neotame™

A Scientific Overview

neotame™

Overview

- A versatile new sweetener and flavor enhancer that delivers great taste.
- FDA approved for general use in foods and beverages after an extensive safety review.
- Over 100 studies confirm its safety and functionality.
- Rapidly eliminated through normal body processes with no accumulation in the body.
- Safe for use by the general population, including pregnant and lactating women, children, and people with diabetes.

table 1

Potential uses for neotame in foods and beverages

- Beverages
- Tabletop sweeteners
- Frozen desserts, ice cream, yogurt
- Chewing gum, candy
- Bakery products
- Toppings, fillings, fruit spreads
- Cereal
- Many others

Neotame is a versatile new food ingredient that can be used as a sweetener and flavor enhancer in foods and beverages. Neotame provides food and beverage manufacturers with greater flexibility and value in developing products that meet consumer expectations for great taste.

FDA Approved. After reviewing more than 100 scientific studies with neotame, the U.S. Food and Drug Administration (FDA) affirmed its safety and functionality by granting general use approval for neotame as a sweetener and flavor enhancer in foods and beverages.

FDA has a detailed and extensive process for evaluating the safety and functionality of new food additives. This rigorous process provides a high level of confidence in the safety of neotame. FDA's review of neotame included evaluation of the comprehensive research done in both humans and animals using amounts of neotame that far exceed expected consumption levels.

The results of these studies confirmed that neotame is safe for use by the general population, including children, pregnant and lactating women, and people with diabetes. In addition, no special labeling for phenylketonuric individuals is needed.

Functionality in Foods and Beverages.

Excellent Taste: Neotame has a clean sweet taste like sugar. It is about 8,000 times sweeter than sugar on a weight basis, thus only very small amounts are needed in products (e.g., only about 6 mg of neotame is needed to sweeten a 12-ounce serving of beverage).

Versatility: Neotame functions effectively in a wide range of foods and beverages (*table 1*). It can be used alone or as part of a blend system with other non-nutritive or nutritive sweeteners to create new sweet tastes.

Flavor Enhancement: Neotame uniquely enhances the flavors of other ingredients, such as mint, in foods and beverages.

Neotame Structure and Metabolism. Neotame (N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester) is a derivative of the dipeptide composed of the amino acids, aspartic acid and phenylalanine (*figure 1*).

Neotame is rapidly metabolized. The major metabolic pathway of neotame is hydrolysis of the methyl ester by esterases that are present throughout the body. This yields de-esterified neotame, the major metabolite, and an insignificant amount of methanol (*figure 2*). Neotame and de-esterified neotame are rapidly cleared from the plasma (*figure 3*). Neotame is completely eliminated in the urine and feces and does not accumulate in the body.

Due to the presence of the 3,3-dimethylbutyl group, peptidases, which would typically break the peptide bond between the aspartic acid and phenylalanine moieties, are essentially blocked, thus reducing the availability of phenylalanine.

The amount of methanol derived from neotame is exceedingly small relative to the amount of methanol derived from common foods, such as fruits and vegetables and their juices. As shown in *figure 4*, the amount of methanol derived from a serving of beverage sweetened with 100% neotame is small compared to that from several common fruit juices. For example, the amount of methanol provided by tomato juice is about 200 times greater than that from neotame in an equivalent volume of beverage.

figure 2 Metabolism of neotame to de-esterified neotame and an insignificant amount of methanol.

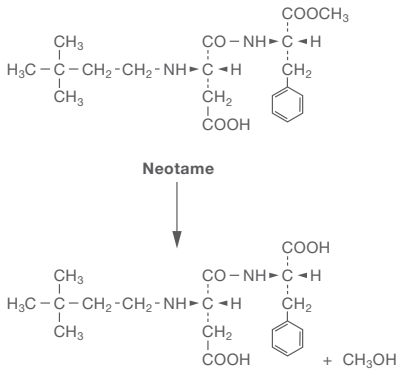
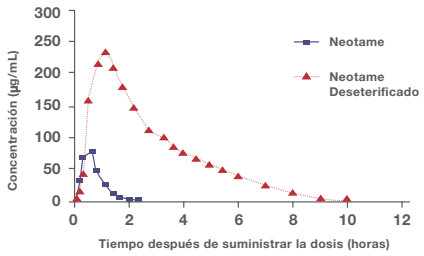


figure 3 Neotame and de-esterified neotame are rapidly cleared from the plasma.*



* Después de una dosis oral de 0.25 mg/kg de peso corporal

figure 1 Structure of neotame.

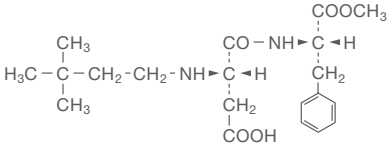
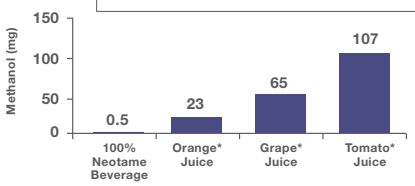


figure 4 Approximate amount of methanol derived from beverages (355 mL).



* Wucherpfennig et al., Flüssiges Obst., 348-354, 1983.

table 2

Preclinical safety studies with neotame

- Metabolism
- Genetic Toxicity
- Subchronic Toxicity
- Chronic Toxicity
- Carcinogenicity
- Reproductive Toxicity
- Teratology
- Pharmacology

table 3

Human safety studies with neotame

- Pharmacokinetics and Metabolism
- Dose-Related Pharmacokinetics
- Repeated Ingestion
- Pharmacokinetic Profile: Solution vs. Capsules
- Single-Dose Tolerance
- Two-Week Tolerance
- 13-Week Tolerance
- Study in Individuals with Type 2 Diabetes

table 4

Parameters measured or evaluated in humans

- Physical Examination
- Vital Signs
- Clinical Chemistry
- Hematology
- Urinalysis
- Electrocardiogram
- Opthalmologic Evaluation
- Adverse Experiences

Safety Research With Neotame. The results of extensive research done in animals and humans using amounts of neotame that far exceed expected consumption levels clearly confirm the safety of neotame for use as a sweetener and flavor enhancer by the general population including children, pregnant and lactating women, and people with diabetes.

Preclinical Studies. A comprehensive battery of safety studies in several animal species demonstrates the safety of neotame (*table 2*). Long-term and lifetime studies in animals, including *in utero* exposure, clearly demonstrate that neotame is not carcinogenic. In addition, there are no effects of neotame on reproduction or growth and development of offspring across multiple generations. There is also no evidence of teratogenicity or genetic toxicity. No toxicological effects were observed, even with amounts up to 40,000 times the expected daily intake (0.1 mg/kg body weight) for high-level consumers (90th percentile). This dosage of neotame is approximately equivalent to consumption of one of the following by an adult human, every day for a lifetime:

- 50,000 cans (12 oz.) of beverage with neotame or,
- 280,000 packets of tabletop sweetener with neotame or,
- the sweetness equivalence of 1,000 (5 lb.) bags of sugar.

Human Studies. In addition to the numerous safety studies done in laboratory animals, clinical studies were done in healthy adults and in people with Type 2 diabetes (*table 3*). A listing of parameters measured or evaluated in the human studies is found in *table 4*. The results of these clinical studies further confirm that neotame, even in amounts well above projected consumption levels, is safe and well tolerated in humans. Two key human studies are summarized below.

13-Week Tolerance Study: A randomized, double-blind, placebo-controlled, parallel design study was done in healthy adult male and female subjects. Subjects received either 0.5 mg/kg body weight of neotame or 1.5 mg/kg body weight of neotame or placebo daily for 13 weeks. The 1.5 mg/kg body weight dose is equivalent to the amount of neotame in about 6 liters of beverage sweetened 100% with neotame consumed every day by an adult. Specific clinical laboratory parameters measured in this study are found

in *table 5*. The results confirm that, even in amounts 15 times the projected daily consumption by high-level (90th percentile) consumers, neotame is safe, well tolerated, and not associated with adverse health effects.

Study in Individuals with Diabetes: Neotame was well tolerated in a clinical study done with individuals with Type 2 diabetes. In this randomized, double-blind, placebo-controlled, multiple-dose, crossover study, subjects received daily doses of 0.5 mg/kg body weight of neotame, 1.5 mg/kg body weight of neotame, and placebo for two weeks on each treatment. There were no observed effects of either of the doses of neotame on plasma glucose (*figure 5*) or insulin concentrations (*figure 6*) or on glycemic control compared to placebo. In addition, there was no association of neotame with adverse health effects in this population.

figure 5 Plasma glucose concentrations in individuals with Type 2 diabetes after neotame and placebo.

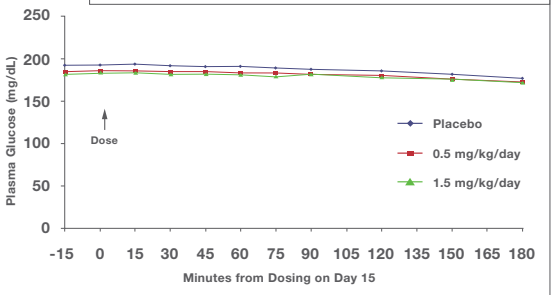


figure 6 Plasma insulin concentrations in individuals with Type 2 diabetes after neotame and placebo.

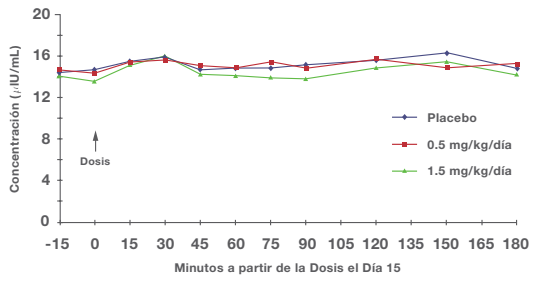


table 5

Clinical laboratory parameters measured in the 13-week tolerance study

Hematology:
hemoglobin
hematocrit
red blood count (RBC)
white blood count (WBC)
differential WBC
platelet count

Clinical chemistry:
sodium
potassium
chloride
glucose
urea nitrogen
total bilirubin
calcium
creatinine
magnesium
total cholesterol
HDL
LDL (calculated)
total triglycerides
uric acid
alkaline phosphatase
AST (SGOT)
LDH
GGT
ALT (SGPT)
total protein
albumin
inorganic phosphorus
CO_2

Thyroid function:
T-4 (thyroxine)

Urinalysis:
specific gravity
pH
glucose
ketones
protein
WBC
RBC

Coagulation:
prothrombin time
partial thromboplastin time

The Neotame Advantage

Neotame represents the culmination of over 20 years of research and development efforts to provide consumers with better tasting, healthier food and beverage choices. Neotame's greater flexibility and value for food and beverage companies combined with its great taste makes for a winning combination in bringing new product innovations to market.

Neotame: A Step Toward Healthful Eating. Health experts agree that eating well and being physically active are key components of a healthful lifestyle. Because eating a healthful diet is a challenge for many people, the American Dietetic Association encourages health professionals to provide consumers with practical nutrition advice that is in line with the "Dietary Guidelines for Americans" released in 2000 by the United States Department of Agriculture and the United States Department of Health and Human Services.

As a sweetener, neotame can reduce or replace the sugar and caloric content of products while maintaining great taste. Neotame offers one simple step that can help consumers move closer to achieving the dietary guideline that states, "Choose beverages and foods to moderate your intake of sugars."

In addition, products sweetened with neotame offer people with diabetes greater variety and flexibility in budgeting their total carbohydrate intake. People with diabetes are more likely to comply with a healthful meal plan when they are able to eat foods that they enjoy.

Questions and Answers about Neotame

What is neotame? Neotame is a new sweetener and flavor enhancer, which has a clean sweet taste like sugar. Because it is so intensely sweet (about 8,000 times sweeter than sugar by weight), only very small amounts are needed to sweeten foods and beverages. Neotame can be used alone or blended with other non-nutritive or nutritive sweeteners.

How can neotame be used? Neotame was approved for general use as a sweetener and flavor enhancer in foods and beverages in 2002 by the U.S. Food and Drug Administration (FDA). Neotame can be enjoyed by all segments of the population.

How was the safety of neotame tested? Over 100 studies confirm the safety of neotame. A comprehensive battery of safety studies in animals at dosages thousands of times greater than projected 90th percentile human consumption levels demonstrated:

- No toxicity, carcinogenicity, teratogenicity, or reproductive effects of neotame;
- No mutagenic effects of neotame in bacterial and mammalian systems; and
- No pharmacological effects of neotame on various organ systems.

Tolerance studies in healthy humans established that neotame has:

- No effect on clinical or biochemical parameters compared to placebo;
- No adverse experiences compared to placebo; and
- No effect on plasma glucose or insulin concentrations in individuals with Type 2 diabetes.

How does the body handle neotame? Does it accumulate in the body? Neotame is rapidly metabolized, completely eliminated, and does not accumulate in the body. The major metabolic pathway is hydrolysis of the methyl ester by esterases that are present throughout the body, which yields de-esterified neotame and methanol. Because only very small amounts of neotame are needed to sweeten foods, the amount of methanol derived from neotame is very small relative to that derived from common foods, such as fruit and vegetable juices. Peptidases, which would typically break the peptide bond between the aspartic acid and phenylalanine moieties, are essentially blocked by the presence of the 3,3-dimethylbutyl moiety, thus reducing the availability of phenylalanine.

Does neotame have any effect on body systems? No. Extensive tests with animals and humans clearly demonstrated no effects of neotame or de-esterified neotame on any body systems.

Are there any adverse health effects from neotame? No. In human studies, there are no significant differences between neotame and placebo in reported adverse experiences, physical examinations, vital signs, clinical laboratory parameters, electrocardiograms, or ophthalmologic exams.

How was the potential for carcinogenicity of neotame assessed? Long-term and lifetime studies in animals, including *in utero* exposure, clearly demonstrate that neotame is not carcinogenic. Further, *in vitro* and *in vivo* studies demonstrated no mutagenic effects of neotame or its major metabolite, de-esterified neotame.

Can neotame be used during pregnancy and lactation? Yes. The FDA approved neotame for use by the general population including pregnant and lactating women. High dietary doses of neotame in animals did not result in any effects on reproductive performance, development of the embryo or fetus or postnatal development. Further, there were no effects on offspring growth, developmental milestones, physical maturation, sensory response, activity, or behavior. Examination of the fetuses for external, visceral, and skeletal abnormalities revealed no fetotoxic or teratogenic effects. In addition, from the results of autoradiography evaluations, there is no apparent distribution of the neotame dose to the fetus.

Thus, neotame can be safely incorporated into the overall diet of pregnant and lactating women. However, most women need to increase their caloric intake during pregnancy and while breastfeeding, so it is important that they consume foods that supply adequate calories and nutrients required to nourish the fetus or infant during this important time. Of course, it is important for all pregnant and lactating women to consult with their physicians regarding their nutritional needs.

Is neotame safe for children? Yes. Preclinical studies in which extremely large doses of neotame were given from the prenatal period all the way to adulthood demonstrated no effects of neotame on growth and development. Thus, neotame can be safely incorporated as part of a healthful diet for children. It is important to keep in mind that children, particularly those under two years of age, need adequate calories for growth and development.

Can neotame be incorporated into the diets of people with diabetes? Yes. Neotame has no effect on plasma glucose and insulin concentrations or on glycemic control in diabetic individuals. Thus, foods sweetened with neotame can be safely incorporated into their meal plans to help them achieve their dietary goals.

Will people with phenylketonuria be able to consume neotame? Yes. Individuals with phenylketonuria may consume foods and beverages that contain neotame, and no special labeling for phenylketonuria is needed on products with neotame.

What is the ADI? The ADI is the amount of an additive, which if consumed daily over a lifetime, is considered safe. Occasional excursions above the ADI do not pose a safety issue. Because the very conservative estimate of 90th percentile projected neotame consumption was well below the ADI, FDA granted general use approval for neotame in foods and beverages.

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