European Foundation of Oncology and Environmental Sciences “B. Ramazzini”

Cesare Maltoni Cancer Research Center

New carcinogenicity data on aspartame and the need to re-evaluate available data on intense artificial sweeteners

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Aspartame (APM): production and use

- 16,000 tons produced as of 2004
- second artificial intense sweetening agent after saccharin
- 62% of the intense sweetening agents market
- present in more than 6,000 products
- hundreds of millions of consumers worldwide

APM: intake

average daily intake among US consumers (1984-1992):

- general population = 2-3 mg/kg b.w.
- children/women of childbearing age = 2.5-5 mg/kg b.w.

intake similar elsewhere, including 7 EU countries:

- Denmark (1999) = 4 mg/kg b.w.

APM: regulatory approval

US FDA

- 1996 all foods
- Acceptable Daily Intake (ADI) = 50mg/Kg bw

European Union

- 1994 determined safe for all use
- ADI = 40mg/Kg bw

APM: hypothetical daily consumption

Average Daily Intake of Aspartame		
Substance	Quantity/day	Concentration of aspartame consumed
Diet soda (200 mg/can)	2 cans	400 mg
Yogurt (125 mg/yogurt)	2 yogurts	250 mg
Diet custard/pudding (75mg/mousse)	1 serving	75 mg
Coffee with sweetener (40/mg packet)	4 cups	160 mg
Candy/chewing gum (2,5/candy)	10 candies	25 mg
Totals		**910 mg**

Equivalent to:

Woman 60 kg = 15,1 mg/kg body weight

Woman 50 kg = 18,2 mg/kg body weight

Child 30 kg = 30,3 mg/kg body weight

Child 20 kg = 45,5 mg/kg body weight

APM: general information

- ➔ Metabolism: in the GI tract as aspartic acid, phenylalanine and methanol, both in humans and animals
- ➔ Genotoxicity: APM has been shown to be non genotoxic in various test
- ➔ Carcinogenicity
  - **1970s and 1980s**: studies on Sprague-Dawley rats, Wistar rats and Swiss mice

ERF integrated project on APM

	Animals		
Experiment	Species	No.	Status
first	S-D rats	1800	published (2005)
second	S-D rats	400	published (2007)
third	S-D rats	429	ongoing (102 weeks)
fourth	S-D rats	430	ongoing (102 weeks)
fifth	Swiss mice	852	ongoing (104 weeks)

5 EXPERIMENTS **3911 RODENTS**

First Experiment on Aspartame

Plan of the first ERF mega-experiment

Age at start	sex	dose/group ppm (mg/kg b.w.) [a,b]							
		100,000 (5,000)	50,000 (2,500)	10,000 (500)	2,000 (100)	400 (20)	80 (4)	0 (control)	**TOTAL**
8	n. males	100	100	100	150	150	150	150	900
8	n. females	100	100	100	150	150	150	150	900

[a] Considering the average weight of a rat as 400g, and average food consumption as 20g per day

[b] The treatment lasts for the entire life span

Results of the first ERF mega-experiment on APM

Significant increased incidence of:

- malignant schwannomas peripheral cranial nerves in males (dose-related)
- preneoplastic lesions with atypia and carcinomas of the renal pelvis and ureter in females
- lymphomas and leukemias in females (dose-related)

EFSA reactions to the first ERF experiment

- “the increased incidence of lymphomas/leukemias reported in treated rats was unrelated to APM…the most plausible explanation is that they developmeed in a colony suffering from chronic respiratory disease”

Summary of Caldwell et al (2007)

- an examination of the bioassays used by the ERF and NTP shows that the ERF bioassy program produces credible results, consistent with that of NTP.
- The few ERF bioassays which have shown positive results for lymphomas and leukemias suggest that the findings are not general, but chemical-specific.
- The absence of scientific literature that links infections and lymphomas contradict infection as a likely hypothesis of MOA for these tumors.

Second Experiment on Aspartame

Plan of the second ERF experiment

Age at start	Animals	Dose/group ppm (mg/kg b.w.) [a,b]			
		2,000 (100)	400 (20)	0 (control)	**TOTAL**
Fetal life	n. males	70	70	95	**235**
Fetal life	n. females	70	70	95	**235**

[a] Considering the average weight of a rat as 400g, and average food consumption as 20g per day
[b] The treatment lasts for the entire life span

Incidence of animals bearing malignant tumors

Animals	ppm in feed (mg/kg b.w.) [a]		
	2,000 (100)	400 (20)	0 (control)
Males (%)	**40.0 ****	**25.7**	**24.2****
Females (%)	**52.9**	**44.3**	**44.2**

[a] p-values associated with the trend test are near the control incidence

** Statistically significant ($p<0.01$) using Cox Regression Model.

Incidence of animals bearing mammary cancers

Animals	ppm in feed (mg/kg b.w.) [a]		
	2,000 (100)	400 (20)	0 (control)
Males (%)	**2.9**	**-**	**-**
Females (%)	**15.7***	**7.1**	**5.3***

[a] p-values associated with the trend test are near the control incidence

* Statistically significant ($p<0.05$) using Cox Regression Model

Incidence of animals bearing lymphomas/leukemias

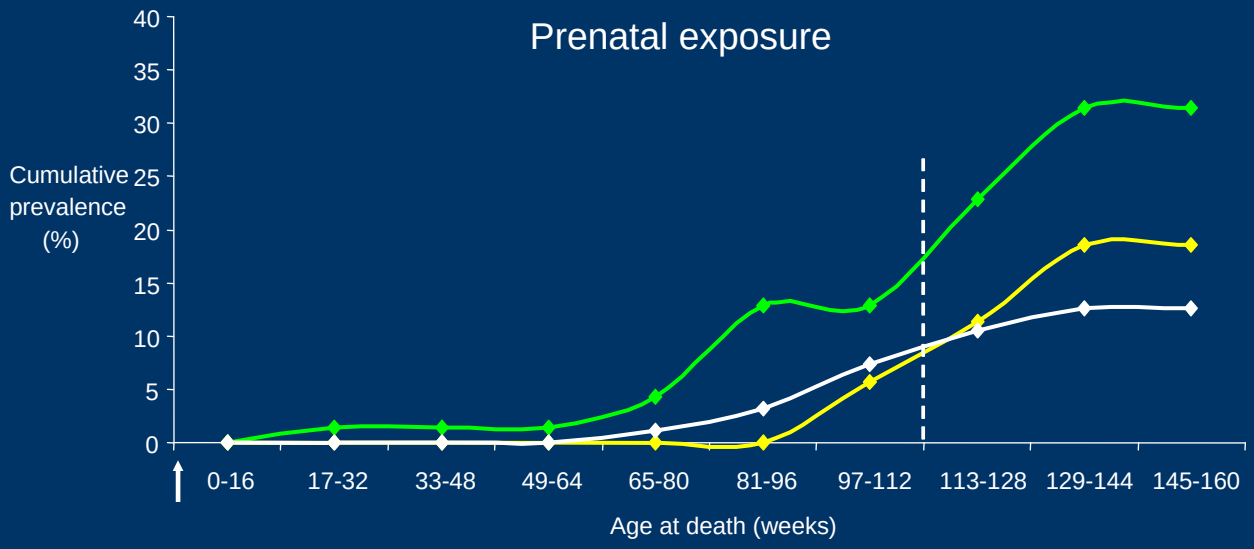
Animals	ppm in feed (mg/kg b.w.) [a]		
	2,000 (100)	400 (20)	0 (control)
Males (%)	**17.1***	**15.7**	**9.5**
Females (%)	**31.4****	**17.1**	**12.6****

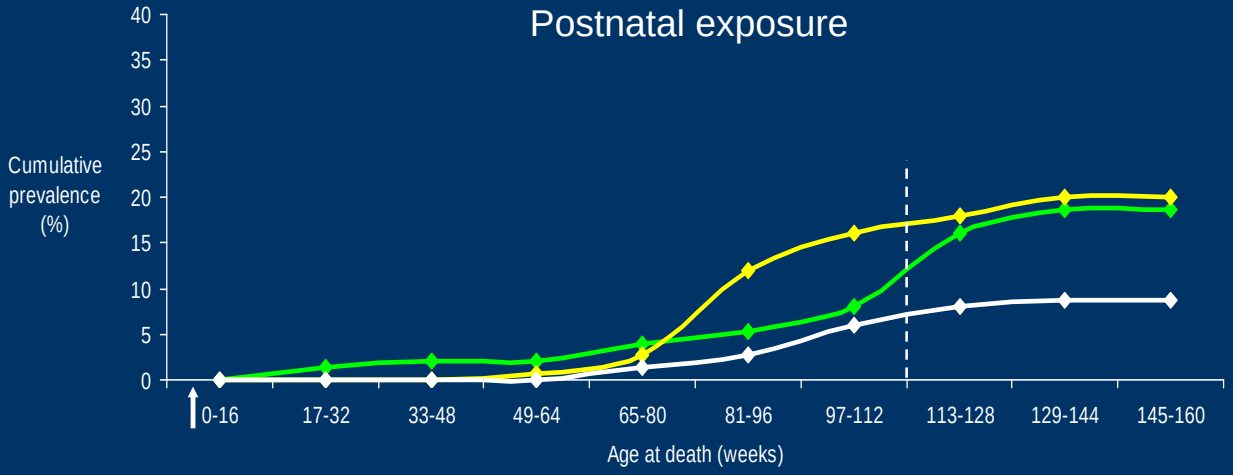
[a] p-values associated with the trend test are near the control incidence

* Statistically significant ($p<0.05$) using Cox Regression Model

** Statistically significant ($p<0.01$) using Cox Regression Model

Comparison of the cumulative prevalence of hemolymphoreticular neoplasia by age of death





Start of the treatment

2000 ppm

400 ppm

0 ppm (control)

Swiss Mice Experiment

on APM

(104 weeks of biophase)

Recommendations

On the basis of the observed carcinogenic effects in long term bioassays, we believe:

1) an epidemiological investigation should be performed among children and adult consumers and APM workers.

2) in accordance with the precautionary principle, a review of the current regulations governing the use of APM for human food is urgent. It merits noting that the incidence of hemolymphoreticular neoplasias has been increasing for women and children over the last 20 years.

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