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What is aspartame?

Aspartame is a potent sweetener. It is about 200 times sweeter than sugar (sucrose), so only low concentrations are needed to make foods and beverages sweet. The amounts used are so small that aspartame provides almost no calories. Because of its excellent taste profile, it has become one of the leading low-calorie sweeteners around the world.

What is aspartame made of?

Aspartame is a simple molecule, made from a combination of two amino acids and a small amount of methanol. Each of these three components occurs as a normal constituent of foods. The amino acids - aspartic acid and phenylalanine - are members of the group of compounds which are the building blocks of protein. Aspartic acid and phenylalanine occur naturally in nearly all proteins, while methanol (strictly a methyl ester group) is widely distributed in polysaccharides, such as pectin, which are present in all fruits and vegetables.

What happens when I eat aspartame?

Like other foods, aspartame is digested in the intestines into its component parts. The two amino acids separate, and the methyl ester group forms methanol. These three are then taken into the bloodstream, and metabolised in the same way as these components would be from any other food. Aspartame itself cannot pass across the lining of the gut intact, and never enters the bloodstream.

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Is aspartame safe?

Yes, aspartame is safe. However, all materials are toxic if you have a large enough amount. Even common foodstuffs like sugar, or materials essential for life, such as salt or vitamins, are toxic when consumed in excess. Toxicologists have recognised for over five centuries that it is the exposure or dose which is important in risk assessment (a factor which is usually ignored by those making allegations that food additives are unsafe). The key question really is "What is a safe amount?", and it is this which guides regulators.

Who decides how much aspartame is safe?

The safety of aspartame has been considered by numerous national and international bodies, including the Food and Drug Administration (FDA) in the USA, the Scientific Committee for Food (SCF) – now the European Food Safety Authority (EFSA) – in Europe, and the Food and Agriculture Organisation/World Health Organisation Joint Expert Committee on Food Additives (JECFA). These are among the foremost toxicological authorities worldwide. Each of these bodies has concluded independently that aspartame is safe for use as a food additive. Based on the safety studies in animals, the SCF and the JECFA allocated an Acceptable Daily Intake (ADI) of 0-40mg/kg body weight. The FDA took a somewhat different view and allocated the slightly higher figure of 0-50mg/kg body weight.

What does this ADI mean?

The ADI is an estimate of the amount of a food additive that can be ingested daily over a lifetime without appreciable health risk. The ADI of 0-40mg/kg body weight for aspartame means that up to 40mg of aspartame can be consumed for every kilogram of a person's body weight, every day, throughout life, without appreciable health risk. That translates to up to 2.8 grams of aspartame daily for a typical 70kg person. In practical terms, 2.8g of aspartame are equivalent to the sweetness of 560g (nearly 1lb 4oz) sugar, or the amount of the sweetener in fourteen 330ml cans of a carbonated beverage sweetened with aspartame at the highest level permitted in the EU. Alternatively, you could view it as the aspartame contained in 125 typical sweetener tablets.

Where does the ADI come from?

It is derived from the results of a battery of toxicological tests, which may include studies in humans as well as animals or laboratory test systems. The tests include searching for effects on reproduction (from mating through to weaning), and looking for any potential of the

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additive to cause cancer (carcinogenicity) or to cause genetic mutations (mutagenicity). Toxicologists then determine the "no observed adverse effect level" (NOAEL) from the results of the most sensitive study with the most sensitive species tested. The NOAEL is the highest dose level that produces no detectable adverse changes in the body, its organs, its functioning, growth, development or life span.

Although the NOAEL is already a level which has no adverse effect, a further safety factor is then applied. Typically this factor is 100, so that the ADI is set at 1% of the NOAEL, but occasionally the factor can be higher or lower depending on the nature of the toxicological data. In the case of aspartame, the NOAEL was 4,000mg/kg body weight and this, divided by 100, produces an ADI of 0-40mg/kg body weight.

The ADI is thus a very conservative estimate, with a substantial safety factor built in. This safety factor takes into account the difference between animals and humans and the variability between individuals, including age, nutrition, pregnancy etc. It does not represent a "toxic limit" which can never be exceeded, but rather it is a means to guide society in ensuring food additives are used safely. The ADI is not immutably fixed. If more information becomes available, the ADI may be revised up or down, so the value reflects the best state of current knowledge.

I've heard that the safety studies on aspartame were flawed.

The history of aspartame's initial approval is as follows:-

Aspartame was discovered in 1965, and subjected to the usual battery of *in vitro* and *in vivo* studies in animals in the 1970s. These included both full-lifetime and shorter-term studies in rats and mice, a long-term study in dogs, as well as reproductive toxicity studies. The doses used in the 2-year rodent bioassays were up to 6-8g/kg body weight every day, thus aspartame represented the equivalent of about 16% by weight of the total diet.

However, there were criticisms of the quality of these studies. This led to reviews by the FDA and by Universities Associated for Research and Education in Pathology (UAREP), which reconsidered the study data, and by the US General Accounting Office, which investigated the FDA's approval process. In addition there was a Public Board of Inquiry (PBOI) to examine the safety of aspartame. A number of specific issues were raised at the PBOI, including the incidence of brain tumours in one of the long-term rat studies. This issue was considered and reported in detail by the FDA in their review, and subsequently by other bodies such as the JECFA, SCF and the Committee on Toxicity (COT) in the UK. The overall

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conclusion was that while there were some flaws in the conduct of the early animal toxicity studies, they did not invalidate the conclusions about safety. Because of the questions about its quality, the aspartame database is probably the most thoroughly assessed and reviewed safety database of any food additive. Moreover, aspartame's safety has been confirmed in many subsequent studies. The toxicological authorities periodically consider all the latest data, and have not modified their assessment of aspartame's safety.

Still, hasn't aspartame caused a lot of medical problems since it was marketed?

No. That is a frequent allegation, but the facts do not bear it out. The original manufacturers of aspartame set up a system to record medical complaints from consumers. The objective was to provide an opportunity for the public to register, without cost, any adverse reaction to aspartame, with a view to detecting any possible untoward effects, however rare. Every complaint was systematically evaluated and followed up with the complainant and, where possible, with the complainant's own physician. The details were forwarded to a separate, but similar, scheme run by the FDA and covering all foods, additives and dietary supplements. This post-market surveillance by the manufacturer was continued for more than ten years in the USA.

The record of complaints peaked early in the marketing of aspartame, in 1985, when almost 800 were recorded. Since 1988 the number of complaints alleging the involvement of aspartame has stabilised at around 300 per year. To put this in context, the FDA receives about 7,000 complaints each year associated with food in general. Interestingly, in the "peak complaint year" of 1985 there were available fewer than 100 products containing aspartame. Since then, complaints have declined while the number of products has risen. By 1993 there were around 6,000 products, a number which has continued to grow since.

The complaints recorded are all "anecdotal", that is, it is the consumer personally who makes some association between an adverse reaction and the intake of aspartame. Further investigation is needed to establish if there is a link or if the association by the consumer is just coincidence. In the case of aspartame, this is made difficult because the majority of symptoms are commonplace and mild. In the sum of all complaints up to 1993, most frequently complained of were headache (23%), dizziness (6%), rash (5%) abdominal pain (5%) and nausea/vomiting (5%). These are all common human experiences and can have many causes. For the latter years of this survey period aspartame was consumed regularly by about half the US population - more than 100 million users. In such a huge group of people it would not be surprising to find purely coincidental associations between common discomforts and aspartame consumption. Nevertheless, medical researchers have done many studies to evaluate anecdotal reports and to follow up the issues raised.

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Often these studies have been done with consumers who were convinced their symptoms were caused by aspartame. For example, in one investigation 40 people complaining of aspartame-induced headaches were each tested alternately with aspartame and non-aspartame containing placebo. There was no difference between aspartame and the placebo as regards the occurrence of headache, its severity, time of onset or duration. Similarly, a trial involving 21 people who claimed to have allergic reactions to aspartame showed that a placebo was just as likely to cause their symptoms. In another investigation of alleged allergic reactions to aspartame by 12 persons, it was impossible to reproduce the symptoms complained of. Similar work has been done to follow up allegations that aspartame was linked to seizures, changes in mood and behaviour, attention deficit disorder, hunger, food intake and body weight. The studies have shown that there is no link between aspartame and the anecdotal reports of adverse effects.

But what about aspartame's components? Why do I see "contains phenylalanine" on labels of products containing aspartame?

Phenylalanine is an essential amino acid, that is to say humans cannot make enough to maintain health and must obtain it from the diet. In the body, phenylalanine is not only a component of protein, but also the precursor for the neurotransmitters dopamine, norepinephrine (noradrenaline) and epinephrine (adrenaline). Some people suffer a rare inherited disorder, phenylketonuria (PKU), which means their ability to metabolise phenylalanine is seriously impaired. These patients can have very high plasma concentrations of phenylalanine, and this can lead to neuronal damage and affect development of the brain. In many countries, therefore, it is a legal requirement that babies are routinely tested for PKU soon after birth. Treatment of the condition involves careful control of all the sources of phenylalanine in the diet. Phenylalanine is one of the components of aspartame, and is released when aspartame is digested. Accordingly, products which contain aspartame give the advice that they contain a source of phenylalanine for the information of PKU patients.

Sufferers of PKU have two defective genes, one from each parent. There are individuals who have just one gene for PKU (heterozygous subjects) who do not have the disease but, although they may not know it, have a reduced ability to metabolise phenylalanine. All other people are able to metabolise and eliminate excess phenylalanine without problem. The extensive clinical database on aspartame (which exceeds that for any other food additive) has defined the rise in plasma concentrations of phenylalanine after doses of aspartame in both normal people and those heterozygous for PKU. An increase in plasma levels of phenylalanine occurred when an intake of aspartame (34mg/kg, roughly equivalent to the aspartame in four litres of diet beverage) was consumed as a single dose. However,

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only slight and insignificant increases were found when this amount was given as three separate doses over a 4-hour period – still a large quantity, but a somewhat more realistic period of intake. The peak, or maximum, changes were higher in subjects who were heterozygous for PKU but, even for these people, the changes were similar to the normal rises seen after consuming a meal.

Further reassurance comes from consideration of the amount of phenylalanine released by digestion of aspartame, compared with that available from other foods. (See Table attached). Aspartame is only a minor source of dietary phenylalanine. The typical adult intake of phenylalanine from all sources is 3 to 5g per day.

I've seen suggestions that aspartic acid is neurotoxic – that it damages your brain.

Aspartic acid is another normal neurotransmitter within the brain. As we have already seen, anything taken to excess can be toxic, and that is also true for aspartic acid. However such doses are simply not achievable from foodstuffs or from consuming aspartame at the ADI. As is the case with phenylalanine, a normal diet supplies far more aspartic acid (which makes up about 10% of the protein in milk and meats) than aspartame.

What about methanol – isn't that especially poisonous?

Methanol, or methyl alcohol, is naturally found in fruits and vegetables. It occurs both as the free alcohol and bound in the form of compounds called methyl esters. Pectin is an example of a food component which contains methyl ester groups and which is present in all fruits and vegetables. Methanol is released when such esters are digested.

Europeans typically consume 2 to 5g of native pectin a day, which provides up to 0.7g methanol. These quantities of methanol, plus those from other sources, are routinely handled by the body with no ill effect. To achieve toxic responses in adults, methanol must be consumed to the extent of 12-30g or more (that is, 200-500mg/kg body weight).

Aspartame is also a methyl ester. It releases 11% of its weight as methanol when digested or otherwise broken down. However, because aspartame is a potent sweetener, only tiny amounts are used and correspondingly minute quantities of methanol are produced. For example, the full ADI of aspartame (40mg/kg body weight) would release 4.4 mg methanol/kg body weight. This is insignificant in comparison to the 200-500mg methanol/kg body weight needed to produce symptoms of methanol poisoning.

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When methanol is metabolised, most ends up as formic acid (formate in the blood and excreted in urine). In experiments, people have swallowed large amounts of aspartame with no detectable effect on blood formate concentration. In one test the quantity of aspartame was 200mg/kg body weight, taken all at once. For a 70kg person this is equivalent to all the aspartame in more than 23 litres (69 cans) of diet soft drink. In sweetness it corresponds to 2.8kg (more than 6lbs) of sugar. In another test, aspartame intake by 50 subjects was 75mg/kg body weight daily for a period of 24 weeks. This did not raise their blood levels of methanol, or formate, or increase the urinary excretion of formate, compared to control subjects who received a placebo.

Doesn't aspartame release its components faster than ordinary foods?

A number of critics of aspartame question the comparisons of post-consumption plasma levels of aspartic acid, phenylalanine and methanol with the levels that occur after a meal. The critics describe the components as "free" in aspartame, but not in foods where they are normally present in complex nutrients such as proteins. Although aspartame is a simple molecule compared with proteins and polysaccharides, it still has to undergo digestion in the intestine prior to absorption. Whereas the rate of release of the amino acids in the intestine would be more rapid from aspartame than complex foods, the plasma profiles in the numerous clinical studies show only minor differences. Thus, while plasma concentrations of aspartic acid do not change significantly with aspartame intakes similar to or below the ADI, plasma phenylalanine levels increase steadily over the first hour after consumption, and then decline. The differences are small, and do not invalidate the comparison with the digestion of food.

I can consume aspartame in a drink without taking any food. Does that make a difference?

A further allegation is that when aspartame is digested in the absence of the other foods, the sweetener's components may produce unexpected effects – even though the plasma concentrations are normal. This criticism, like most others, ignores the totality of the scientific and clinical studies in which aspartame was given at much higher doses than would result from its normal use. In such trials, the three components of aspartame would be highly elevated compared to normal consumption, but all other nutrients would be unaffected.

For example, in one test, 53 subjects were given almost twice the ADI of aspartame every day for 24 weeks. No significant adverse effects were found, nor were there any significant

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changes in blood biochemistry. The study was conducted as a classical clinical trial, and was double-blind and placebo-controlled, with 55 subjects receiving placebo. Even this, the most comprehensive, long-term clinical study ever undertaken on a food additive, is not accepted by the critics of aspartame. It would seem reasonable to wonder if the critics will ever accept the toxicological evidence.

AMOUNTS OF PHENYLALANINE FROM VARIOUS FOODS

FOOD	QUANTITY grams	PHENYLALANINE CONTENT milligrams
Meat		
Beef, raw	100	880
Chicken, raw	100	960
Liver, raw	100	1180
Dairy		
Egg, one, in shell	50	320
Milk, full cream	250 ml	420
Cheese, 30% fat Gouda	100	2200
Cheese, 35% fat Cheddar	100	2110

Yoghurt	100	220
Fish		
White fish, raw	100	600
Cereals		
Bread, white	100	430
Rice, dry	100	330
Rice, boiled	100	110
Vegetables		
Peas, dry	100	860
Peas, fresh	100	230
Haricot beans, dry	100	1190
Potato, raw	100	90
Nuts		
Almonds	100	1050
Peanuts	100	1400
Hazelnuts	100	600
Aspartame products		
Sweetener, one typical tablet (= 1 spoon sugar)		11
Diet cola drink (sweetened with aspartame at the highest concentration permitted in the EU)	330 ml (1 can)	100