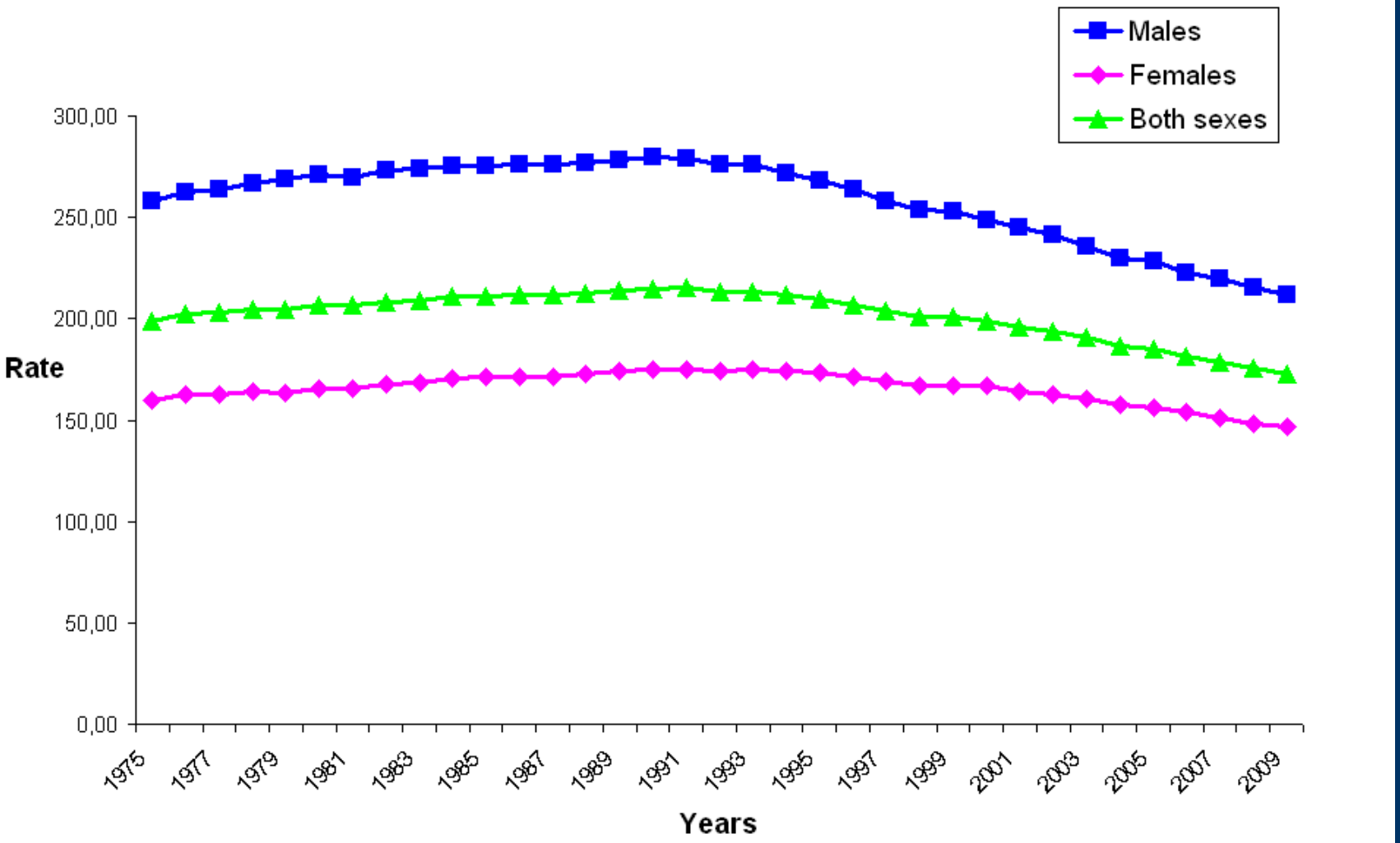
Primary prevention for control of occupational and environmental carcinogens

Dr. Morando Soffritti

Yerevan, Armenia
April 23, 2013

Cancer Mortality, all sites combined/all rates, USA (1975-2009)



The death rate is age-adjusted to the 2000 US standard population and is expressed per 100,000.
Source: SEER Cancer Statistics Review 1975-2009 - http://statecancerprofiles.cancer.gov/

Cancer: an environmental disease

According to data from the American Cancer Society:

- 1 out of 2 males and 1 out of 3 females will develop cancer over the course of his or her lifetime
- the number of people over the age of 70 will double in the next 25 years and the number of tumors will double by 2050 in the US alone

Cancer: an environmental disease

$$C = f\,(P \times E \times T \times A)$$

C = cancer
P = predisposition
E = environmental exposure
T = time when exposure starts
A = aging

Cancer: evidence of environmental risks

- Elevated incidence of some types of tumors in geographic areas compared to others.
- Studies on immigrants and tumor incidence
- Occupational tumors
- Transplancental carcinogenesis
- Behavior and Lifestyle
- Results of long term carcinogenicity studies on rodents

The available tools for cancer control

- Therapy
- Early detection
- May be chemoprevention
- Primary prevention

Cancer: the rôle of primary prevention

- Primary prevention is the identification of potential carcinogenic risks present in the general and occupational environment
- The action to reduce exposure to these risks as much as possible.
- Primary prevention can lower the incidence and mortality of specific types of cancer.

Tools for the identification of carcinogenic risks (Part I)

EPIDEMIOLOGICAL STUDIES

- Human investigations

> These studies measure the pathological effects (morbidity/mortality) of the risk undergone

Tools for the identification of carcinogenic risks (Part II)

EXPERIMENTAL STUDIES

- Basic and applied research, and carcinogenicity studies
  - Study of mechanism-based interferences
  - Short-term *in vivo* assays and *in vitro* assays
  - **Long-term carcinogenicity *in vivo* bioassays**

- Long-term experimental carcinogenicity bioassays (life-span), when well planned and conducted, may allow us retrospectively to quantify the risks and prospectively to avoid them.

Scientific basis for carcinogenesis bioassays

- Rodents and humans are mammals which share many basic genetic, pharmacologic, toxicology and carcinogenic responses
- All known human carcinogens that have been tested adequately have also been shown to be carcinogenic in animals, and almost always share identical target sites
- Nearly 1/3 of human carcinogens were first discovered to induce cancer in animals

Results of major international bioassay programs

	US NTP[a]	RI
Chemicals/agents studied and published	599	112
Overall carcinogenicity results		
-Clear evidence	51%	44%
-Equivocal evidence	20%	16%
-No evidence	28%	40%
-Inadequate bioassays	1%	-%

[a] Updated 2012 from NTP website

The problem of the extrapolation of the data from animals to humans (Part I)

Experimental studies on animals, if conducted in keeping with certain binding scientific requirements, may provide information that leads not only to qualitative identification of cancer risk, but also to the quantification of those risks.

The problem of the extrapolation of the data from animals to humans (Part II)

In particular the following must be considered:

- the animal model;
- the experimental groups and group size
- the route of exposure
- the concentration/dose/ intensity of the agent studied
- the start of the experiment
- the duration of treatment
- the duration of the experiment
- the conduct of the experiment
- the pathology
- the availability of adequate historical control

The Case of Ethyl Alcohol

Carcinogenicity bioassay on ETHYL ALCOHOL, administered with drinking water,to Sprague-Dawley rats (Exp. BT6004)

Results: CARCINOMAS OF THE ORAL CAVITY, TONGUE AND LIPS

Group No.	Treatment	Animals			Animal bearing oral cavity, tongue and lips carcinoma	
		Age	Sex	No.	No.	%
I	Ethyl alcohol 10%	Breeders	M	110	15	13.6 **
			F	110	12	10.9 *
			M+F	220	27	12.3
II	Drinking water	Breeders	M	110	3	2.7
			F	110	2	1.8
			M+F	220	5	2.3
III	Ethyl alcohol 10%	Offspring	M	30	10	33.3 **
			F	39	16	41.0 **
			M+F	69	26	37.7
IV	Drinking water	Offspring	M	49	2	4.1
			F	55	3	5.5
			M+F	104	5	4.8

* Statistically significant ($p<0.05$) using χ^2 test; ** Statistically significant ($p<0.01$) using χ^2 test

The case of Vinyl Acetate

Carcinogenicity bioassay on VINYL ACETATE MONOMER, administered with drinking water,to Sprague-Dawley rats (Exp. BT51)

Results: CARCINOMAS (CaSq) AND THEIR PRECURSORS (DiSq) OF THE UPPER GIT TRACT

(Part II)

Group/ Dose (ppm, v/v)	Animals			DiSq	CaSq	DiSq + CaSq
	Age	Sex	No.	No. per 100 animals	No. per 100 animals	No. per 100 animals
IV	Offspring	M	53	71.7	41.5	113.2 **♦♦
(5,000)		F	57	80.7	26.3	107.0 **♦♦
		M+F	110	76.4	33.6	110.0
V	Offspring	M	83	19.3	7.2	26.5 **♦♦
(1,000)		F	87	25.3	3.4	28.7 **♦♦
		M+F	170	22.4	5.2	27.6
VI	Offspring	M	107	4.6	1.9	6.5
(0 (a))		F	99	5.1	1.0	6.1
		M+F	206	4.8	1.5	6.3

(a) Drinking water; ** Statistically significant ($p<0.01$) using χ^2 test; ♦♦ Statistically significant ($p<0.01$) using Cochrane-Armitage test test for dose-response relationship

The case of exposure in a vulnerable age

Lifespan inhalation bioassays on VC administered at 2,500 ppm to Sprague-Dawley rats

Group No.	Treatment		Animals			Animals bearing tumors		
	Conc. (ppm)	Schedule	Age (weeks)	Sex	No.[a]	Haemangiosarc. (%)	Hepatocarc. (%)	Neuroblast. (%)
I	2,500	4-7 hd/5dw/76 ws	Br (13)[b]	F	54	50.0	9.2	59.2
II	0		Br (13)	F	60	-	-	-
III	2,500	4-7 hd/5dw/76 ws	E[c]	F	64	**71.9**	**59.4**	**42.2**
				M	63	57.1	42.8	49.2
				F+M	127	64.6	51.2	45.7
IV	2,500	4-7 hd/5dw/15 ws	E[c]	F	60	46.7	**71.7**	18.3
				M	59	40.7	**71.2**	11.9
				F+M	119	43.7	**71.4**	15.1
V	0		E	F	148	-	-	-
				M	157	-	0.6	-
				F+M	305	-	0.3	-

[a] The number of animals refers to the corrected number
[b] Treated from 12th day of pregnancy
[c] Treated from 12th day of embryonic life

The problem of diffuse carcinogenic risks

The problem of diffuse carcinogenic risks (Part I)

DEFINITION

- Diffuse carcinogenic risks are defined as the exposure to single or multiple agents or mixtures that are expected to have limited carcinogenic potential because of the agent type (weak carcinogen) and/or dose/concentration (low), but that involve large groups of the population, in some cases all of mankind.
- Probably, this type of exposure in quantitative terms contributes more to the worldwide increase in incidence of tumours than do strong carcinogenic risks involving limited categories of the population.

The problem of diffuse carcinogenic risk (Part II)

DIFFUSE CARCINOGENIC RISKS: SOME EXAMPLES

Type	People's perception
ELFEMF (electric current)	+ + +
RF-EMF (mobile phone)	+ + + +
Particulate matter (PM_{10}, $PM_{2,5}$, PM_1)	+ + + +
Artificial Sweeteners	+ + +
OGM	+ +
Depleted uranium	+

The problem of diffuse carcinogenic risk (Part III)

TOOLS FOR EVALUATION

- Diffuse carcinogenic risks cannot be identified and quantified by ordinary long-term carcinogenicity bioassays
- To characterize and quantify diffuse carcinogenic risks appropriate, ample, sophisticated experiments must be performed, which we call MEGA-EXPERIMENTS

The Mega-experiments

CHARACTERISTICS

- They must, as far as possible, reproduce the human exposure scenario
- The biophase must be protracted for the life-span, from embryonal-life until spontaneous death, to allow all neoplastic potential to become manifest
- They must include sufficiently large groups of animals to ensure the significance of the results
- Finally, they must be planned to evaluate the contribution of genetic factors

The Mega-experiments: the experience of the RI

- Vinyl Chloride
- Vitamin A, C, E
- Low dose of ionizing radiation
- Non-ionizing radiation

The integrated experimental project of the Ramazzini Institute on ELF-MF started in 2002

The integrated project on 50 Hz MF: overall design

Experiments	No. of animals	MF treatment [a] μ-Tesla	Other treatment
Experiment 1 [b]	5029	1000; 100; 20; 2; 0	—
Experiment 2	805	1000; 0	Formaldheyde, 50 ppm in drinking water from 6 weeks of age
Experiment 3	657	1000; 20; 0	γ- radiation: 10 rads one shot at 6 weeks of age
Experiment 4	642	1000; 0	Aflatoxin B1, 70 μg/rat 9 times between 6-7 weeks of age
Total	**7133**		

[a] The treatment started from fetal life until spontaneous death

[b] The control group of over 500 M and 500 F is shared with experiments 2 and 3

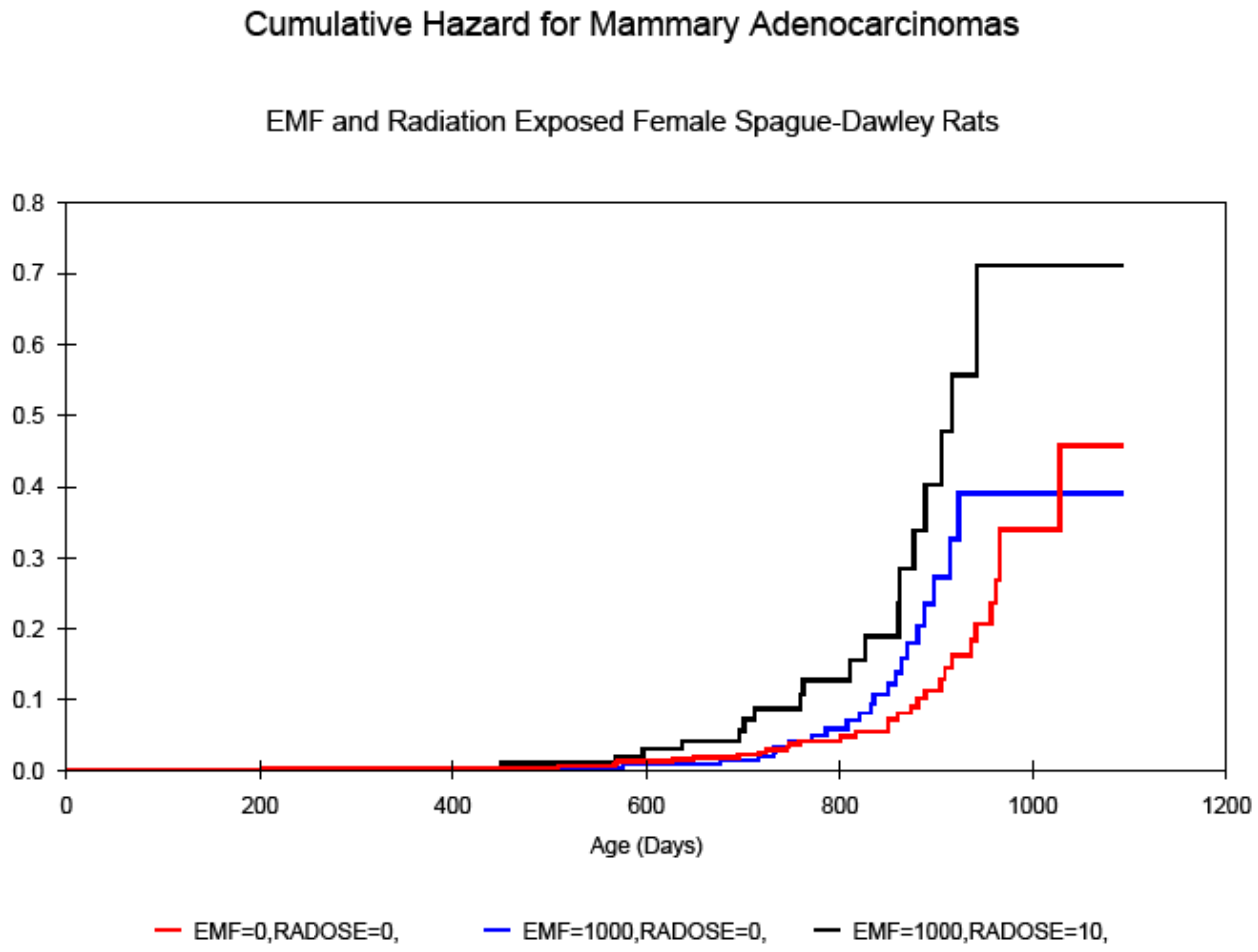
50-Hz magnetic fields exposure system

Experiment N. 3 on 50 Hz MF and γ-radiation exposure: mammary carcinomas

Females No.	Treatment		Carcinomas	
	μT	Rad	Bearing animals %	Total per 100 animals
112	1000	10	**16.1****	**17.0**
107	20	10	7.5	8.4
270	1000	-	8.1	8.5
105	-	10	7.6	7.6
501	-	-	6.4	6.4

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

Experiment 3 on 50 Hz MF and γ-radiation exposure



Conclusive comments on cancer primary prevention (Part I)

1. Because of its epidemiological dimension and because of factors and agents which determine it, cancer represents the most important public health problem in industrialized countries, and is coming to represent this also in the developing countries
2. For such a major problem, it is impossible to consider to controlling cancer by the use of magic pills
3. An efficacious strategy must be based on prevention and in particular on the identification of agents and situations of carcinogenic risk

Conclusive comments on cancer primary prevention (Part II)

4. Carcinogenesis bioassays are the foundation for identifying chemical carcinogens
5. Bioassays are useful both prospectively and retrospectively
6. All known human carcinogens are also carcinogenic when studied adequately in animals
7. Nearly 1/3 of known human carcinogens were first shown to be carcinogenic in animals