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Consequences of Exposure to Carcinogens Beginning During Developmental Life

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Abstract: The increased incidence of cancer over the last 50–60 years may be largely attributed to two factors: the ageing of the population and the diffusion of agents and situations presenting carcinogenic risks. Today, we have entered into a new era in which populations are ever-increasingly exposed to diffuse carcinogenic risks, present not only in the occupational, but also in the general environment. We must now also consider an additional factor in the carcinogenic process, that is, the age in which exposure to carcinogenic risks begins. Apart from the paradigmatic cases of diethylstilboestrol and ionizing radiation, the available epidemiological data concerning the adult consequences of developmental exposure to carcinogens is very limited. However, important data have been provided by long-term experimental carcinogenicity bioassays conducted using rodents. This paper reports a selection of studies conducted in the laboratories of the Cesare Maltoni Cancer Research Center of the European Ramazzini Foundation in which exposure to the chemical agents vinyl acetate monomer, ethyl alcohol and aspartame was started during developmental life and continued into adulthood. The results of these studies provide supporting evidence that lifespan exposure to carcinogenic agents beginning during developmental life produces an overall increase in the carcinogenic effects observed. Moreover, when comparing prenatal and postnatal exposure, the data demonstrate that the development of cancers may appear earlier in life.

Cancer represents one of the most important issues in public health today, both in the industrialized and developing worlds. The epidemiological dimension of the disease is epidemic, with one out of two males and one out of three females destined to become ill with cancer during their lifetimes [1]. Above all, cancer affects the oldest segment of the population, from 60–84 years of age. Data from the Nominative Mortality Register of European Ramazzini Foundation from the period 1982–2002 show that more than 30% of the mortality in the province of Bologna, Italy, is cancer-related. Of these deaths, 80% occurred after the age of 60–65 years [2]. If we consider the estimates that in 25 years, the number of persons over than the age of 70 years will have doubled, it is necessary to prepare for a dramatic increase in the number of tumours. In the USA alone, it is predicted that the number of cancers will indeed double by 2050 [1].

Although the scientific effort and economic resources dedicated to cancer have increased over the last 30 years (directed especially towards the discovery of effective cancer drug therapies), in the USA, the 5-year relative survival rates based on patient follow-up from 1976–2000 have not substantially improved (table 1), with the exception of female breast, prostate and colon–rectal cancer for which early diagnosis has certainly played an important role. Other exceptions are cancers of the lung and bronchus in males that reflects the decrease in smoking more than the past 30 years.

The increased incidence of cancer over the last 50–60 years may be attributed to two increasing trends: (i) the increase in life expectancy (about 10 years for males and 15 years for females); and (ii) the increase in the diffusion of agents and situations presenting carcinogenic risks in both the occupational and general environment. A third factor in the carcinogenetic process is genetic predisposition; however, it is unlikely that this factor has changed significantly over the last decades.

In addition, a fourth factor must also be considered; that is, the age in which exposure to carcinogenic risks begins. In this context, the present epidemiological dimension of cancer is undoubtedly a sign of the previous era in which the majority of the population had been exposed to carcinogenic risks either in the occupational environment as adolescents or adults.

Today, however, we are facing an era characterized by two new trends: (i) lifetime exposure to carcinogenic risks beginning during developmental life (prenatally or postnatally). This exposure during early development, when cell mutiplication and differentiation make an organism more vulnerable, may cause an increase in carcinogenic effects later in life; and (ii) exposure to 'diffuse carcinogenic risks'. This term is used to describe carcinogenic risks of low potency, but to

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Table 1.

Relative survival* (%) during three time periods, by cancer site in the USA.†

Site	1974–1976	1983–1985	1995–2000
All sites	50	53	64
Breast (female)	75	78	88
Colon	50	58	63
Leukaemia	34	41	46
Lung and bronchus	13	14	15
Melanoma of the skin	80	85	91
Non-Hodgkin lymphoma	47	54	59
Ovary	37	41	44‡
Pancreas	3	3	4
Prostate	67	75	99
Rectum	49	55	64
Urinary bladder	73	78	82

*Five-year relative survival rates based on follow-up of patients through 2001.
†Source: American Cancer Society, 2005 [1].
‡Recent changes in classification of ovarian cancer have affected 1995–2000 survival rates [1].

which almost the entire population of the planet may be exposed. Examples of diffuse carcinogenic risks include: (i) agents that are slightly carcinogenic at any dose; (ii) low or extremely low doses of strong carcinogenic agents; or (iii) mixtures of small doses of any carcinogenic agent [3].

Apart from the paradigmatic cases of diethylstilboestrol and ionizing radiation, the available epidemiological data concerning the adult consequences of developmental exposure to carcinogenic agents are very limited. We now know much more about the effects of this early exposure thanks to experimental long-term bioassays. If adequately designed and conducted, these bioassays can produce data that can be effectively used to identify/predict carcinogenic risks and, consequently, to make decisions to protect public health.

Numerous long-term carcinogenicity studies have been conducted at the Cesare Maltoni Cancer Research Center of the European Ramazzini Foundation (CMCRC/ERF) that demonstrate the life-time consequences of chemical/physical exposures beginning during developmental life and lasting for life. This paper presents a selection of these exemplary cases including vinyl acetate, ethyl alcohol and aspartame.

The case of vinyl acetate monomer

Vinyl acetate monomer is an important compound used in the plastics industry. It is also used in the production of resin in chewing gum. The limited available epidemiological data on vinyl acetate monomer do not allow for an evaluation of its potential carcinogenic risks in human beings. Carcinogenicity studies on rats and mice, conducted prior to the most recent International Agency for Research on Cancer

Table 2.

Incidence of malignant tumours in male (M) and female (F) Sprague–Dawley rats in a lifespan carcinogenicity study on vinyl acetate monomer administered in drinking water supplied *ad libitum* for 104 weeks and then observed until natural death [7].

Dose (p.p.m. v/v)	Animals			Animals bearing malignant tumours (%)	Animals bearing oral cavity and tongue cancers† (%)	Animals bearing oesophagus and forestomach cancers† (%)	Animals bearing upper GIT‡ cancers† (%)
	Age	Sex	No.				
I	Breeders	M	13	61.5	–	7.7	7.7
(5000)	(17 weeks old)	F	37	48.6	8.1	8.1	16.2*††
		M + F	50	52.0	6.0	8.0	14.0
II	Breeders	M	13	53.8	–	7.7	7.7
(1000)	(17 weeks old)	F	37	54.1	5.4	–	5.4
		M + F	50	54.0	4.0	2.0	6.0
III	Breeders	M	14	35.7	–	–	–
(0§)	(17 weeks old)	F	37	59.5	–	–	–‡‡
		M + F	51	52.9	–	–	–
IV	Offspring	M	53	58.5*	26.4**	15.1**	41.5**
(5000)	(Embryos)¶	F	57	56.1	19.3**	7.0*	26.3**
		M + F	110	57.3	22.7	10.9	33.6
V	Offspring	M	83	45.8	–	7.2*	7.2
(1000)	(Embryos)¶	F	87	48.3	–	3.4	3.4
		M + F	170	47.1	–	5.3	5.3
VI	Offspring	M	107	40.2	1.9‡‡	–‡‡	1.9‡‡
(0§)	(Embryos)¶	F	99	43.4	1.0‡‡	–	1.0‡‡
		M + F	206	41.7	1.5	–	1.5

†The P-values associated with the trend test are near the control incidence.
‡GIT: gastrointestinal tract (comprehensive of oral cavity, tongue, oesophagus and forestomach).
§Drinking water alone.
¶Treatment began on the 12th day of foetal life.
*Significant ($P < 0.05$) using χ^2 test.
**Significant ($P < 0.01$) using χ^2 test.
††Significant ($P < 0.05$) using Fisher's exact test.
‡‡Significant ($P < 0.01$) using the Cochran–Armitage test.

Table 3.

Incidence of malignant tumours in male (M) and female (F) Wistar rats in a lifespan carcinogenicity study on vinyl acetate monomer administered in drinking water supplied *ad libitum* for 104 weeks and then observed until natural death [7].

Dose (p.p.m. v/v)	Animals			Animals bearing malignant tumours (%)	Animals bearing oral cavity and tongue cancers† (%)	Animals bearing oesophagus and forestomach cancers† (%)	Animals bearing upper GIT‡ cancers† (%)
	Age	Sex	No.				
I	Breeders	M	13	61.5	23.1	7.7	30.8
(5000)	(17 weeks old)	F	37	54.1	5.4	8.1	13.5
		M+F	50	56.0	10.0	8.0	18.0
II	Breeders	M	13	53.8	7.7	–	7.7
(1000)	(17 weeks old)	F	37	59.5	13.5	5.4	18.9
		M + F	50	58.0	12.0	4.0	16.0
III	Breeders	M	14	35.7	7.1	–	7.1
(0§)	(17 weeks old)	F	37	35.1	5.4	–	5.4
		M + F	51	35.3	5.9	–	5.9
IV	Offspring	M	82	43.9**	17.1**	8.5*	25.6**
(5000)	(Embryos)¶	F	95	73.7**	31.6**	8.4*	40.0**
		M + F	177	59.9	24.9	8.5	33.3
V	Offspring	M	64	23.4	1.6	–	1.6
(1000)	(Embryos)¶	F	73	45.2	15.1	1.4	16.4
		M + F	137	35.0	8.8	0.7	9.5
VI	Offspring	M	86	19.8¶	3.5	–	3.5
(0§)	(Embryos)¶	F	69	50.7	7.2***	–***	7.2***
		M + F	155	33.5	5.2	–	5.2

†The P-values associated with the trend test are near the control incidence.
‡GIT: gastrointestinal tract (comprehensive of oral cavity, tongue, oesophagus and forestomach).
§Drinking water alone.
¶Treatment began on the 12th day of foetal life.
*Significant ($P < 0.05$) using χ^2 test.
**Significant ($P < 0.01$) using χ^2 test.
***Significant ($P < 0.01$) using the Cochran–Armitage test.

evaluation [4], have been in one way or another inadequate to evaluate the carcinogenic potential of vinyl acetate monomer.

In the 1980s, a series of experiments were simultaneously conducted at the CMCRC/ERF using Sprague–Dawley rats, Wistar rats and Swiss mice. A similar protocol was applied for all three experiments. Vinyl acetate monomer was administered by ingestion in drinking water supplied *ad libitum* at the concentrations of 5000, 1000 or 0 p.p.m. to 17-week-old males and females (breeders) and 12-day-old embryos (offspring). The treatment lasted 104 weeks in rats and 78 weeks in mice. All animals were monitored until natural death (130–150 weeks). The plan of each experiment and the significant carcinogenic results are reported in tables 2–4.

In the tested conditions, vinyl acetate monomer was demonstrated to be a multipotent carcinogenic agent, inducing malignant tumours of the oral cavity, tongue, oesophagus and forestomach in both strains of rats and mice. A slight increase of the incidence of adenomas/carcinomas of the lung and of malignant tumours of the uterus in mice was also observed [5–7]. Furthermore, the carcinogenic effects were strongly increased when exposure began during foetal life.

The case of ethyl alcohol

Various epidemiological studies have shown a positive relationship between consumption of alcoholic beverages and the increase of cancer risks of the oral cavity, pharynx, larynx, oesophagus and liver. However, as reported in the most recent International Agency for Research on Cancer monograph on this agent [8], many experimental studies conducted on rats and mice exposed to various concentrations of ethyl alcohol administered in drinking water did not show the same effects.

In an experiment performed at the CMCRC/ERF laboratories, ethyl alcohol was administered by ingestion in drinking water at the concentration of 10% or 0% and supplied *ad libitum* to male and female Sprague–Dawley rats, both breeders and offspring. In order to detect carcinogenic risk when exposure begins during adult life, treatment of breeders started at 39 weeks of age, 7 days before mating. Treatment of offspring began during embryonic life. Treatment of all rodents lasted for 104 weeks and all animals were observed until spontaneous death. The plan of the experiment and the significant carcinogenic results are reported in table 5. In contrast with previous studies, in the test conditions of the CMCRC ethyl alcohol was indeed demonstrated to be carcinogenic for various organs and tissues, in particular inducing malignant tumours of oral cavity, tongue and lips, and oesophagus, the same sites that were shown to be target organs in the aforementioned epidemiological studies [9]. Importantly, the incidence of malignant tumours of the oral cavity was higher when exposure began during embryonic life.

Table 4.

Incidence of malignant tumours in male (M) and female (F) Swiss mice in a lifespan carcinogenicity study on vinyl acetate monomer administered in drinking water supplied *ad libitum* for 78 weeks and then observed until natural death [7].

Dose (p.p.m. v/v)	Animals			Animals bearing malignant tumours (%)	Animals bearing oral cavity and tongue cancers[†] (%)	Animals bearing oesophagus and forestomach cancers[†] (%)	Animals bearing lung adenomas and carcinomas (%)	Animals bearing cancers of the uterus[†‡] (%)
	Age	Sex	No.					
I	Breeders	M	13	84.6	15.4	–	30.8	
(5000)	(17 weeks old)	F	37	70.3	10.8	24.3**[‡‡]	18.9	21.6*[††]
		M + F	50	74.0	12.0	18.0	22.0	
II	Breeders	M	13	46.2	–	–	30.8	
(1000)	(17 weeks old)	F	37	75.7	2.7	–	16.2	5.4
		M + F	50	68.0	2.0	–	20.0	
III	Breeders	M	14	50.0	–	–	28.6	
(0[§])	(17 weeks old)	F	37	56.8	–	–	8.1	2.7[¶¶]
		M + F	51	54.9	–	–	13.7	
IV	Offspring	M	49	83.7	34.7**	28.6**	26.5	
(5000)	(Embryos)[¶]	F	48	93.8**	43.8**	52.1**	22.9	25.0
		M + F	97	88.7	39.2	40.2	24.7	
V	Offspring	M	37	64.9	–	–	16.2	
(1000)	(Embryos)[¶]	F	44	75.0	–	–	9.1	18.2
		M + F	81	70.4	–	–	12.3	
VI	Offspring	M	38	68.4	2.6	–	18.4	
(0[§])	(Embryos)[¶]	F	48	62.5***	–	–	12.5	10.4
		M + F	86	65.1	1.2	–	15.1	

[†]The P-values associated with the trend test are near the control incidence.
[‡]Including leiomyosarcomas and adenocarcinomas.
[§]Drinking water alone.
[¶]Treatment began on the 12th day of foetal life.
*Significant ($P < 0.05$) using χ^2 test.
**Significant ($P < 0.01$) using χ^2 test.
[††]Significant ($P < 0.05$) using Fisher's exact test.
[‡‡]Significant ($P < 0.01$) using Fisher's exact test.
[¶¶]Significant ($P < 0.05$) using the Cochran–Armitage test.
***Significant ($P < 0.01$) using the Cochran–Armitage test.

Table 5.

Incidence of malignant tumours in male (M) and female (F) Sprague–Dawley rats in a lifespan carcinogenicity study on ethyl alcohol administered in drinking water supplied *ad libitum* for 104 weeks and then observed until natural death [9].

Dose (% v/v)	Animals			Animals bearing malignant tumours (%)	Animals bearing oral cavity cancers[†] (%)	Animals bearing oesophagus and forestomach cancers (%)
	Age	Sex	No.			
I	Breeders	M	110	60.0	13.6**	1.8
(10%)	(39 weeks old)	F	110	71.8**	10.9*	3.6
		M + F	220	65.9	12.3	2.7
II	Breeders	M	110	46.4	2.7	–
(0[‡])	(39 weeks old)	F	110	43.6	1.8	–
		M + F	220	45.0	2.3	–
III	Offspring	M	30	76.7*	33.3**	3.3
(10%)	(Embryos)[§]	F	39	66.7	41.0**	2.6
		M + F	69	71.0	37.7	2.9
IV	Offspring	M	49	46.9	4.1	–
(0[‡])	(Embryos)[§]	F	55	56.4	5.5	–
		M + F	104	51.9	4.8	–

[†]Includes tongue and lips.
[‡]Drinking water alone.
[§]Treatment began on the 12th day of foetal life.
*Significant ($P < 0.05$) using χ^2 test.
**Significant ($P < 0.01$) using χ^2 test.

Table 6.

Incidence of malignant tumours in male (M) and female (F) Sprague–Dawley rats in a lifespan carcinogenicity study on aspartame administered in feed supplied *ad libitum* from 8 weeks of age until natural death [11,12].[†]

Dose p.p.m. (mg/kg body weight)	Animals			Animals bearing malignant tumours (%)	Animals bearing tumours of peripheral nerves and malignant schwannomas (%)	Animals bearing carcinomas of the renal pelvis and ureter (%)	Animals bearing lymphomas/ leukaemias (%)
	Age	Sex	No.				
100,000	8 weeks	M	100	43.0	4.0	1.0	29.0
(5000)		F	100	51.0	2.0	4.0[‡]	25.0[§]
		M + F	200	47.0	3.0	2.5	27.0
50,000	8 weeks	M	100	38.0	3.0	1.0	20.0
(2500)		F	100	58.0[§]	1.0	3.0	25.0[§]
		M + F	200	48.0	2.0	2.0	22.5
10,000	8 weeks	M	100	34.0	2.0	1.0	15.0
(500)		F	100	40.0	1.0	3.0	19.0[‡]
		M + F	200	37.0	1.5	2.0	17.0
2000	8 weeks	M	150	40.0	1.3	0.7	22.0
(100)		F	150	44.7	2.0	2.0	18.7[‡]
		M + F	300	42.4	1.7	1.3	20.3
400	8 weeks	M	150	32.0	2.0	–	16.7
(20)		F	150	46.7	–	2.0	20.0[§]
		M + F	300	39.4	1.0	1.0	18.3
80	8 weeks	M	150	29.3	0.7	–	15.3
(4)		F	150	42.7	1.3	0.7	14.7
		M + F	300	36.0	1.0	0.3	15.0
0	8 weeks	M	150	35.3*	0.7[§]	–	20.7*[‡]
(0)		F	150	36.7**	–	–	8.7**[‡]
		M + F	300	36.0	0.3	–	14.7

[†]The P-values associated with the trend test are near the control incidence.
*Significant ($P \leq 0.05$) using Cochran–Armitage test.
**Significant ($P \leq 0.01$) using Cochran–Armitage test.
[‡]Significant ($P \leq 0.05$) using poly-k test ($k = 3$).
[§]Significant ($P \leq 0.01$) using poly-k test ($k = 3$).

The case of aspartame

Aspartame is an artificial sweetener consumed by hundreds of millions of people worldwide. It is used in over 6000 products, including soft drinks, chewing gum, candy, desserts and yogurt, as well as in more than 500 pharmaceutical products, in particular, syrups and antibiotics for children. Prior to the commercialization of aspartame in the 1970s, the manufacturers of the compound conducted various experimental studies on rats and mice to test its carcinogenicity. When taken together, the results of these studies were considered negative with regard to the carcinogenicity of aspartame. Doubts were, however, raised by some in the scientific community about the conduct of the experiments and the fact that some cases of malignant brain tumours were found among animals treated with aspartame while none were found among the control group. Given the limitations of these studies due to the number of animals per sex and group, the duration of the experiment, and the ever growing use of aspartame throughout the years, the CMCRC/ERF decided in the late 1990s to plan and perform an experiment that would provide an adequate evaluation of the potential carcinogenic effects of aspartame.

The first CMCRC/ERF study [10–12] was conducted on 1800 Sprague–Dawley rats (100–150/per sex/per group). Aspartame was added to the standard rat diet in quantities of 100,000; 50,000; 10,000; 2000; 400; 80 or 0 p.p.m. in order to simulate daily intake of 5000, 2500, 500, 100, 20, 4 or 0 mg/kg of body weight. Treatment of the animals began at 8 weeks of age and continued until spontaneous death.

The results, reported in table 6, show that aspartame causes a significant, dose-related increase of lymphomas/leukaemias and malignant tumours of the renal pelvis and ureter in females and malignant tumours of peripheral nerves in males. These results demonstrate for the first time that aspartame is a carcinogenic agent, capable of inducing malignancies at various dose levels, including those lower than the current acceptable daily intake for humans (50 mg/kg of body weight in the USA, 40 mg/kg of body weight in the European Union).

As soon as we perceived the carcinogenic effects of aspartame during the elaboration of the data in our first mega-experiment, we planned an integrated programme of long-term bioassays, beginning treatment from prenatal life, on an additional 1500 rats and mice in order to better quantify the carcinogenic risks of aspartame.

The second CMCRC/ERF study [13] was conducted on 400 Sprague–Dawley rats (70–95/per sex/per group). Aspartame was added to the standard rat diet in quantities of 2000, 400 or 0 p.p.m. in order to simulate daily intake of 100, 20 and

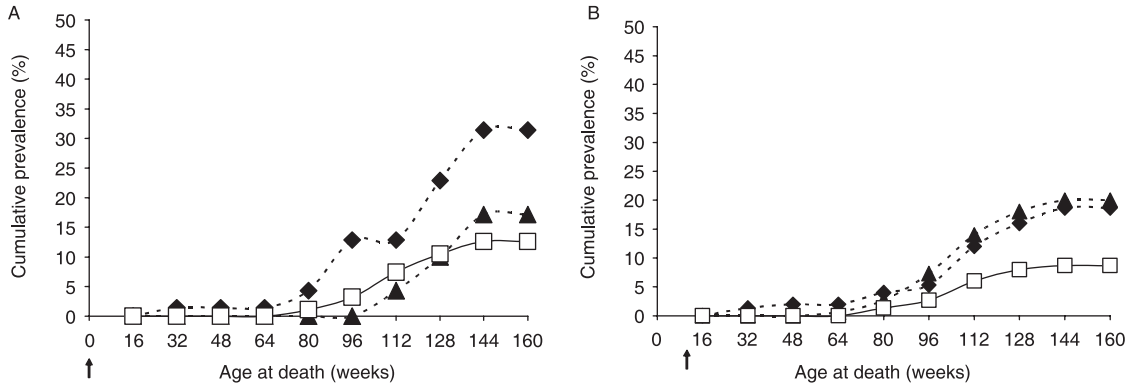

Fig. 1. Lifespan carcinogenicity study of aspartame administered with feed to Sprague–Dawley rats from foetal life until natural death: cumulative prevalence by age of death of female rats bearing haemolymphoreticular neoplasias (HLRN) when treatment began prenatally (A) or postnatally (B). (—◆— 2000 p.p.m.; —▲— 400 p.p.m.; —□— Control; ↑ start of the experiment). The incidence of HLRN appeared earlier in life when treatment began prenatally (A).

0 mg/kg of body weight. Treatment of the animals began on the 12th day of foetal life and lasted until natural death. The results of the second study show an increased incidence of lymphomas/leukaemias in female rats with respect to the first study. Moreover, the study shows that when lifespan exposure to aspartame begins during foetal life, the age at which lymphomas/leukaemias develop in females is anticipated (fig. 1). In addition, for the first time, a significant increase in mammary cancers in females was also observed. The results of this second study confirm the first experimental demonstration of aspartame's multipotential carcinogenicity and demonstrate that developmental exposure aggravates the carcingogenic effects (tables 7 and 8).

Conclusions

It is well known that the latency time of most cancers (i.e. the time elapsing between the start of exposure to carcinogenic risks and the clinical manifestation of cancers) may span from 20 to 40 years [14]. In light of the fact that 80% of cancers are diagnosed over the age of 55–60 years, we may attribute the present epidemiological dimension of cancer to exposure beginning during adolescence or adulthood. Nowadays, we are facing a new era in which exposure to carcinogenic risks begins during developmental life (prenatal and postnatal) and continues into adulthood.

Based on the results of long-term carcinogenicity bioassays testing chemical and physical agents using rodents, there is ample evidence demonstrating that developmental, in conjunction with adult exposure to carcinogenic risks, produces an overall increase in the incidence of malignant tumours and an increased incidence of specific neoplasms related to exposures to specific carcinogens. Moreover, when comparing prenatal and postnatal exposure, the development of certain tumours may appear earlier in life.

We must take into serious consideration the warnings provided by long-term carcinogenicity studies and take adequate action today. Based on the evidence presented,

Table 7.

Incidence of malignant tumours in male (M) and female (F) Sprague–Dawley rats in a lifespan carcinogenicity study on aspartame administered in feed supplied *ad libitum* from prenatal life until natural death [13].†

Dose p.p.m. (mg/kg body weight)	Animals			Animals bearing malignant tumours (%)	Animals bearing lymphomas/ leukaemias (%)	Animals bearing mammary cancers (%)
	Age	Sex	No.			
2000	Embryonic life‡	M	70	40.0**	17.1*	2.9
(100)		F	70	52.9	31.4**	15.7*
		M + F	140	46.5	24.3	9.3
400	Embryonic life‡	M	70	25.7	15.7	–
(20)		F	70	44.3	17.1	7.1
		M + F	140	35.0	16.4	3.6
0	Embryonic life‡	M	95	24.2**	9.5	–
(0)		F	95	44.2	12.6**	5.3*
		M + F	190	34.2	11.1	2.7

†The P-values associated with the trend test are near the control incidence.
‡Treatment began on the 12th day of foetal life.
*Significant ($P \leq 0.05$) using Cox regression model.
**Significant ($P \leq 0.01$) using Cox regression model.

Table 8.

Comparison of the incidence of lymphomas/leukaemias and mammary cancers in female Sprague–Dawley administered aspartame in feed supplied *ad libitum* beginning exposure from prenatal or postnatal life and lasting until natural death [13].

	Animals bearing lymphomas/leukaemias (%)		Animals bearing mammary cancers (%)	
Dose p.p.m. (mg/kg body weight)	Prenatal exposure (no. of animals at start)	Postnatal exposure (no. of animals at start)	Prenatal exposure (no. of animals at start)	Postnatal exposure (no. of animals at start)
2000 (100)	31.4 (70)	18.7 (150)	15.7 (70)	8.0 (150)
400 (20)	17.1 (70)	20.0 (150)	7.1 (70)	10.7 (150)
0 (0)	12.6 (95)	8.7 (150)	5.3 (95)	5.3 (150)

increased attention must be given to developmental exposures to diffuse carcinogens. It is only in this way that in the future we can hope to avoid a passive registration of a worsening epidemiological situation.

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