The Safety of Low-calorie Sweeteners

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The safety of all food additives, including low-calorie sweeteners, is assessed by a series of *in vitro* and *in vivo* studies in animals, and human data (usually limited).

The studies are sponsored by the manufacturer and usually performed by contract research laboratories.

The studies have to address a wide range of predefined endpoints and must be performed to internationally recognised criteria before the data can be accepted.

The data are assessed by national and international scientific committees, such as the JECFA and the EFSA Panel, and an *acceptable daily intake* established, before any proposed additive can be added to food.
THE RISK ASSESSMENT PARADIGM

1. HAZARD IDENTIFICATION
   What can it do?

2. HAZARD CHARACTERISATION
   What is the dose-response?
   What would be a “safe” dose for humans?

3. INTAKE ASSESSMENT
   What is the intake by humans?

4. RISK CHARACTERISATION
   What is the risk associated with that intake?
“All things are toxic and there is nothing without poisonous qualities: it is only the dose which makes something a poison”

PARACELSUS (1493-1541)
<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic</td>
<td>Various genetic endpoints in bacteria and mammalian cells; screen for potential carcinogens</td>
</tr>
<tr>
<td>Acute</td>
<td>Usually single dose study</td>
</tr>
<tr>
<td>Short-term</td>
<td>Repeated daily doses for 14-28 days; identifies the target organ</td>
</tr>
<tr>
<td>Sub-chronic</td>
<td>Repeated daily doses for 90 days; gives dose-response, and used for dose selection in chronic studies</td>
</tr>
<tr>
<td>Chronic</td>
<td>Repeated daily doses for two years in rodents; used to investigate carcinogenicity; usual NOAEL for ADI</td>
</tr>
<tr>
<td>Reproductive</td>
<td>Dosing occurs before during and after reproduction to investigate effects on foetal and neonatal development</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Used to define possible active metabolites, potential for accumulation and species differences compared to human</td>
</tr>
</tbody>
</table>

In all studies the dose is increased until an effect is detected
“All things are toxic and there is nothing without poisonous qualities: it is only the dose which makes something a poison”

PARACELSUS (1493-1541)
THE RISK ASSESSMENT PARADIGM

1. HAZARD IDENTIFICATION
   What can it do?

2. HAZARD CHARACTERISATION
   What is the dose-response?
   What is the ADI?

3. INTAKE ASSESSMENT
   Is human intake below the ADI?

4. RISK CHARACTERISATION
   If so, then there is negligible risk
HAZARD CHARACTERISATION

Analyse dose-response data to define most sensitive toxic effect – i.e. that produced at the lowest doses in the most sensitive species

Define a daily intake which does NOT produce that effect

The acceptable daily intake (ADI) is determined by dividing the experimental no-observed-adverse-effect level (NOAEL) in the most sensitive animal studies by an uncertainty factor to give a margin of safety to allow for possible species differences and human variability
Dose-response in animals

“Safe” intake for humans

Divide NOAEL by safety or uncertainty factors

Safe” intake for humans

Divide NOAEL by safety or uncertainty factors
The NOAEL is divided by an uncertainty factor of 100-fold to derive the ADI expressed in mg/kg body weight.
<table>
<thead>
<tr>
<th>Sweetener</th>
<th>Sweetness (x sucrose)</th>
<th>ADI (JECFA) (mg/kg/day)</th>
<th>Date of latest ADI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspartame</td>
<td>180</td>
<td>0 - 40</td>
<td>1980</td>
</tr>
<tr>
<td>Cyclamate</td>
<td>30</td>
<td>0 - 11</td>
<td>1982</td>
</tr>
<tr>
<td>Ace-K</td>
<td>200</td>
<td>0 - 15</td>
<td>1991</td>
</tr>
<tr>
<td>Sucralose</td>
<td>600</td>
<td>0 - 15</td>
<td>1991</td>
</tr>
<tr>
<td>Saccharin</td>
<td>300</td>
<td>0 - 5</td>
<td>1993</td>
</tr>
<tr>
<td>Alitame</td>
<td>2000</td>
<td>0 - 1</td>
<td>2002</td>
</tr>
<tr>
<td>Neotame</td>
<td>7000</td>
<td>0 - 2</td>
<td>2004</td>
</tr>
<tr>
<td>Steviol glycosides (as steviol)</td>
<td>250 - 450</td>
<td>0 - 4</td>
<td>2008</td>
</tr>
</tbody>
</table>
THE RISK ASSESSMENT PARADIGM

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INTAKE ASSESSMENT

There have been more studies on the intakes of sweeteners than any other food additive.

Studies have been performed in most countries around the world including UK

In all cases the average intakes of all sweeteners by all groups (including children and diabetics) are well below the relevant ADI value

High percentile intakes (90-97.5\textsuperscript{th} percentile) are below the ADI for all sweeteners except cyclamate in Australia where intake was slightly above the ADI (but the ADI is based on its metabolite CHA and applies to only about 3% of the population)
THE RISK ASSESSMENT PARADIGM

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COMBINATIONS OF SWEETENERS

Sweetener blends can provide a better taste profile and in some cases provide synergism for sweetness.

Sweeteners are tested by high dose animal studies in which each is sweetener tested separately – could interactions occur in relation to safety?

Interactions could arise from:

- **Kinetics**: One compound interferes with the elimination of the other.
- **Dynamics**: One compound interferes with the toxic action of the other.
<table>
<thead>
<tr>
<th>Sweetener</th>
<th>Kinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ace-K</td>
<td>poorly absorbed; eliminated unchanged</td>
</tr>
<tr>
<td>Alitame</td>
<td>well absorbed; eliminated by hydrolysis and S-oxidation</td>
</tr>
<tr>
<td>Aspartame</td>
<td>hydrolysed in gut to dietary constituents</td>
</tr>
<tr>
<td>Cyclamate</td>
<td>unabsorbed fraction hydrolysed by gut flora to CHA: absorbed fraction excreted unchanged</td>
</tr>
<tr>
<td>Neotame</td>
<td>20-30% absorbed; hydrolysed by esterases</td>
</tr>
<tr>
<td>Saccharin</td>
<td>well absorbed; eliminated unchanged</td>
</tr>
<tr>
<td>Stevioside(s)</td>
<td>unabsorbed and hydrolysed by gut flora to steviol; steviol is absorbed and conjugated</td>
</tr>
<tr>
<td>Sucralose</td>
<td>poorly absorbed; largely excreted unchanged</td>
</tr>
</tbody>
</table>
## DYNAMICS OF SWEETENERS

<table>
<thead>
<tr>
<th>Sweetener</th>
<th>Dynamics (at &gt;100times the ADI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ace-K</td>
<td>non-specific; decreased body weight gain</td>
</tr>
<tr>
<td>Alitame</td>
<td>increased liver and body weight</td>
</tr>
<tr>
<td>Aspartame</td>
<td>decreased growth rate and organ weight changes</td>
</tr>
<tr>
<td>Cyclamate</td>
<td>CHA produces testicular atrophy; ADI based on CHA and assumes 20% conversion</td>
</tr>
<tr>
<td>Neotame</td>
<td>increased serum alkaline phosphatase in dogs</td>
</tr>
<tr>
<td>Saccharin</td>
<td>non-specific; decreased body weight gain</td>
</tr>
<tr>
<td>Stevioside(s)</td>
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ASPARTAME

A simple methylated dipeptide

There is a larger safety database on aspartame than on almost any other food additive

The database comprises the usual safety studies for

- genotoxicity
- short-term toxicity in animals
- long-term toxicity in animals
- metabolism data
L-aspartyl-L-phenylalanine methyl ester

Hydrolysis in gastro-intestinal tract

Aspartic acid  Phenylalanine  methanol

All components occur naturally in the diet
All can produce toxicity at very high exposures (everything can!)
All components occur naturally in the diet

**Aspartic acid**

- 100% Aspartame Beverage (355 ml): 72 mg
- Chicken* (100 g, Roasted): 2578 mg
- No-fat Milk* (355 ml): 948 mg
- Banana* (Medium): 133 mg

**Phenylalanine**

- 100% Aspartame Beverage (355 ml): 90 mg
- Chicken* (100 g, Roasted): 1130 mg
- Black Beans* (1 Cup, Cooked): 824 mg
- No-fat Milk* (355 ml): 598 mg

**Methanol**

- 100% Aspartame Beverage: 18 mg
- Orange Juice*: 23 mg
- Apple Juice*: 29 mg
- Red Grape Juice*: 65 mg
- Tomato Juice*: 107 mg
There are more data from studies on aspartame in humans than for any other food additive.

A major study found no adverse effects in 53 subjects given 75mg/kg/day for 24 weeks.

Studies in individuals claiming to suffer adverse effects (such as headache) found no effects under double-blind placebo controlled conditions.

Despite extensive human data, the ADI of 40mg/kg body weight was established in 1980 based on the traditional method using a no-observed adverse effect (NOAEL) from animal studies and a 100-fold uncertainty factor.
Recent findings

The Ramazzini studies and the EFSA Opinion

Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food (AFC) on a request from the Commission related to a new long-term carcinogenicity study on aspartame

Question number EFSA-Q-2009-122
Adopted on 3 May 2006

SUMMARY

The European Food Safety Authority (EFSA) has been asked by the European Commission to review the carcinogenicity study performed by the European Ramazzini Foundation of Epidemiology and Environmental Sciences (ERF) on the artificial sweetener aspartame, which was required in 1999 and 2006. The ERF considered that the results of their study showed that aspartame is a “multipotential carcinogenic agent”, based on increases in malignant neoplasm incidence, lymphomas/sarcomas (primarily in female rats), transplacental and tumoral transmission of the visual system and testis, increase in female rats, and histopathological abnormalities in peripheral nerve. EFSA asked for Scientific Opinions on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) to review the study as a matter of high priority.

Aspartame has been used in a number of soft drinks in a number of countries for more than 30 years. It is widely consumed throughout the world. In Europe, it was first authorised in the EU by Council Directive 86/295/EEC of 15 June 1986. It is therefore subject to regular safety evaluation by the European Commission (SCO Scientific Committee on Food (SCF)).

Aspartame has undergone extensive testing in animals and studies in humans, including four animal carcinogenicity studies conducted during the 1970s and early 1980s. These studies, together with studies on genotoxicity, were evaluated by regulatory bodies worldwide and it included extensive and comprehensive evaluation by the European Food and Safety Authority (EFSA). The European Commission has also been asked to review the study as a matter of high priority.

EFSA has been asked to review the study as a matter of high priority. The ERF study was performed in a single study, but it included extensive and comprehensive evaluation by the European Food and Safety Authority (EFSA). The European Commission has also been asked to review the study as a matter of high priority.

2006


SCIENTIFIC OPINION

Updated opinion on a request from the European Commission related to the 2nd ERF carcinogenicity study on aspartame, taking into consideration study data submitted by the Ramazzini Foundation in February 2009

Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food

(EFSA-Q-2009-122

Adopted on 20 April 2009

This opinion replaces the earlier version published on 20 April 2009.

Panel Members:


SUMMARY

Following a request from the European Commission, the Panel on Food Additives and Nutrient Sources added to Food (AFC) was asked to deliver a scientific opinion on the results of a long-term carcinogenicity study with premalignant exposure in the artificial sweetener aspartame, performed by the European Ramazzini Foundation (ERF) and published in June 2007 by Soffritti et al. The authors concluded that the results of their study not only confirm, but also reinforce their first experimental demonstration (published in 2003 and 2004) of aspartame’s multipotential carcinogenicity in a dose level close to the human Acceptable Daily Intake (ADI) based on

Total haematological cancers

Dose-response “relationship” is bizarre

Data confounded by chronic bronchial pneumonia (due to \textit{Mycoplasma pulmonis}?) causing lymphocyte hyperplasia (linked to the use of closed animal colony)
<table>
<thead>
<tr>
<th>EFSA CONCLUSIONS ON RAMAZZINI FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>The increased incidence of lymphomas/leukaemias reported in treated rats <strong>was unrelated to aspartame.</strong> It is well known that such tumours can arise in the lungs of rats suffering from chronic respiratory disease (Ramazzini 1 and 2)</td>
</tr>
<tr>
<td>Mammary carcinomas found in Ramazzini 2 were not found in Ramazzini 1 – which used much higher doses</td>
</tr>
<tr>
<td>The Panel notes that [.....] dietary exposure to aspartame is well below the ADI of 40 mg/kg bwt (up to 10 mg /kg bw), even in high consumers. (Ramazzini 1 and 2)</td>
</tr>
<tr>
<td>In summary, the Panel concludes, on the basis of all the evidence currently available [.....] there is no reason to revise the previously established ADI for aspartame of 40 mg/kg bw.</td>
</tr>
</tbody>
</table>
CONCLUSIONS

Low-calorie sweeteners are amongst the most extensively studied components of our diet.

The use of high doses *in vitro* and in animal studies ensures that some hazard will be identified.

The application of testing guidelines and safety factors (combined with the setting of suitable use levels) ensures that there is negligible risk at human intakes.

Despite this, the media continually run “stories” based on the hazard NOT the risk.