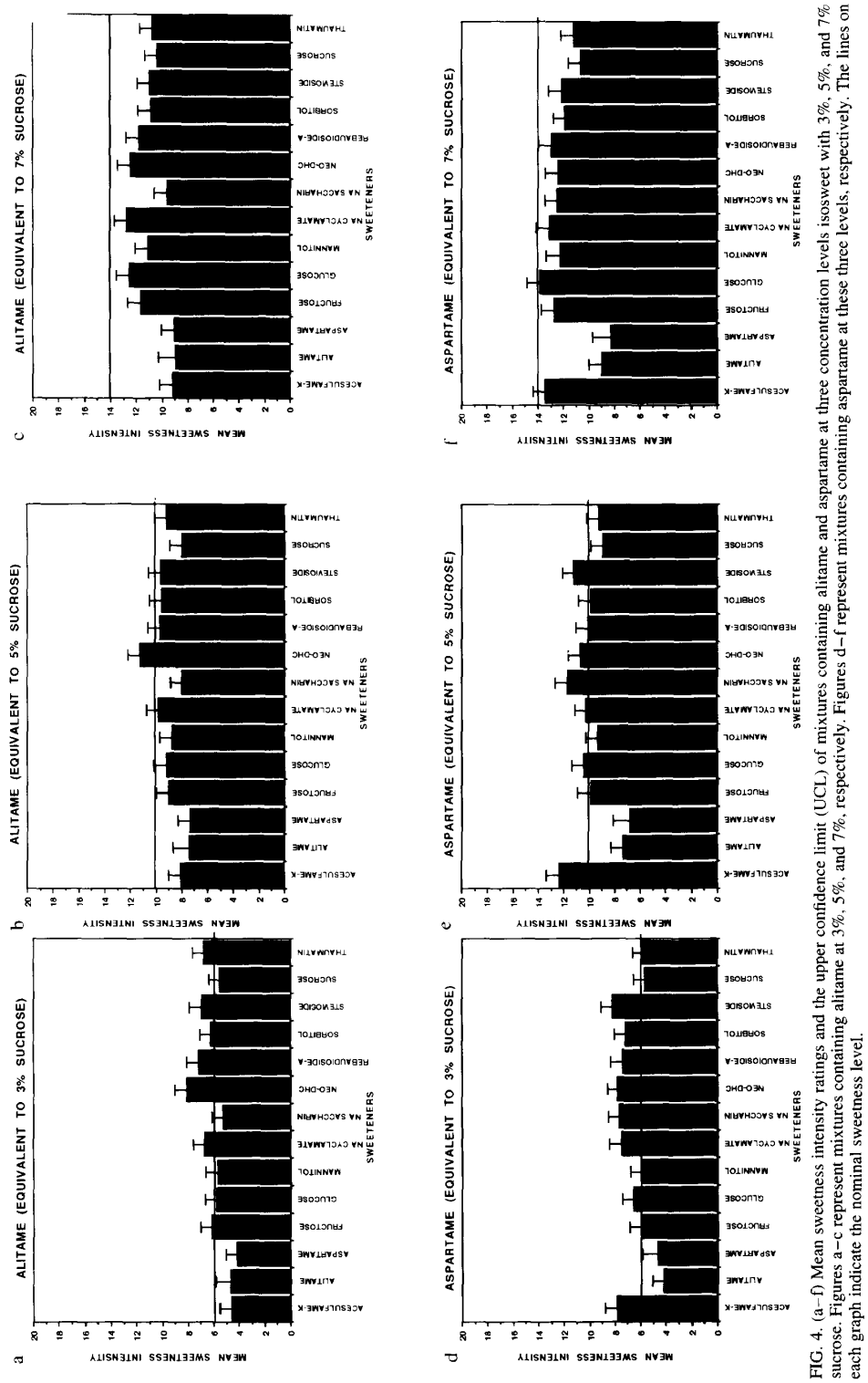

FIG. 4. (a–f) Mean sweetness intensity ratings and the upper confidence limit (UCL) of mixtures containing alitame and aspartame at three concentration levels isosweet with 3%, 5%, and 7% sucrose. Figures a–c represent mixtures containing alitame at 3%, 5%, and 7%, respectively. Figures d–f represent mixtures containing aspartame at these three levels, respectively. The lines on each graph indicate the nominal sweetness level.

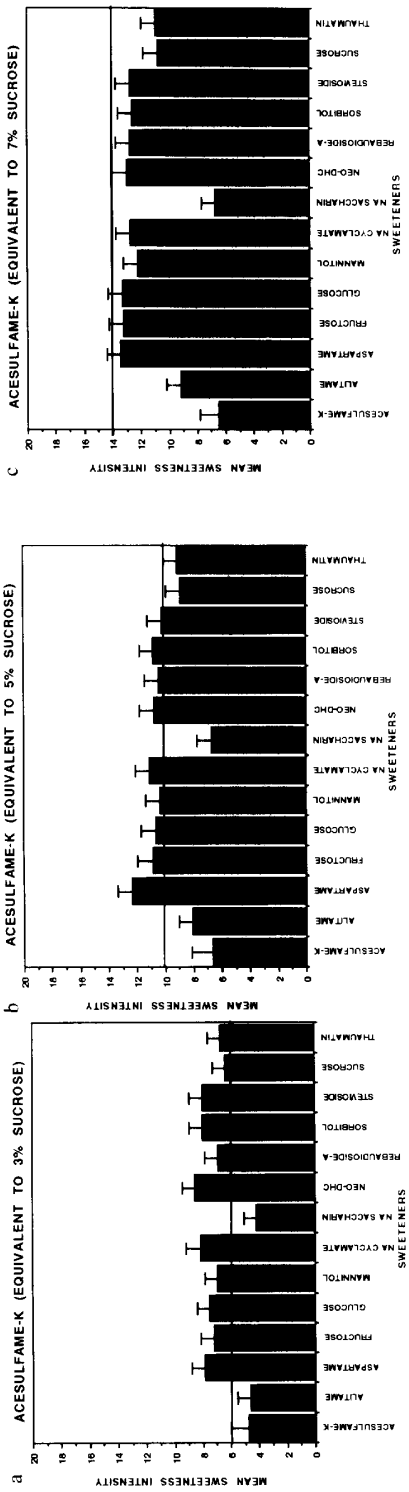

FIG. 5. (a–f) Mean sweetness intensity ratings and the upper confidence limit (UCL) of mixtures containing acesulfame-K and sodium saccharin at three concentration levels isosweet with 3%, 5%, and 7% sucrose. Figures a–c represent mixtures containing acesulfame-K at 3%, 5%, and 7%, respectively. Figures d–f represent mixtures containing sodium saccharin at these three levels, respectively. The lines on each graph indicate the nominal sweetness level.

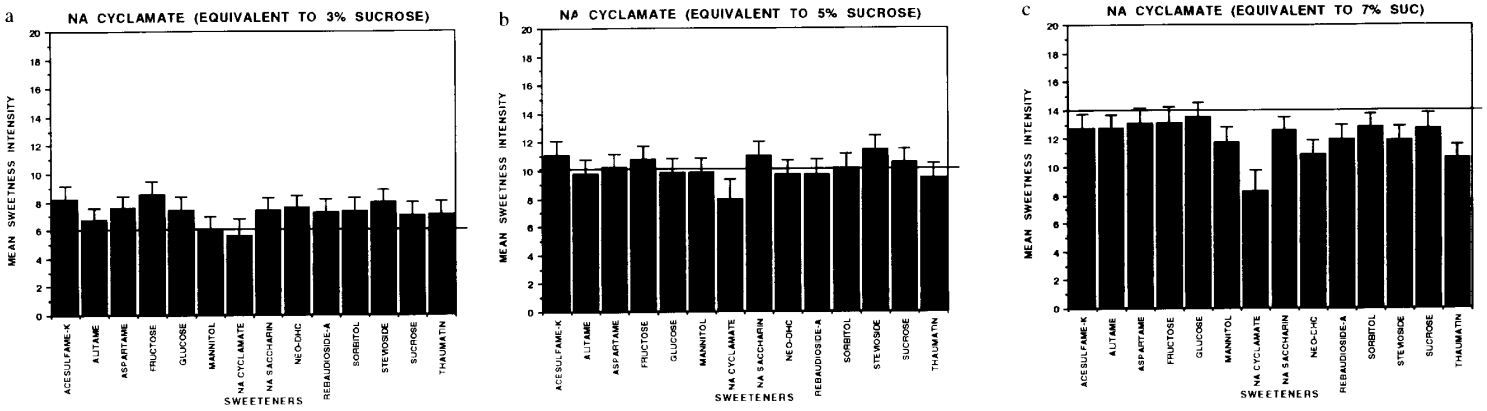

FIG. 6. (a–c) Mean sweetness intensity ratings and the upper confidence limit (UCL) of mixtures containing sodium cyclamate at three concentration levels isosweet with 3%, 5%, and 7% sucrose, respectively. The lines on each graph indicate the nominal sweetness level.

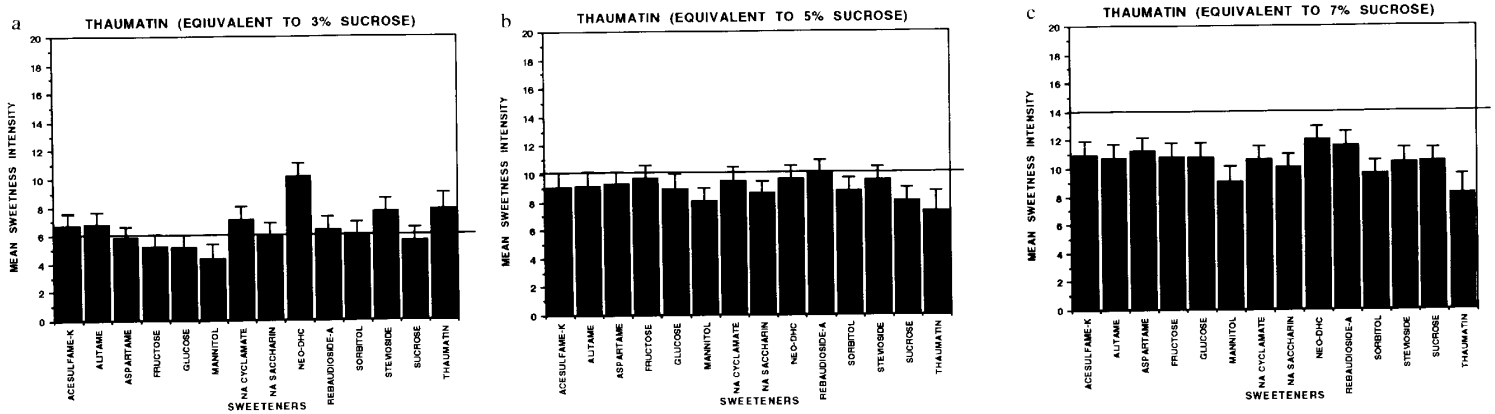

FIG. 7. (a–c) Mean sweetness intensity ratings and the upper confidence limit (UCL) of mixtures containing thaumatin at three concentration levels isosweet with 3%, 5%, and 7% sucrose, respectively. The lines on each graph indicate the nominal sweetness level.

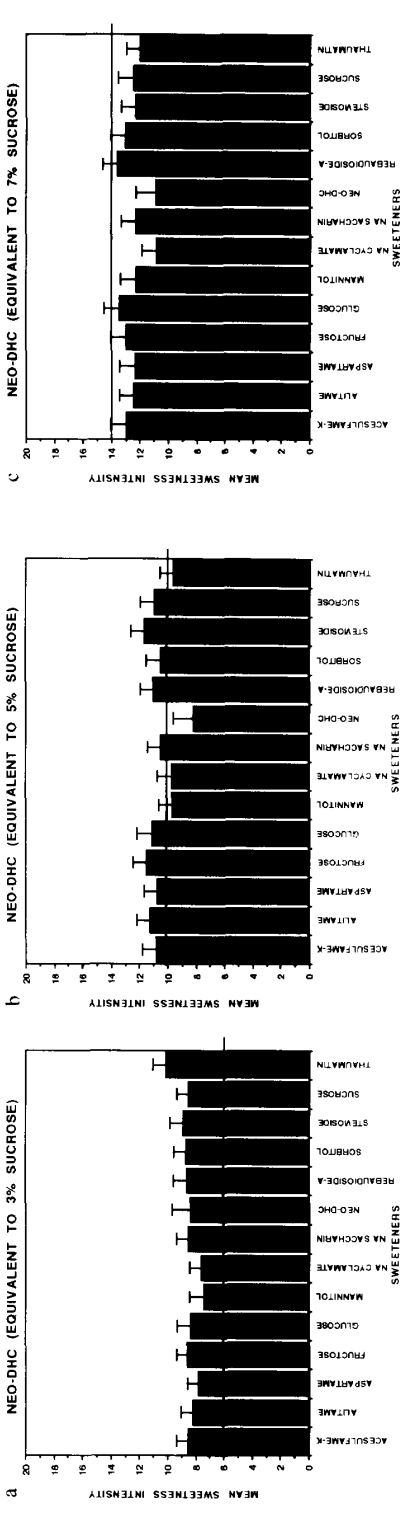

FIG. 8. (a–c) Mean sweetness intensity ratings and the upper confidence limit (UCL) of mixtures containing neohesperidin dihydrochalcone at three concentration levels isosweet with 3%, 5%, and 7% sucrose, respectively. The lines on each graph indicate the nominal sweetness level.

TABLE 7

NUMBER OF BINARY COMBINATIONS FOR EACH OF THE 14 SWEETENERS FOUND TO BE SYNERGISTIC BY TWO DIFFERENT STATISTICAL PROCEDURES (METHODS I AND II) FOR EACH SWEETENER

Sweetener	Intensity of Component Concentrations					
	3%		5%		7%	
	I	II	I	II	I	II
Acesulfame-K	8	9	2	10	0	11
Alitame	3	5	1	5	0	7
Aspartame	7	6	3	9	0	10
Fructose	5	7	2	8	0	6
Glucose	6	5	2	6	0	4
Mannitol	5	3	0	3	0	7
Na Cyclamate	11	9	2	10	0	12
Na Saccharin	7	9	2	11	0	10
Neo-DHC	14	9	5	10	0	7
Rebaudioside	6	8	2	10	0	11
Sorbitol	11	2	2	3	0	4
Stevioside	12	10	3	12	0	10
Sucrose	6	5	0	5	0	3
Thaumatin	4	1	0	0	0	8

Possible Mechanisms for Synergism

Although different conclusions can be drawn from the two statistical treatments of the data regarding which binary combinations are synergistic, it is clear that synergism frequently occurs in sweetener mixtures. The precise mechanisms that produce synergism among sweeteners are not known at the present time. However, it is probable that multiple receptors as well as multiple transduction mechanisms play a role. Indication of multiple sweet receptors comes from at least seven lines of evidence [43]. These lines include the nonhomogeneous variability among sweeteners in individual subjects for thresholds, and intensity ratings [20,21,41] as well as different responses among individual sweeteners in crossadaptation experiments [45], area of the tongue that is stimulated [55], shape of the concentration–response functions [18], loss in perceived intensity with age [45], sensitivity to temperature [23,26], and effect of modifiers such as methylxanthines [42]. Multiple mechanisms for sweet taste transduction and modulation include the adenylate cyclase second-messenger system [4,32,37,51–53], lipid-derived second-messenger systems [47], sodium channels [17,46,48], potassium channels [4,9,28,53], and receptor-independent activation of G proteins [38]. Activation of multiple receptors and transduction mechanisms may produce a response that is significantly greater than the response when only a single mechanism is activated.

Final Comment

Sweeteners can be used in binary combinations to take advantage of their synergistic effects. Synergism permits the blending of low concentrations of sweeteners such as saccharin or acesulfame-K, which are bitter at higher concentrations with sweeteners without salient bitter components such as aspartame and fructose to achieve a desired level of sweetness.

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