Introduction:

Aspartame is an artificial, non-saccharide sweetener used as a sugar substitute in many foods and beverages. In the European Union, it is known under the E number E951. Aspartame consists of phenylalanine, aspartate and methanol. Because of these components it is suspected of causing seriously damage to human’s health. In this elaboration the discovery, use, synthesis and risks of Aspartame are shown.

These topics follow a short conclusion about the dangerousness of aspartame.

Chemical Facts:

- \( N-(\text{L-}\alpha-\text{Aspartyl})-\text{L-phenylalanine}, \ 1\text{-methyl ester} \)
- Molecular formula: \( C_{14}H_{18}N_2O_5 \)
- Molar mass: 294.3 g mol\(^{-1}\)
- Melting point 246–247 °C
- CAS number: 22839-47-0
- Solubility in water: sparingly soluble

Discovery:

The sweetening effect of aspartame was discovered in 1965 by chance. Jim Schlatter, a chemist working for G.D.Searle, synthesized the dipeptide aspartyl-phenylalanin methylester as a intermediate of a tetrapeptid of which he hoped it would be an anti-ulcer-drug.

Accidentally, he got some of the dipeptide on his hand without noticing and later licked his finger which tasted sweet. He noticed that the only possible source of the sweet taste could be the dipeptid. Knowing that the components of the peptide were natural amino acids he felt safe to have a taste of it in coffee and noticed that the sweetening effect was much higher then the one of sucrose. In addition, there was no bitter aftertaste which is normally typical for artificial sweeteners.

His superior, Dr. Bob Mazur, saw the potential value of this discovery, and in the 1970s he started studies to prove the safety of aspartame.
Between the discovery and the admission to use aspartame in food lie many years, for the reason that it was suspected that aspartame may be causing nerve cell and brain damage, even brain tumours. Tough there were many studies from different scientists about the consequences of aspartame consumption neither did prove clearly whether there was any danger. The studies carried out by Searle showed no negative effect of aspartame, other studies for example carried out by John Olney, a scientist of the Wash-low-University St.Louis, were not as clear though there also was no direct evidence that aspartame causes cancer or damages the nerves. Olney called aspartame a inconclusive substance which is of dubious reliability. Therefore he advised to wait with the authorization of aspartame in food some more years until the studies show a clear result.

Nevertheless, in Juli 1981 the Food and Drug Administration (FDA) under the commissioner Arthur Hayes allowed aspartame for use in dry products such as chewing gum, table top sweeteners or puddings. In carbonated drinks it was not allowed because it was not stable at this time.

Two years later, in 1983 the permission for use in carbonated drinks was given.

In Germany aspartame has been allowed for use since 1990. The use is bound to the restriction of admission for additives.

Since 1993 it also can be used in any drinks, bakery produce or sweets.

In the USA there are no restrictions for use of aspartame any longer.

The studies were continued after the authorization of aspartame in food but they still bring controversial results.

However, Aspartame is still allowed to be used in food and drinks and the safety of it is again and again confirmed by the European Food Safety Authority (EFSA).
Use:

Aspartame, also known as E951 and under the trade-names Equal, Canderel, Nutrasweet, Spoonful or E951, today is used in many products, which are declared not to contain sugar or are calorie reduced.

It is obtainable as table top sweetener in tablet and liquid form.

The acceptable daily intake (ADI) value lies at 40 mg/kg per day.

Originally, aspartame has four calories per gram which corresponds to the declaration of value of calories of sucrose per gram. But because of the high sweetening ability which is about 180 times higher than the one of sucrose much less of the sweetener to reach the same sweetening grade is required.

Therefore, aspartame can be used in a deliberate low-calorie nourishment and can help fighting overweight.

It is also suitable for people suffering from diabetes, because sweeteners like aspartame do not influence the insulin and blood sugar levels. So people affected, may consume sweet food without having to worry about their insulin level.

In addition, aspartame is not supporting tooth decay because the bacteria causing this disease cannot metabolise it.

Aspartame can also be used in combination with other sweeteners such as acesulfam. This compound is called aspartame-acesulfame salt and consists of approx. 64% of aspartame and 35% of acesulfam. Though acesulfam, which is a calorie free, heat-resistant sweetener that is not metabolised has nearly the same sweetening effect as aspartame, the combination of the two sweeteners has a sweetening effect which is 350 times higher than the one of sucrose.

The aspartame-acesulfame-salt disintegrates in the body. Aspartame is metabolised as usual, acesulfame is eliminated unrevised and without having been metabolised.
Structure of aspartame-acesulfame salt:

These days aspartame is used in about 90 countries. Nearly 9000 products like several soft drinks without sucrose, jams, alcoholic drinks, but also snacks made of nuts and corn and even canned food contain the sweetener.

16000 tons of aspartame are produced every year.

**Synthesis:**

Aspartame contains two amino acids, aspartic acid and phenylalanine, connected through one amide bond. Aspartame is made in two steps. The first is to produce the amino acids and the second is a synthesis process.

The amino acids are made through fermentation. Therefore a culture of bacteria is needed. For L-aspartic acid and L-phenylalanine B. flavum and C. glutamicum are used. When the population is sufficient, it is put into a seed tank and everything needed to grow and produce the amino acids is added. The environment includes besides glucose or sucrose, carbon sources like acetic acid, alcohols or hydrocarbons, and nitrogen sources such as liquid ammonia or urea. These are required for the bacteria to synthesize large quantities of the desired amino acid. When the required growth of the bacteria is achieved, it is transferred to the fermentation tank. The fermentation tank is similar to the seed tank, but has more volume. Consequently the amino acid production is much larger. When sufficient amino acids are produced, the isolation follows by means of a centrifuge, which isolates the acids from the organic remains. The acids will be conditioned through ion-exchange and a crystal separator. The amino acids are now ready for the chemical synthesis process. As can be seen, Aspartame is made of (S)-phenylalanine methyl ester and (S)-aspartic acid.
The reaction is based on protection groups. The first step is to protect the NH2 (2) – group of the aspartic acid with the protecting group carboxybenzyl (Cbz). After that, the two carbonyl acids react with benzyl alcohol (BnOH) (3). These acids are now protected as benzyl esters. The next step is to hydrolyze one of those benzyl ester. It’s fascinating that this chemo selective hydrolyze, to let only one benzyl-ester-groups react, works. (4)

Now the molecule is able to respond to 2,4,6-trichlorophenol. The product is a new ester (5,6). Finally the molecule is ready for deciding reaction with phenylalanine methyl ester hydrochloride. Under influence of base the dipeptid is formed (7). Now you just need to remove the protecting groups with palladium catalyst and you get a sweet substance, which James Schlatter got on his hand by accident. (8)

Source: Organic Chemistry by Jonathan Clayden, Nick Greeves, Stuart Warren, Peter Wothers
Metabolism of aspartame and the effects:

Aspartame consists of methanol and two amino acids, aspartate and phenylalanine. When consumed, aspartame is broken down into these components by a peptidase-enzyme as follows:

- 50% Phenylalanine
- 40% Aspartate
- 10% Methanol

The products are metabolised in the human body as usual.

Phenylalanine:

Phenylalanine is a chirale and aromatic amino acid, which is essential for humans.

It is the precursor of the amino acid tyrosine, but also for catecholamines like epinephrine, norepinephrine and dopamine, which are hormones acting as neurotransmitters.

This amino acid takes part in the amino acid metabolism, the protein structure and the neurotransmitter regulation.

The body can assimilate it in two ways: Either it is absorbed by the liver or it is transported to the brain via the blood brain barrier.

In the liver phenylalanine reacts to tyrosine. The important enzyme is called phenylalanine hydroxylase.

The rest of the phenylalanine which is not turned into tyrosine can be taken over the blood brain barrier (BBB) by binding to a large neutral amino acid transporter called NAAT. The NAAT can transport several amino acids, so which of them is transported depends on the concentration of each amino acid.

If there is a higher concentration of phenylalanine than of other amino acids, NAAT mainly transports these molecules and therefore can block the transporting of other important amino acids into the brain like tyrosine. Tyrosine is a preliminary stage of dopamine. This reaction is catalysed in the brain by the enzyme tyrosine hydroxylase. Therefore tyrosine is necessary to produce the inhibitory neurotransmitter dopamine.

So if the transport of tyrosine into the brain is blocked by a higher concentration of phenylalanine, there is not enough dopamine and other catecholamines. This changes the regular concentrations of these substances and can lead to influences on the tasks of the brain.
Phenylketonuria (PKU)

(PKU) is an inheritable error of metabolism caused by a deficiency in the enzyme phenylalanine hydroxylase. Due to the absence of the enzyme, Phenylalanine cannot be hydroxylated to Tyrosine. The cause is a high concentration of Phenylalanine in the blood plasm. The consequences are developmental disorders, like mental retardation or brain damage. PKU usually is detected by a routine newborn screening test. In order to reduce the Phenylalanine concentration, patients are prescribed a low-phenylalanine diet.

Since Phenylalanine is a degradation product of Aspartame, every product which contains Aspartame has to refer to the Phenylalanine source.

Aspartic acid:

Aspartic acid is a non-essential amino acid. It is the precursor of glutamate, L-asparagine and glutamine.

This amino acid has an important function in brain and the central nervous system because it can act as an excitatory neurotransmitter at glutamate receptors. These receptors work primarily with glutamate, but aspartate has also a high affinity to these molecules.

As an excitatory neurotransmitter in synapses it opens ion channels and causes a depolarisation of the postsynaptic membrane.

If the concentration of aspartate in the synapses rises extremely, it can lead to neuroendocrine disturbance.

Aspartate is metabolised fast, the uptake to the brain is relative slow.

Methanol:

Methanol becomes formaldehyde and formic acid in the body by the enzyme alcohol dehydrogenase.

Because of these products, it has a toxic effect. Formate is considered to cause the toxicity of methanol.

One negative effect of formate is that it alters the mitochondrial DNS and also the nucleic one.

In addition, formaldehyde has a carcinogen and mutagenic effect. Too much formaldehyde in the retina of the eye can cause blindness.

Formate can accumulate and it is believed that part of the toxicity mechanism is metabolic acidosis, which means that the pH-value is reduced.
A high concentration of methanol in the body can not only cause blindness, but can also lead to death.

There are also antidotes against a poisoning with methanol like for example ethanol, which works as a competitive inhibitor.

**Conclusion:**

The conclusion is, that the effect of consume of aspartame is still not clarified beyond any doubt. Some studies prove the above negative shown effects to the human body as a result of an excessive consumption of aspartame. Other studies show the opposite and state that the usual consumption of aspartame is still too low to cause serious, if any damage.

The aspartic acid concentration in the brain will not increase as long as the concentration in the blood is lower than the one in the brain. Should the blood concentration of aspartic acid rise, the concentration of it in the brain is still higher, so there is no effect to the brain and to the neurons at all. In addition, the brain is protected by the blood brain barrier.

It also was found that a meal containing other amino acids and in addition aspartame will not result in an increase of the blood concentration in comparison with the same meal without aspartame.

This also applies to the other two components.

Methanol is not only part of aspartame but also of other natural products like fruit. It can also be cleared up rapidly when taken in low dose, which applies for both fruit juice and aspartame.

Phenylalanine is an amino acid many kinds of food contains, for example vegetables, nuts and soya.

In particular the amount of aspartame which is consumed daily is important to asses the effect. Normally, the amount of aspartame is so low that it does not have a negative effect to the health of human beings.

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