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

Cesare Maltoni Cancer Research Center

ASPARTAME: NEW DATA ON CARCINOGENICITY

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Ramazzini Days 2006

Globalization and North South Disparities
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APM: General Information (part I)

- ➔ 16,000 tons produced as of 2004
- ➔ Over 200 million consumers worldwide
- ➔ Average daily intake in US (1984-1992) and Europe:
  - General population: 2-3 mg/kg b.w.
  - Children/women of childbearing age: 2.5-5 mg/kg b.w.
- ➔ Regulatory approval:
  - US FDA, 1981. Acceptable daily intake: 50 mg/kg b.w.
  - EU, 1994. Acceptable daily intake: 40 mg/kg b.w.

APM: General Information (part II)

- ➔ 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
  - **2005**: NTP studies on genetically altered mice
  - **2006**: NCI epidemiological study

The European Ramazzini Foundation (ERF)

Sweeteners Project

Aspartame: the first experiment

APM: Study design of the First CMCRC Experiment

Group No.	Animals			Treatment		
	Age at start (weeks)	Sex	No.	Dose		Duration
				ppm	mg/Kg b.w. [a, b]	
I	8	M	100	100,000	5,000 (100 X)	Life span
		F	100			
		M+F	200			
II	8	M	100	50,000	2,500 (50 X)	Life span
		F	100			
		M+F	200			
III	8	M	100	10,000	500 (10 X)	Life span
		F	100			
		M+F	200			
IV	8	M	150	2,000	100 (2 X)	Life span
		F	150			
		M+F	300			
V	8	M	150	400	20 (0.4 X)	Life span
		F	150			
		M+F	300			
VI	8	M	150	80	4 (0.08 X)	Life span
		F	150			
		M+F	300			
VII	8	M	150	0	–	Life span
		F	150			
		M+F	300			
TOTAL			1,800			

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

[b] Between brackets: the human acceptable daily intake (ADI) equivalent, considering an ADI of 50 mg/Kg b.w. for humans

APM First Experiment: Results (part I)

INCIDENCE OF MALIGNANT SCHWANNOMAS OF PERIPHERAL NERVES IN MALES [a]

Tumor-bearing animals	ppm in feed (mg/kg b.w.) [b]						
	100,000 (5,000)	50,000 (2,500)	10,000 (500)	2,000 (100)	400 (20)	80 (4)	0 (control)
Incidence (%)	**4.0**	**3.0**	**2.0**	**1.3**	**2.0**	**0.7**	**0.7 *#**

[a] Historical control incidence of malignant schwannomas in males (2,265): 0.4% (range: 0-2.0%)

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

* Statistically significant ($p<0.05$) using Cochran-Armitage test.

Statistically significant ($p<0.05$) using poly-k test ($k = 3$)

APM First Experiment: Results (part II)

INCIDENCE OF PRENEOPLASTIC LESIONS WITH ATYPIA (PLA) AND CARCINOMAS (CA) OF THE RENAL PELVIS AND URETER IN FEMALES

Tumor-bearing animals	ppm in feed (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)
PLA Incidence (%)	11	7.1	7.0	4.7	4.0	3.3	1.3**
CA Incidence (%) [c]	**4.0**#	3.0	3.0	2.0	2.0	0.7	-
Total Incidence (%)	**15.0**##	**10.1**##	**10.0**##	**6.7**#	**6.0**#	4.0	1.3 **##

[a] p-values corresponding to pairwise comparison between the controls and the dosed group are near the dosed group incidence.

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

[c] Historical control incidence of renal pelvis CA in females (2,274): 0.04% (range: 0-1.0%)

** Statistically significant ($p<0.01$) using Cochran-Armitage test

Statistically significant ($p<0.05$) using poly-k test (k = 3)

Statistically significant ($p<0.01$) using poly-k test (k = 3)

APM First Experiment: Results (part III)

INCIDENCE OF LYMPHOMAS AND LEUKEMIAS IN FEMALES [a]

Tumor-bearing animals	ppm in feed (mg/kg b.w.) [b, c]						
	100,000 (5,000)	50,000 (2,500)	10,000 (500)	2,000 (100)	400 (20)	80 (4)	0 (control)
Incidence (%)	**25.0**##	**25.0**##	**19.0**#	**18.7**#	**20.0**##	14.7	8.7**#

[a] Historical control incidence of lymphomas and leukemias in females (2,274): 13.3% (range: 4.0-25.0%)

[b] p-values corresponding to pairwise comparison between the controls and the dosed group are near the dosed group incidence.

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

** Statistically significant ($p<0.01$) using Cochran-Armitage test

Statistically significant ($p<0.05$) using poly-k test (k = 3)

Statistically significant ($p<0.01$) using poly-k test (k = 3)

APM: reactions to the results: EFSA

➔ Lymphomas and leukemias

"[…] In detail the Panel concluded the following:

The slight increase in incidence of cancers known as lymphomas and leukemias in treated rats was considered to be unrelated to aspartame treatment and most likely attributed to the high background incidence of inflammatory changes in the lung. In addition, there was no dose-response relationship with respect to increasing doses of aspartame.

APM: reactions to the results: EFSA

➔ Kidney tumors

The findings in the kidney, ureter and bladder, observed mainly in female rats, are not specific to aspartame and have been observed with a number of chemicals administered to rats at high dose levels. Such changes are normally the result of irritation or imbalances in calcium metabolism specific to rats and are of no relevance for humans.

APM: reactions to the results: EFSA

➔ Peripheral nerves tumors

Concerning the malignant tumors of the peripheral nerves, the numbers of tumours were low with no clear dose- response relationship over a wide dose range. There is also uncertainty about the diagnosis of these tumours. The Panel indicated that this finding can only be fully evaluated by an independent peer-review of the relevant tissues. […]"

APM: reactions to the results: EFSA

➔ Conclusions

"[…] The Panel concluded that based on all the available data to date there is no reason to further review the previous scientific opinion on the safety of aspartame nor to revise the Acceptable Daily Intake (ADI) for aspartame of 40 mg/kg body weight. […]"

Project of lifespan bioassays on artificial sweeteners at the ERF: status of studies

Products	No. of bioassays	Animals		Study status [a]
		Species	No.	
Aspartame	5	Rat, mouse	3,796	P, E, BO
Sucralose	1	Mouse	624	BO
Formaldehyde	5	Rat, mouse	1,919	P,BO
TOTAL			**6,339**	

[a] Abbreviations: BO, biophase ongoing; E, in elaboration; P, published

Aspartame: the first results of the second experiment

APM: Study design of the Second CMCRC Experiment

data awaiting publication

APM: First Results of the Second Experiment

data awaiting publication

Comparison of the incidence of lymphomas and leukemias in females in the 2 APM experiments

data awaiting publication

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

data awaiting publication

“The end judges everything”

Herodotus, Greek Historian (480-425 BC)

the History