Letter to the Editor

Theoretical Risk Assessment of Dietary Exposure to Advantame among the Chinese Population*

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Advantame, with the chemical name N-[N-[3-(3-hydroxy-4-methoxyphenyl) propyl]-α-aspartyl]-L-phenylalanine 1-methyl ester, monohydrate, is an artificial sweetener made by a chemical reaction between vanillin and aspartame, which are both permitted as flavoring and food additives by the China National Food Safety Standard-Standards for Use of Food Additives (GB 2760). As an intense sweetener, advantame is approximately 90–120 times sweeter than aspartame and approximately 14,000–48,000 times sweeter than saccharose.

The National Health Commission of the People's Republic of China (NHC) permitted advantame as a new food additive in the No. 8 Notification[1] in 2017, and it can be used as a sweetener in the following food categories: fermented and flavored fermented milk; frozen drinks; cocoa products, chocolate and chocolate products (including imitation chocolate and chocolate substitutes), and candy; table-top sweetener; flavoring syrup; other sweeteners; blended condiments; tea, coffee, or plant-based drinks; powdered drinks; and jelly. The Codex Alimentarius Commission[2], the European Union[3], Australia New Zealand[4], and Japan[5] have also allowed the use of advantame as a sweetener.

Advantame has been evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA)[6], the European Food Safety Authority (EFSA)[7], and Food Standards Australia New Zealand (FSANZ)[8]. Based on a no-observed-adverse-effect level for maternal toxicity in a developmental toxicity study in rabbits, JECFA established an acceptable daily intake (ADI) of 0–5 mg/kg body weight (BW) for advantame.

Advantame may be used in several food categories, but its ADI (0–5 mg/kg BW) is relatively lower than that of other artificial sweeteners, such as sodium cyclamate, calcium cyclamate (0–11 mg/kg BW), aspartage (0–40 mg/kg BW), and acesulfame potassium (0–15 mg/kg BW). Advantame is a newly proven food additive in China, and there is little research on dietary exposure among the Chinese population. Considering that in recent years the Chinese government has been promoting the policy of 'Three minus, Three health', which refers to eating less salt, oil and sugar, keep the health of dental, body weight and bones, food industries are encouraged to reduce sugar levels in their final products; therefore, sweeteners are possibly used more frequently and extensively than before to compensate for the loss of sweetness among food flavor profiles. This study aims to assess the intake and potential health risks of advantame among the Chinese population. This evaluation is based on the Nutrition and Health Survey of Chinese Residents in 2002 and the maximum usage levels of advantame in the No. 8 notification of the NHC or actual usage levels in food categories lacking quantified usage information.

The assessment is mainly designed for the Chinese population above 2 years of age. According to consumption patterns and habits, the population was divided into the following age groups: 2–3, 4–9, 10–17, 18–59, and over 60 years.

In this study, the concentration of advantame in foods was identified based on the hypothesis that its use would comply with the provisions in the No. 8 notification of NHC in 2017. Meanwhile, in consideration of several food categories do not have a numerical maximum usage level the data on actual usage levels reported by industries were assessed as

doi: 10.3967/bes2019.117

*This work was supported by the National Key Research and Development Program [No.2018YFC1603300]; and the Beijing Key Laboratory for Quality Evaluation Technology of Hygiene and Safety of Plastics (Beijing Technology and Business University) Open Fund Project [No.QETHSP2018002].

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well. Food consumption data were obtained from the Nutrition and Health Survey of Chinese Residents in 2002.

Based on the actual food consumption and weight of the respondents as indicated in the aforementioned Nutrition and Health Survey and the maximum and actual usage levels in various food categories, a simple distribution model was used to calculate the intake of advantame per kilogram per day for each individual, as per the following formula:

$$EXP = \sum_{i=1}^{n} \frac{(Fi \times Ci)}{1{,}000 \times BW}$$

where EXP is the dietary exposure to advantame per kilogram per day of one individual (mg/kg BW), *Fi* is the consumption of food category *i* (g/day or mL/day), *Ci* is the maximum usage level in food category *i* (mg/kg), and BW is the actual weight of one individual (kg).

The frequency distribution of dietary exposure to advantame for the subjects was obtained on the basis of the intake of each individual. The average dietary exposure to advantame for the general population, the intake level in the high exposure population (P97.5), and dietary exposure in various age groups were calculated. The groups involved in this study include the general population (including those who do and do not eat advantame-added food) and consumers who eat advantame-added food. Groups are mainly targeted at consumers over 2 years of age and divided according to age.

Dietary exposure to advantame was calculated based on the maximum levels in various food categories allowing the use of this additive according to the No. 8 notification/actual usage levels and the consumption data on advantame in these food categories, considering that the ADI is 5.00 mg/kg BW per day. Detailed assessment results are shown in Tables 1 and 2.

For the general population, the findings showed that the mean dietary exposure to advantame was estimated at 0.0025 mg/kg BW per day (0.05% of ADI). At 97.5%, exposure was estimated at 0.0004 mg/kg BW per day (0.001% of ADI). The maximum exposure (99%) was estimated at 0.0009 mg/kg BW per day (0.002% of ADI). The ADI did not exceed the maximum exposure for individual food categories when the calculations for each individual food category were conducted separately. The highest exposure was by fermented and flavored fermented milk, and the average and 97.5% exposure were 0.0191 mg/kg BW and 0.0782 mg/kg BW, which accounted for 0.382% and 1.564% of ADI, respectively. This was followed by processed fruit, with the average and 97.5% exposure at 0.4763 mg/kg BW (9.526% of ADI) and 2.2727 mg/kg BW (45.454% of ADI), respectively.

The results showed that neither the average nor the highest percentile exposures to advantame

Table 1. Dietary exposure to advantame of chinese general population and consumer only (mg/kg BW per day)

Food category	Maximum usage level (mg/kg)	General population		Consumer	
		Mean	P97.5	Mean	P97.5
Fermented and flavored fermented milk	6	0.0000	0.0000	0.0191	0.0782
Frozen drinks	0.5	0.0000	0.0000	0.0007	0.0029
Processed fruit	120	0.0025	0.0000	0.4763	2.2727
Cocoa products, chocolate and chocolate products, and candies	0.5	0.0000	0.0000	0.0002	0.0011
Egg products (changed physical properties)	0.4	0.0000	0.0000	0.0003	0.0012
Table-top sweetener	16.4[a]	0.0000	0.0000	0.0000	0.0000
Flavoring syrup	16.4[a]	0.0000	0.0000	0.0000	0.0000
Other sweeteners	16.4[a]	0.0000	0.0000	0.0000	0.0000
Blended condiments	0.5	0.0000	0.0004	0.0002	0.0007
Tea, coffee, or plant-based drinks	3	0.0000	0.0000	0.0000	0.0000
Powdered drinks	4	0.0000	0.0000	0.0042	0.0190
Jelly	0.4	0.0000	0.0000	0.0000	0.0000
Total exposure to all food categories		0.0025	0.0004	0.5010	2.3758

Note. [a]Actual usage levels reported by the China condiment association.

exceeded the JECFA ADI of 0–5 mg/kg BW in any age group and that the average daily exposure decreased with increasing age. According to the estimation, the average intake of 2–3-year-old children was the highest (0.012 mg/kg BW), followed by that of 4–9-year-old children (0.011 mg/kg BW). The intake of those with high exposure to advantame among the age categories 2–3, 4–9, and 10–17 years (P97.5) was 0.0016 mg/kg BW (0.03% of ADI), 0.0013 mg/kg BW (0.03% of ADI), and 0.0005 mg/kg BW (0.01% of ADI), respectively. The maximum exposure (P99) in people under 2–3, 4–9, and 10–17 years of age was 0.92%, 6.33%, and 0.35% of ADI, respectively. Detailed results are presented in Table 2.

According to these results, the major food that contributed to advantame dietary intake for the general population was processed fruit (99.82%), frozen (0.1%), and powdered (0.08%) drinks. Among children, the major sources of advantame intake were processed fruit (98.85%), flavored fermented milk (0.62%), and blended condiments (0.14%). For adults, the main contributors were processed fruit (42%), blended condiments (1.70%), cocoa products, chocolate and chocolate products, and candies (0.42%). In summary, processed fruit is the main contributor of advantame intake among the Chinese population.

As an artificial sweetener, advantame is widely used in many foods. In recent years, the Codex Alimentarius Commission, the European Union, Australia, New Zealand, China, and other countries have allowed the use of advantame as a food additive. The criteria for use among various food categories and relevant maximum usage levels have been set in different countries. JECFA established an ADI of 5 mg/kg BW for advantame in 2013, which is relatively lower than that for other sweeteners that are already permitted. Thus, it is necessary to re-evaluate provisions to study the safe use of advantame in China.

Following the international assessment principle and methods for food additives, we conducted a theoretical risk assessment of advantame among the Chinese population on the basis of the food consumption data in China and the maximum usage levels in various food categories in accordance with the No. 8 Notification of the NHC. The assessment results indicated that the estimated dietary exposure to advantame in the Chinese population was low, both for the general population and for all age groups, and no health concern was observed when estimated high exposures were compared with the health-based guidance value established by JECFA.

This study involves the following uncertainties: (1) we assumed that the concentration of advantame in foods was equal to the maximum level of the additive allowed for use in all food categories; however, the actual usage level may be lower, thereby resulting in a likely overestimation of the risk of advantame. (2) The food categories indicated in the notification of NHC were general, thereby causing difficulty in identifying specific food subcategories and calculating food consumption levels. (3) The consumption data used in this evaluation were generated from the Nutrition and Health Survey in 2002. However, an increasing variety of food types have become available and economic prosperity has spread in recent years. Consequently, the recent dietary structure and habits of the Chinese population have changed greatly compared with those in 2002, and the food contribution to advantame dietary intake for the Chinese population may have

Table 2. Detailed estimated dietary exposure to advantame among the Chinese population

Age group	*N*	Dietary exposure (mg/kg BW per day)			ADI	
		Mean	P97.5	P99	P97.5	P99
2–3	1,351	0.0120	0.0016	0.0460	0.0003	0.0092
4–9	5,829	0.0114	0.0013	0.3167	0.0003	0.0633
10–17	8,380	0.0053	0.0005	0.0177	0.0001	0.0035
18–59	43,397	0.0010	0.0003	0.0006	0.0001	0.0001
≥ 60	9,996	0.0002	0.0002	0.0005	0.0000	0.0001
General	68,953	0.0025	0.0004	0.0009	0.0001	0.0002

Note. High exposure accounting for a proportion of ADI (%) = 97.5% or 99% dietary intake. The following formula was used: $x = \frac{A}{B} \times 100\%$, x is high exposure intake accounting for a proportion of ADI, A is 97.5% or 99% dietary intake (mg/kg BW), and B is ADI (mg/kg BW).

also changed. The aforementioned uncertainties should be considered when applying the results and conclusions of this assessment to actual management decisions.

This study was a theoretical evaluation based on currently available data. According to the principles of risk assessment for food additives, when no abuse has occurred, an actual intake evaluation is unnecessary if the theoretical evaluation results show minimal health risk. Through the theoretical evaluation of advantame, the current provisions of the No. 8 Notification of NHC provides sufficient health protection for the general population in China, including all age groups. However, a study has shown several cases of abuse of advantame during the manufacture of processed fruit in China. Therefore, it is necessary to ascertain the actual concentration of advantame in various foods, update food consumption data, and conduct an actual intake assessment for advantame among the Chinese population.

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Received: May 21, 2019;
Accepted: October 28, 2019

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