Transplacental and developmental genotoxicology: complex dynamic of carcinogenesis

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Carcinogenesis research involves multidisciplinary and international studies using large datasets and fast data exchange.

The result is a

“ noosphere “

with a unique potency to integrate and interpret collected knowledge.

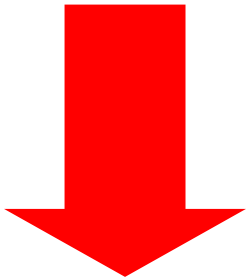
Despite invested efforts, cancer incidence is on the rise.

It is particularly alarming in children and adolescents !!!

- Mutation
- Structural rearrangement of chromosomes
- Aneuploidy
- Methylation; reversible
- Mitogen

Intrauterine development and **early childhood** may be critical for elucidating the cancer aetiology.

It seems that all cancers are oestrogen-positive



traditional concept of sex hormones has to be changed

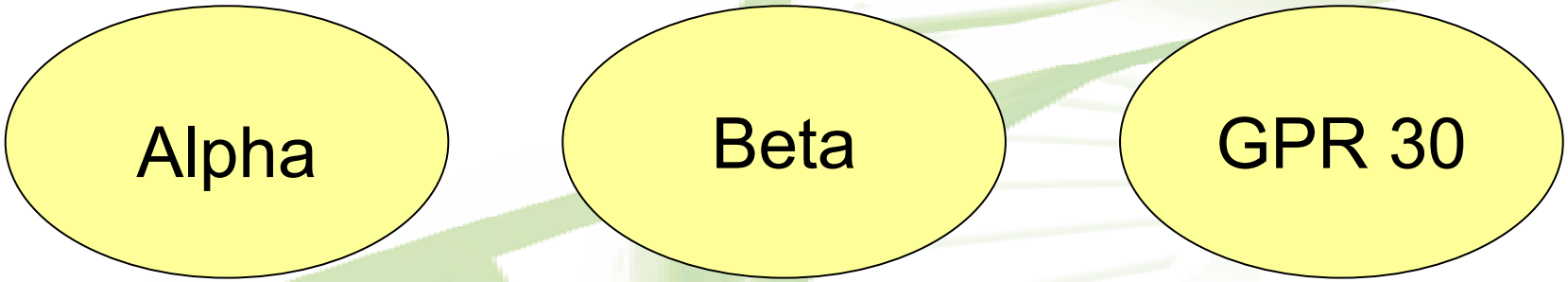
Xenoestrogens

do not follow known genotoxic pathways due to their specific molecular characteristics

Estrogen

- Evolutionary old molecule present in animals and plants
- endocrine, paracrine agent and neurotransmitter
- modulates development of organs during intrauterine life via receptors and postnatal maturation (bones)
- In non-physiological levels it is mutagen, aneugen, demethylating agent
- it is involved in number of biological pathways - from GABA synthesis in brain to synthesis of membranes in fungi

ESTROGEN RECEPTORS



- Number of chemical agents synthesized by our civilization are estrogen like or have impact on aromatese activity- enzyme that synthetise estrogen.

Estrogen-like activity has been described for

metals (aluminium, uranium, lead)
polycyclic aromatic hydrocarbons (PAH),
heterocyclic amines,
some pesticides,
dioxins,
some antiobiotics,
arsenic

Multiple functions of agents

Heavy metals bind to estrogen receptors

DNA damage via

1. interference with cellular redox regulation causing oxidative DNA damage or trigger signaling cascade stimulating cell growth;

Multiple functions of agents

binds to estrogen receptors

DNA damage via

1. interference with cellular redox regulation causing oxidative DNA damage or trigger signaling cascade stimulating cell growth;
2. inhibition of major DNA repair systems resulting in genomic instability and accumulation of critical mutations;

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3. deregulation of cell proliferation by induction of signaling pathways or inactivation of growth controls such as tumor suppressor genes

Multiple functions of agents

binds to estrogen receptors

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-aneugen
-hypomethylation

Aromatase inhibitors

- **cotinine**
- **fungicides**
- **antiepileptic drugs**

Foetus is transplacentally exposed to:

- food additives
- radiochemically contaminated water and air
- sometimes drugs (antiepileptics, antibiotics, antimycotics)

- **Foetus's detoxification capacity buffers some of genotoxic agents.**

- **Target organs for xenobiotics (and genotoxic effects) may be different in mother and the foetus due to a specific stage of developmental physiology and enzyme distribution.**

- **This in turn may lead to different levels of clastogenic or aneugenic metabolites or DNA methylation after exposure to the same xenobiotic in the mother and the foetus.**

Transplancental genotoxicity

Genome damage is result of complex interaction between:

- **maternal and fetal metabolism (hepatic and extrahepatic)**
- **fetal developmental stage and pregnancy-related bioacumulation**
- **detoxification capacity of the fetus and mother (including endometrium)**

- Epidemiological studies on parental exposure and cancer risk in children are limited.

- The correlation between cancer in children and occupational exposure of parents was found in a case of parental occupational exposure to pesticides, paternal exposure to motor vehicle-related occupations, chemical and petroleum industry, glue, nuclear plant (more than 100 mSv) and paint, maternal exposure to solvents, professional cooking,

Miscarriage incidence

- the miscarriage incidance in women occupationally exposed to radioisotopes (iodine, chromium, thallium, technetium, thorium) in hospitals is significantly increased in comparison with women occupataionally exposed to X rays showing that health effect of radioisotopes or mixtures (contaminated due to technology of production by lead, tin, nickle)
- Elements in application for diagnostics is not limited on their radioactivity but also may act as heavy metals or xenoestrogens

Correlation of miscarriage rate and follow up by genetical toxicology (Fučić et al., 2008)

Cytogenetic Endpoints	Study Groups		
	Referents (No. = 36)	**X-ray exposed (No. = 170)**	**R-isotope exposed (No. = 61)**
Chromosome aberrations	Mean ± SD	Mean ± SD	Mean ± SD
Chromatide	1.71 ± 1.08	1.97 ± 1.41	1.98 ± 1.47
Chromosome	0.15 ± 0.33	0.51 ± 0.82 [a]	0.63 ± 0.99 [a]
Acentric	0.36 ± 0.47	0.60 ± 0.90	0.61 ± 1.09
Dicentrics	0.0	0.12 ± 0.36 [b]	0.16 ± 0.36 [b]

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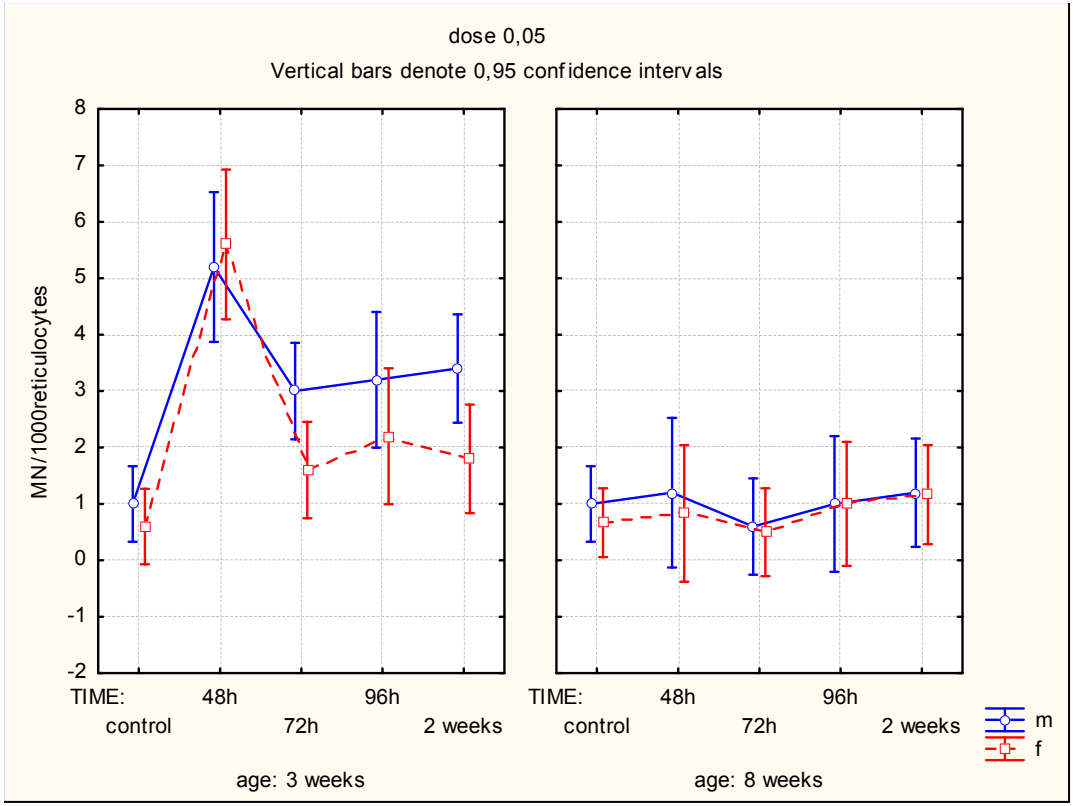
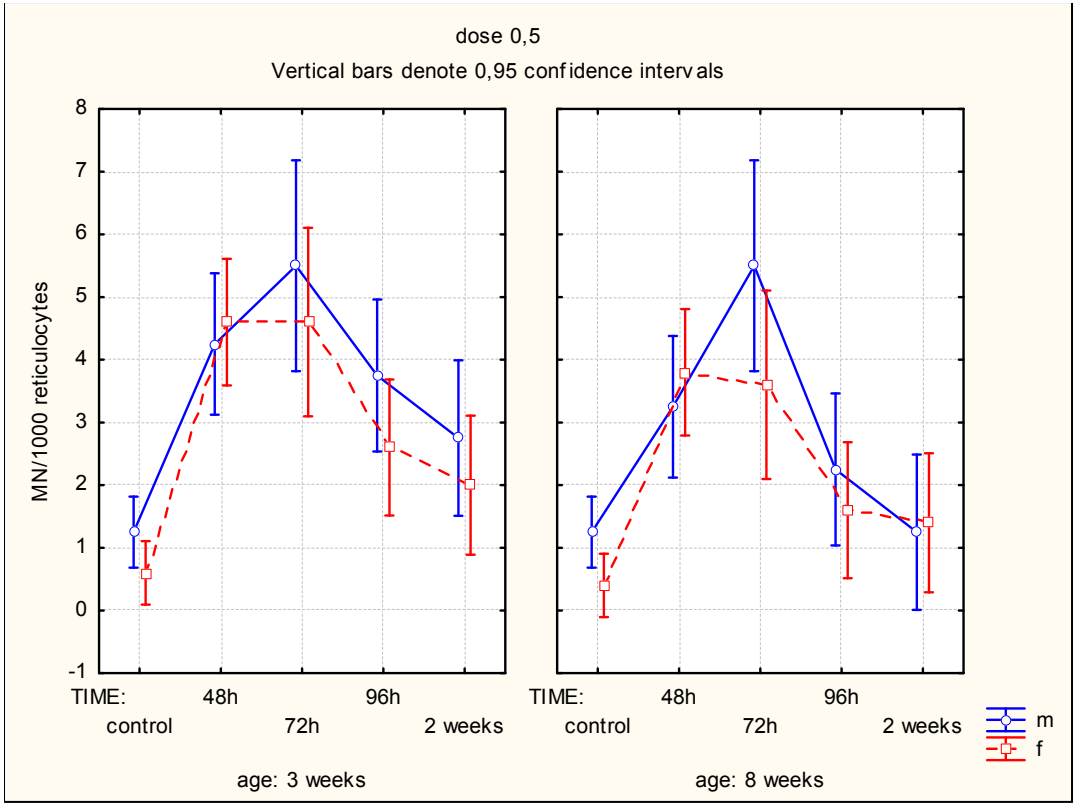
Health Endpoints	Female population [a]	Study Groups	
		X-ray exposed (No. = 170)	R-isotope exposed (No. = 61)
No. of pregnancies	465712	187	112
No. of miscarriages	35165	19	33 [b]
Miscarriage Rate (%)	7.6	10.2	29.5

- **Diethylstilbestrol** /Fucic *et al*. submitted

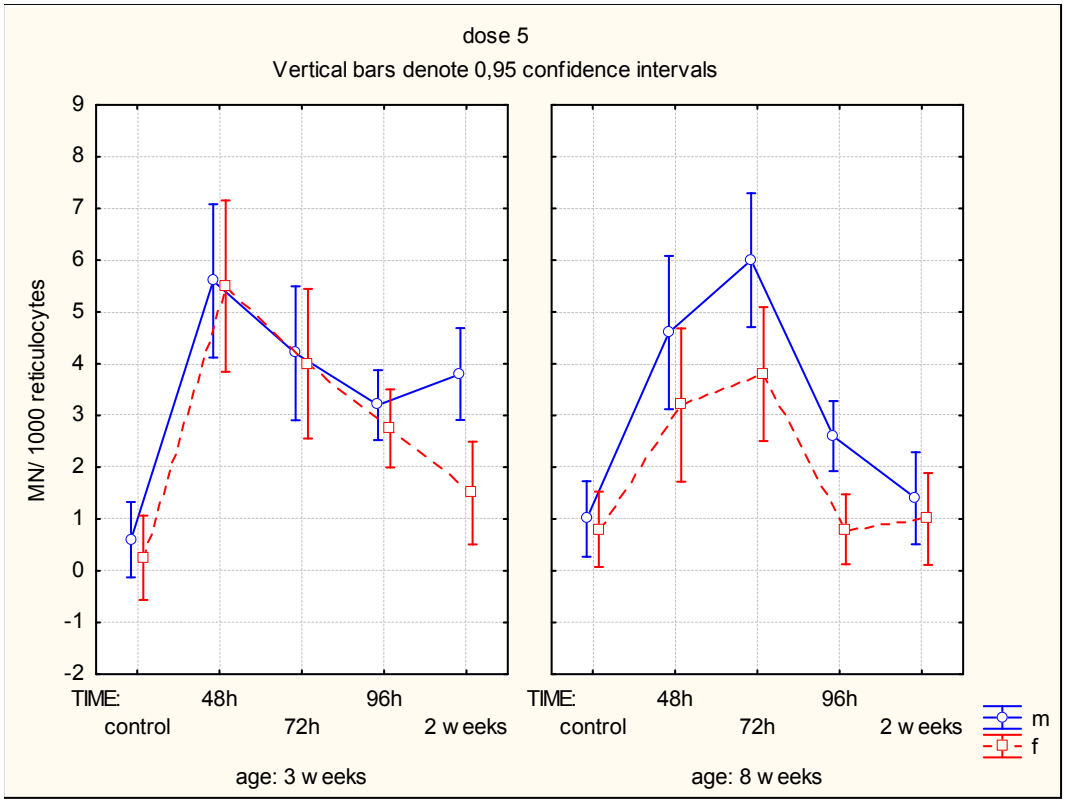
Micronucleus frequency in three and twelve-week-old mice exposed to 0.05 μg/kg in males and females



Micronucleus frequency in three and twelve-week-old mice exposed to 0.5 μg/kg in males and females



Micronucleus frequency in three and twelve-week-old mice exposed to 5 μg/kg in males and females.

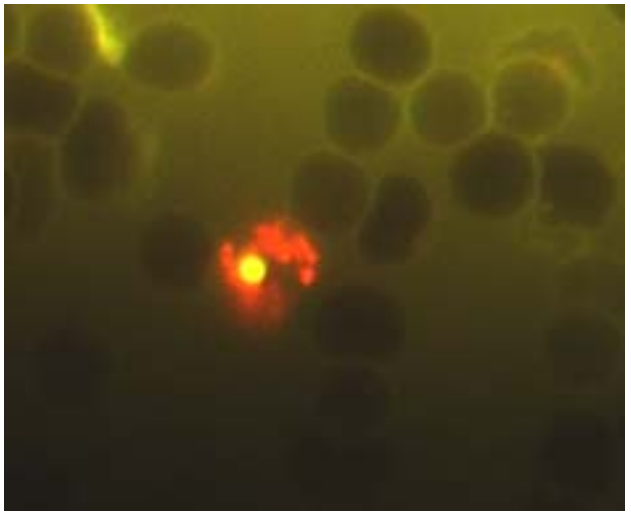


Transplacental genotoxicity

Mothers & newborns

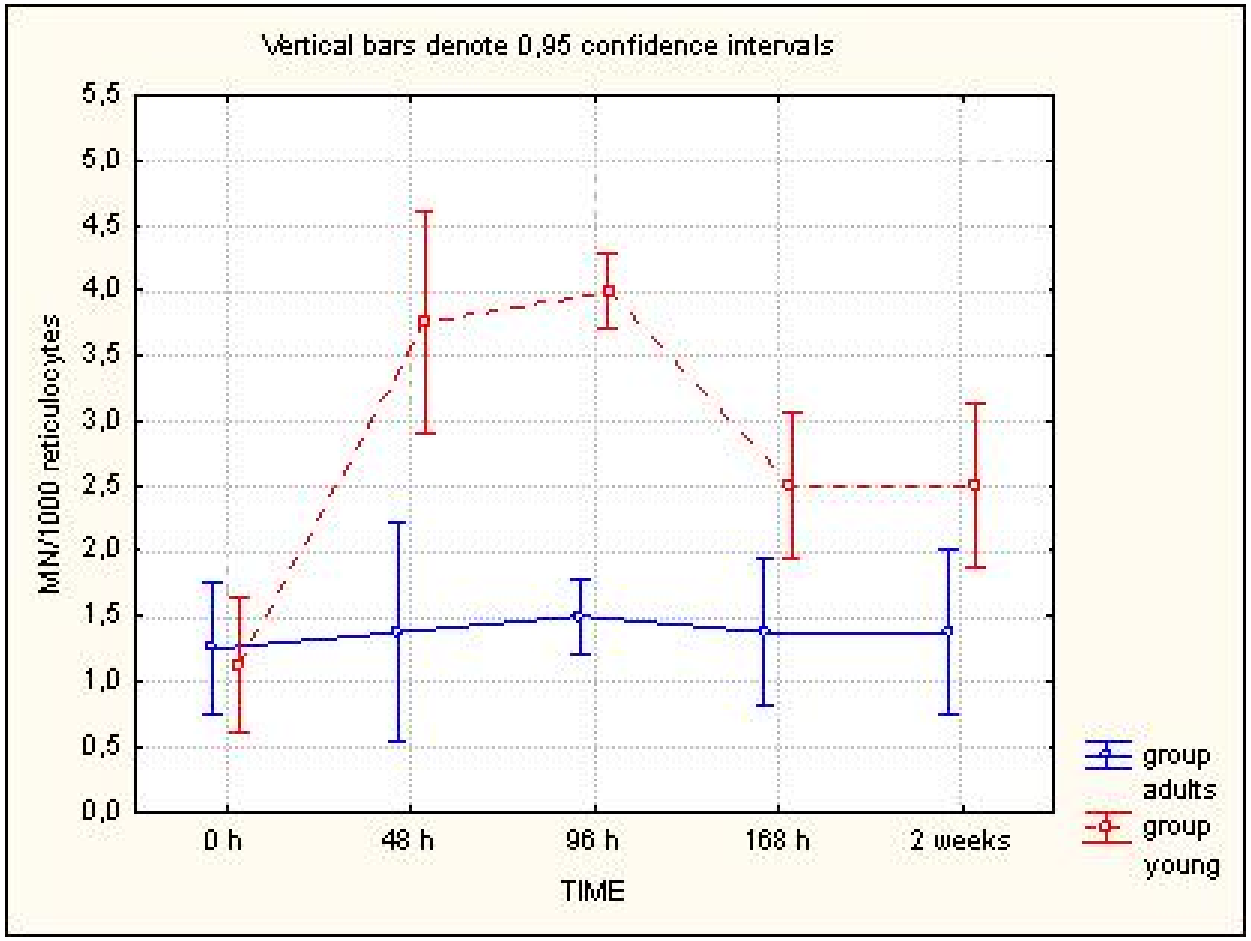
- Antiepileptic drugs
- (aromatese inhibitors or estrogen coupling agents)
- 50 couples over the last 2 years

  - Sampling of the mother and the 3-day-old newborn



Fluconazole (aromatase inhibitor)

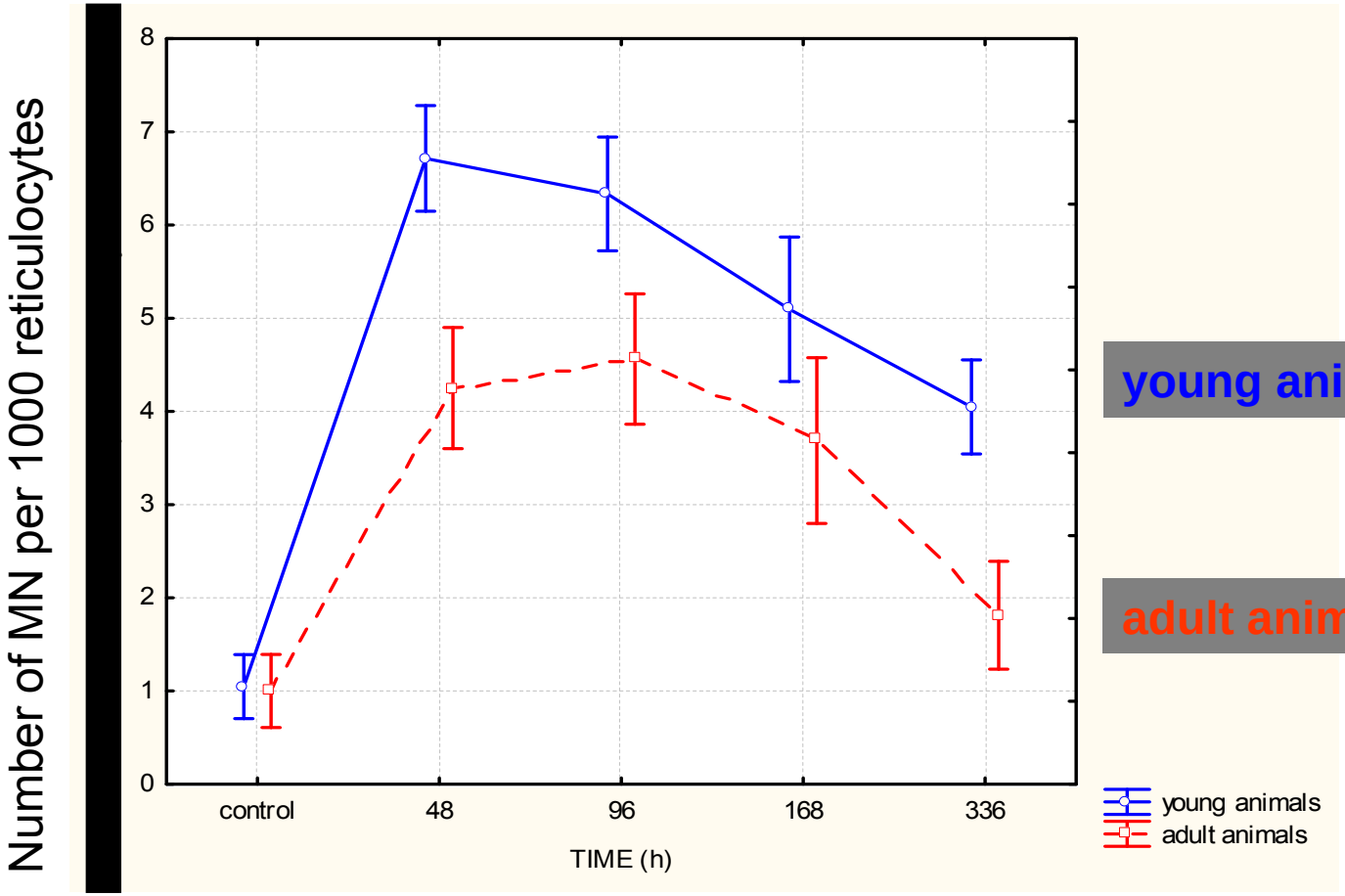
(Fucic et al, *2008)*



- 5-nitrofurantoin
- Metabolism liver, cecum and colon

5-Nitrofurantoin

Fucic *et al, EMS 2005*



young animals

adult animals

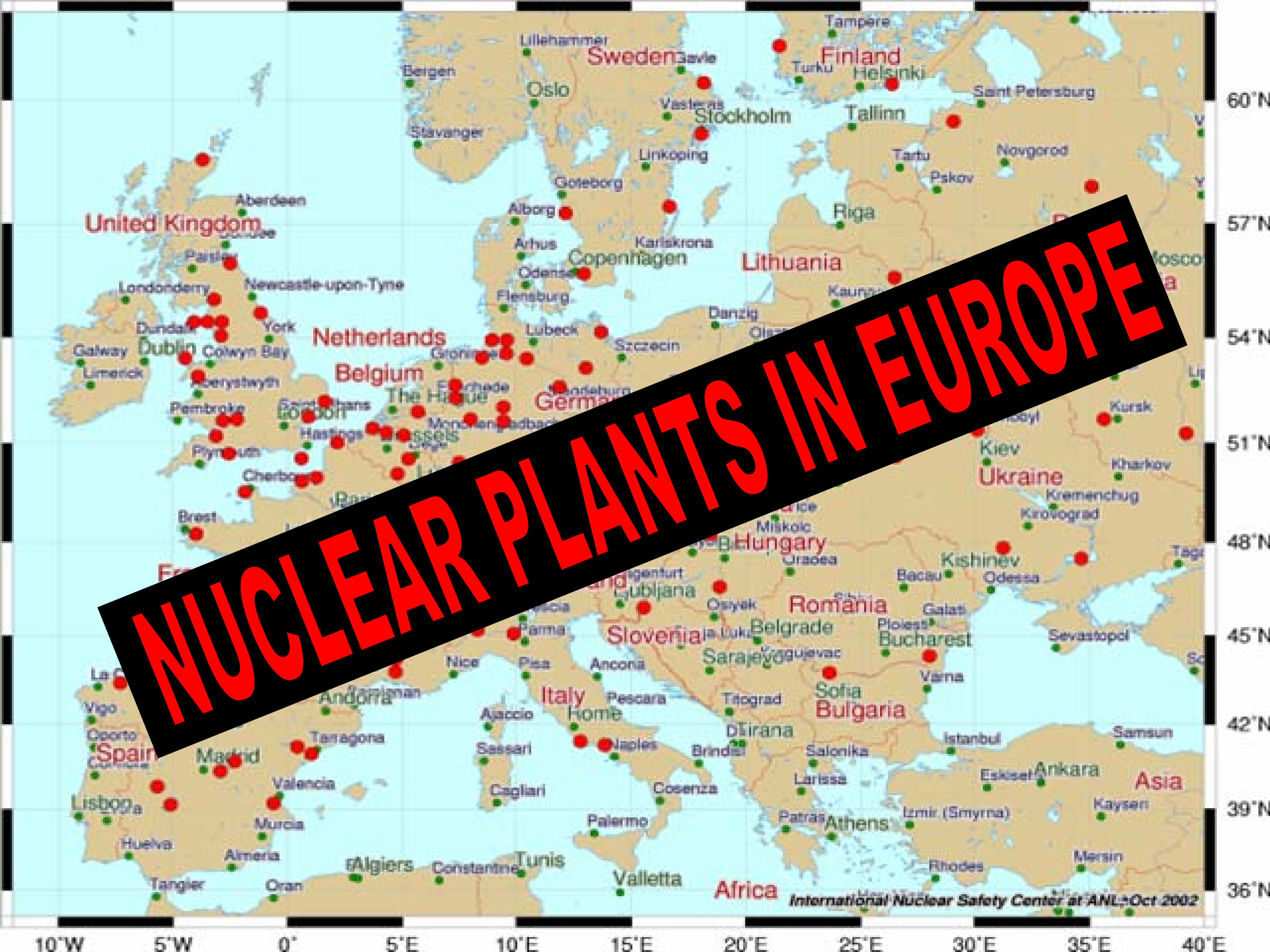
Ionizing radiation

Indoor radon

- Chronic exposure to indoor radon is associated with childhood cancers; correlation coefficient for all cancers 0.78 ($p < 0.01$), leukemia 0.61 ($p< 0.02$), brain and spinal 0.62 ($p< 0.02$), osteosarcoma 0.56 ($p< 0.05$), melanoma 0.56 ($p<0.05$)

WATER

- use of bottled water, beverages popular in children and adolesecents.
- the total body concentration of radionuclides and equivalent doses to red bone marrow are age dependent and it is higher in children, especially in infants for ^{226}Ra, ^{210}Pb, ^{228}Th, ^{210}Po
- ^{226}Ra follows the metabolic pathway of calcium
- the increased effective dose from mineral water might be even seven time higher in infants and teens than recommended by WHO (100 μSv). This may be related to a specific hormonal activity of testosterone and estrogen.
- highest absorption of ^{226}Ra is in newborns and in children in age between 13 and 17 years of age
- high water intake in newborns and children
- un-nursed infants up to 1 year of age may receive doses up to 0,2 mSv/y if their diet is exclusively prepared with mineral water with elevated radon concentrations.


NUCLEAR PLANTS IN EUROPE
Sweden
Finland
Tampere
Lillehammer
Gavle
Turku
Helsinki
Bergen
Oslo
Saint Petersburg
Vasteras
Stockholm
Tallinn
Stavanger
Linkoping
Tartu
Novgorod
Pskov
Goteborg
Riga
Aberdeen
Alborg
United Kingdom
Arhus
Karlskrona
Copenhagen
Lithuania
Paisley
Odense
Londonderry
Newcastle-upon-Tyne
Flensburg
Danzig
York
Netherlands
Lubeck
Galway
Dublin
Colwyn Bay
Szczecin
Limerick
Belgium
Aberystwyth
The Hague
Pembroke
London
Hastings
Plymouth
Kiev
Ukraine
Kursk
Kharkov
Cherbourg
Kremenchug
Brest
Kirovograd
Miskolc
Hungary
Oradea
Kishinev
Odessa
Bacau
Ljubljana
Osijek
Romania
Galati
Parma
Slovenia
Belgrade
Bucharest
Sevastopol
Nice
Pisa
Ancona
Sarajevo
Kragujevac
Varna
Andorra
Italy
Pescara
Titograd
Sofia
Bulgaria
Vigo
Ajaccio
Rome
Tirana
Oporto
Tarragona
Istanbul
Samsun
Spain
Madrid
Sassari
Naples
Brindisi
Salonika
Valencia
Larissa
Ankara
Asia
Cagliari
Cosenza
Lisbon
Murcia
Palermo
Patras
Athens
Izmir (Smyrna)
Kayseri
Huelva
Almeria
Algiers
Constantine
Tunis
Rhodes
Mersin
Tangier
Oran
Valletta
Africa
International Nuclear Safety Center at ANL, Oct 2002
60°N
57°N
54°N
51°N
48°N
45°N
42°N
39°N
36°N
10°W
5°W
0°
5°E
10°E
15°E
20°E
25°E
30°E
35°E
40°E

EPIDEMIOLOGY

- Significant correlation between cancer incidence in children and residence within 0-5 km from nuclear plants in Germany, RR 1,22

- Occupational exposure of fathers working in nuclear plant, receiving a total preconceptual dose of 100 mSv or more is associated with increased rate of childhood leukemia and lymphoma RR 6.4 (1.57-26.3)

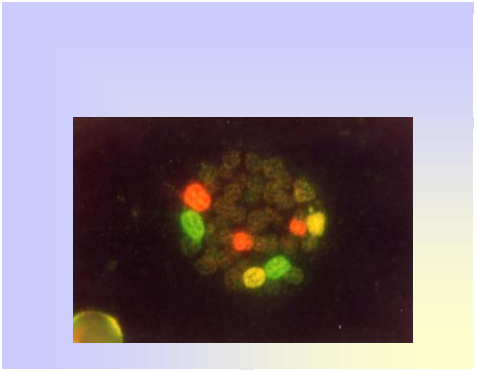
- For childhood lymphatic leukemia 1.55 (CI 1.00-2.41) incidence and mortality 2.74 (CI 1.42-5.27)

Techa River

(M. Bauchinger, 1998)

Year of birth	No. of persons studied	Mean year of birth+SD	No. of cells scored	*F_G per 1000 cells+SEM
1914-1936	14	1927±6	6510	9.7 ± 2.3
1937-1949	14	1944 ± 5	6905	22.0 ± 4.3
Total	28	1936 ± 10	13415	16.0 ± 2.7

* F_G value (full genomic equivalent)

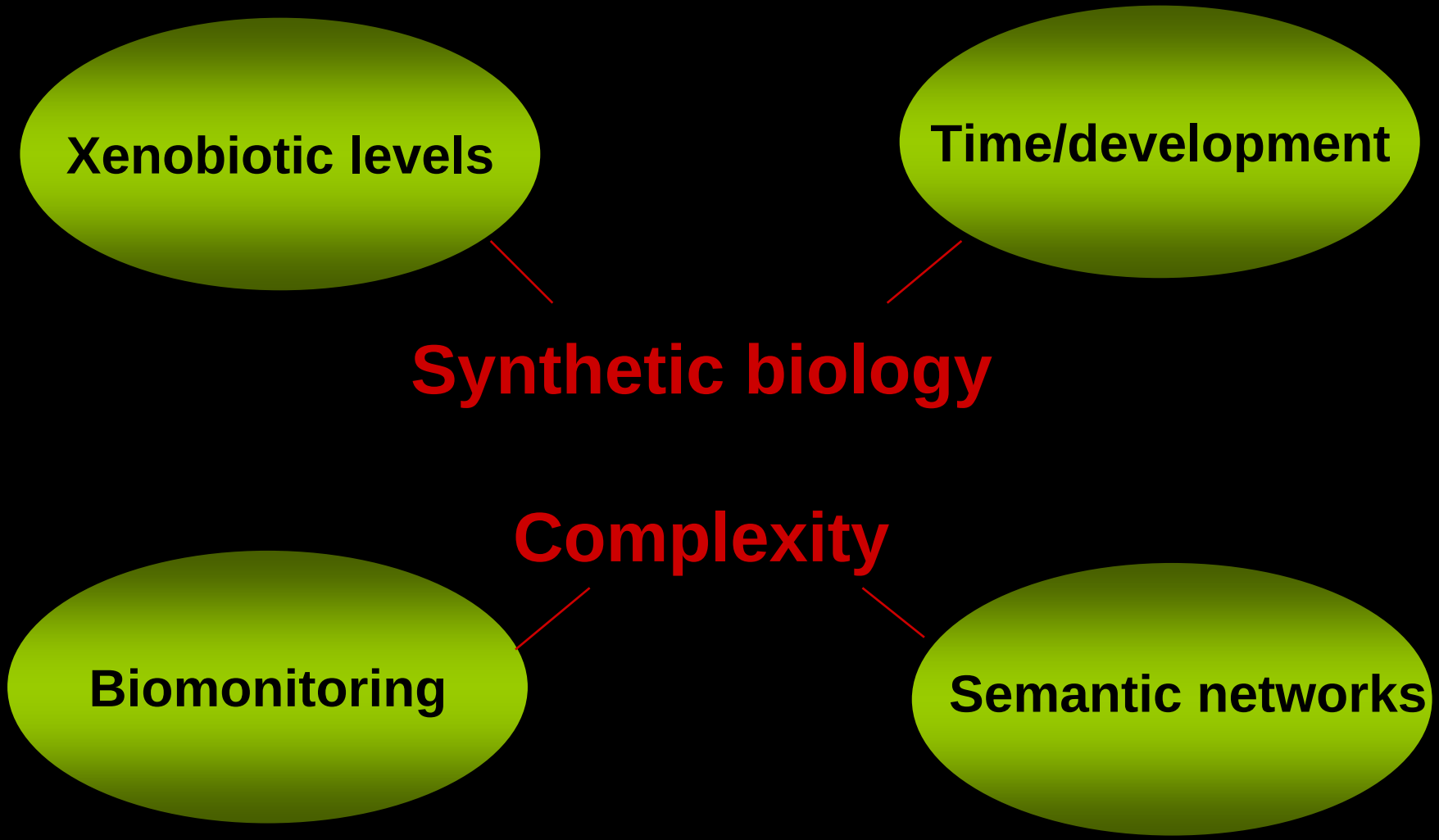


Evacuated children from Chernobyl and contol children from St Petersburg

(Lyubimova, NE, Vorobtsova, IE, Rad Biol Radioecol, 2008)

- Lymphocytes irradiated with 1.5Gy (gamma)

Age	Control	Exposed
1-10 (7.2)	38.6±1.1	47.3 ±0.8
11-20 (12.7)	40.4 ±1.1	49.4 ±1.3
21-30 (26.2)	42.4 ±1.2	36.2 ±0.9
31-40 (36.3)	39.8 ±1.0	36.5 ±0.6

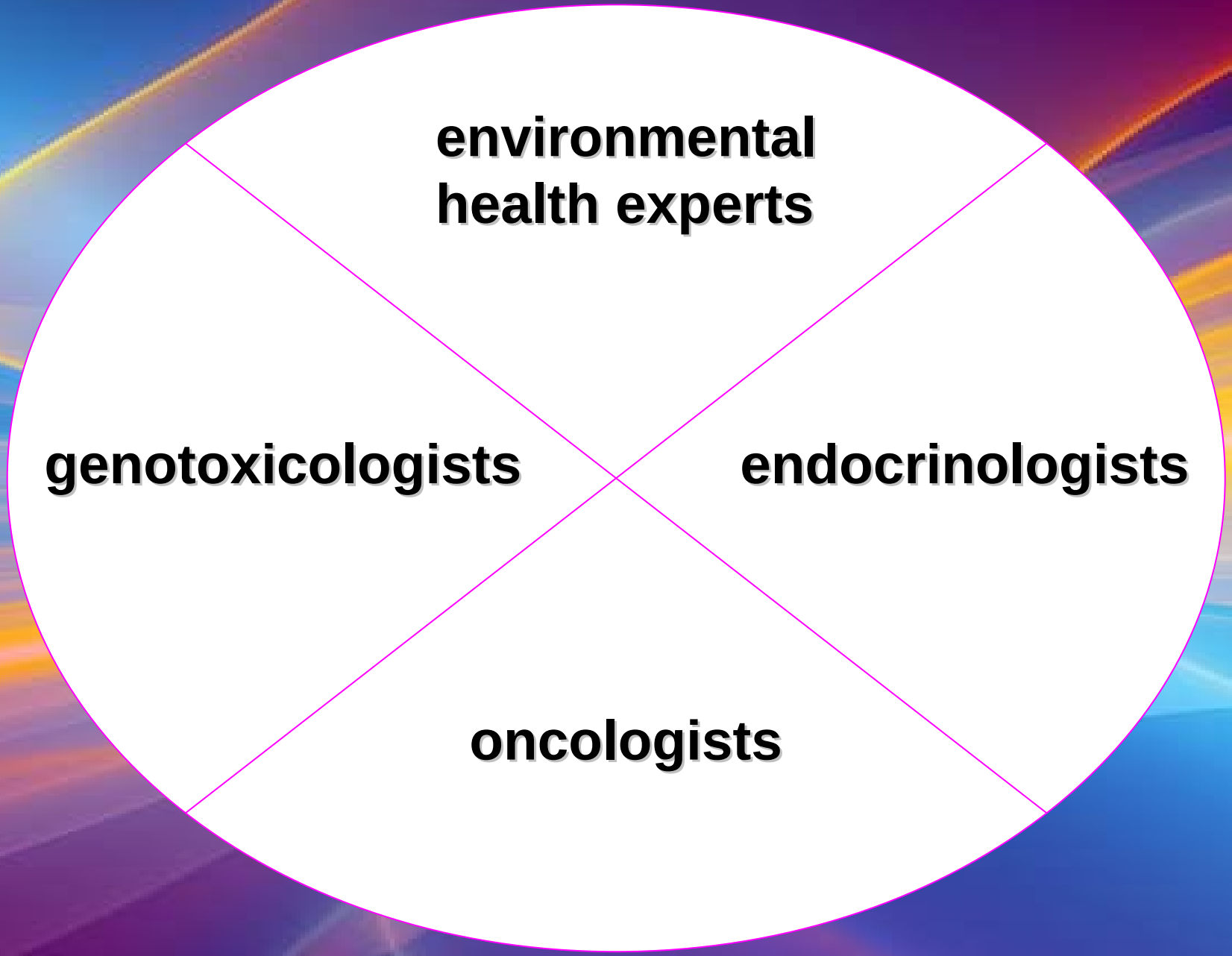

Xenobiotic levels
Time/development
Synthetic biology
Complexity
Biomonitoring
Semantic networks

- Oncology in front of genotoxicology and environmental health.

- Oncology departments have data on metabolism, environmental and occupational background which can be easily incorporated in already exsiting clinical questionaires.

Large datasets produced by molecular biology (functional genomics)

encourage scientists to take systems biology as a tool to synthesise interpretations of the interaction between complex radiochemical (living and occupational) environment and the organisms.


environmental
health experts
genotoxicologists
endocrinologists
oncologists

Free data flow

Artificial intelligence

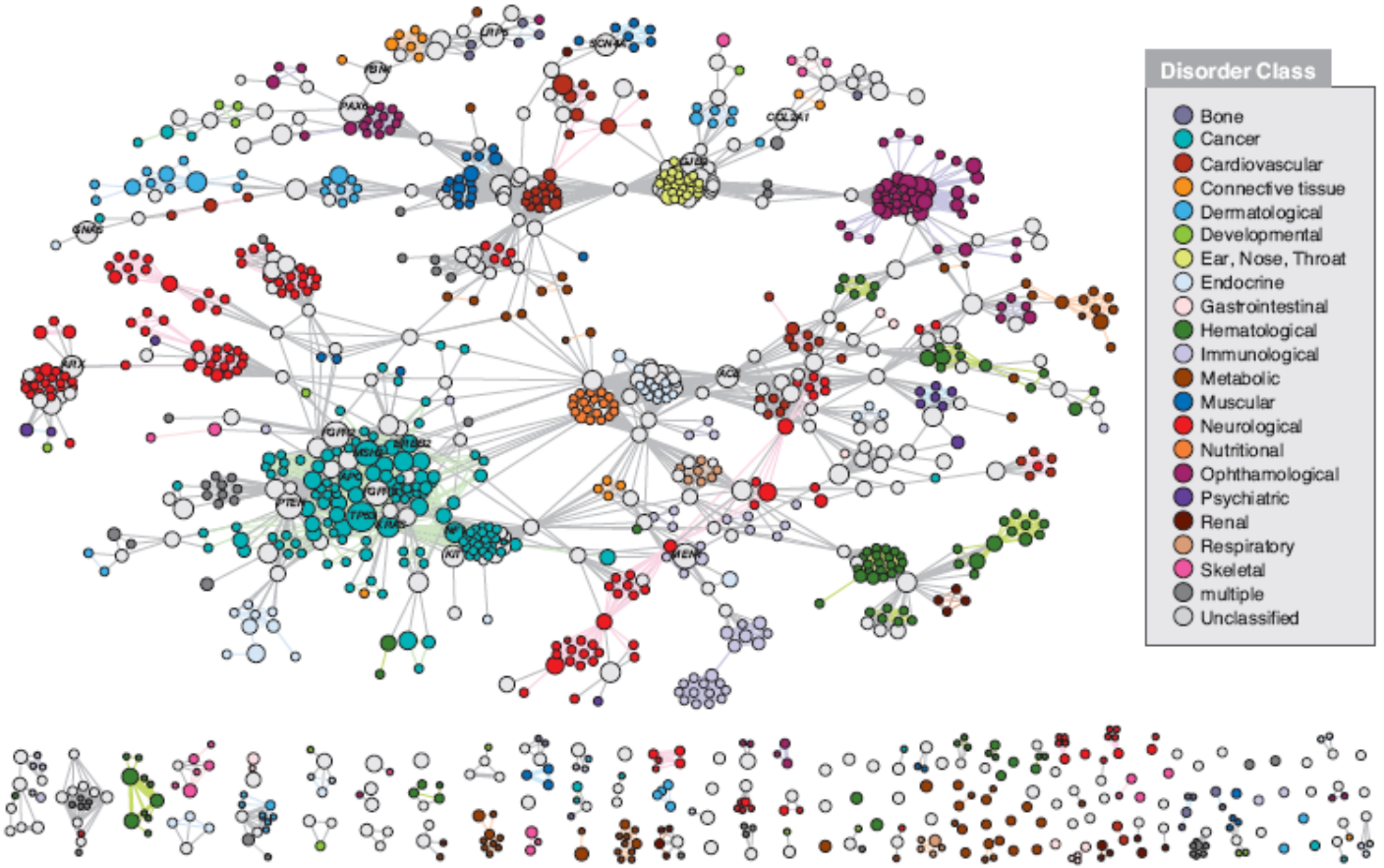
System freedom
(change its own structure)

Scientists are those who are
fearful if they cannot control and understand

Chris Busby

No more random and by chance

Disease Gene Network



Kwang-II Goh *et al.* 2007

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