

Superior Health Council

Physical chemical environmental hygiene
(limiting exposure to mutagenic or endocrine
disrupting agents) and the importance of
exposures early in life



THE ISSUE: Life expectancy increased, but high and often increasing incidence or prevalence of “diseases of civilization”

Socioeconomic conditions, availability of food items, medical care have improved [e.g. cardiovascular mortality 36,0% (1998) \longrightarrow 28,4% (2015)].

Incidence and prevalence of many diseases of civilization has increased after correction for ageing

Life expectancy without chronic illness (Netherlands) 1985 to 2012:

51.4 \longrightarrow 48.1 (men)

48.8 \longrightarrow 40.5 (women)

Childhood-onset type 1 diabetes (Europe) annual increment : 2% to 5%

Belgian "Diabetes Liga": prevalence of diabetes has more than doubled in the past decades

The incidence and prevalence of the metabolic syndrome, hypertension and obesity increased

World Allergy report: allergic diseases are increasing



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Asthma has been reported to increase in the last few decades

Since more than a decade, cognitive capacities have decreased in some Western countries

Prevalence of neurodegenerative diseases has increased

Netherlands, Persistent Cognitive Decline 1992/1993 to 2015/2016

Age 65-88 : 2.5% \longrightarrow 3.4%

In de USA , cancer incidence has risen by 85,9% (yearly increase 1,5%) between 1950 and 2001.



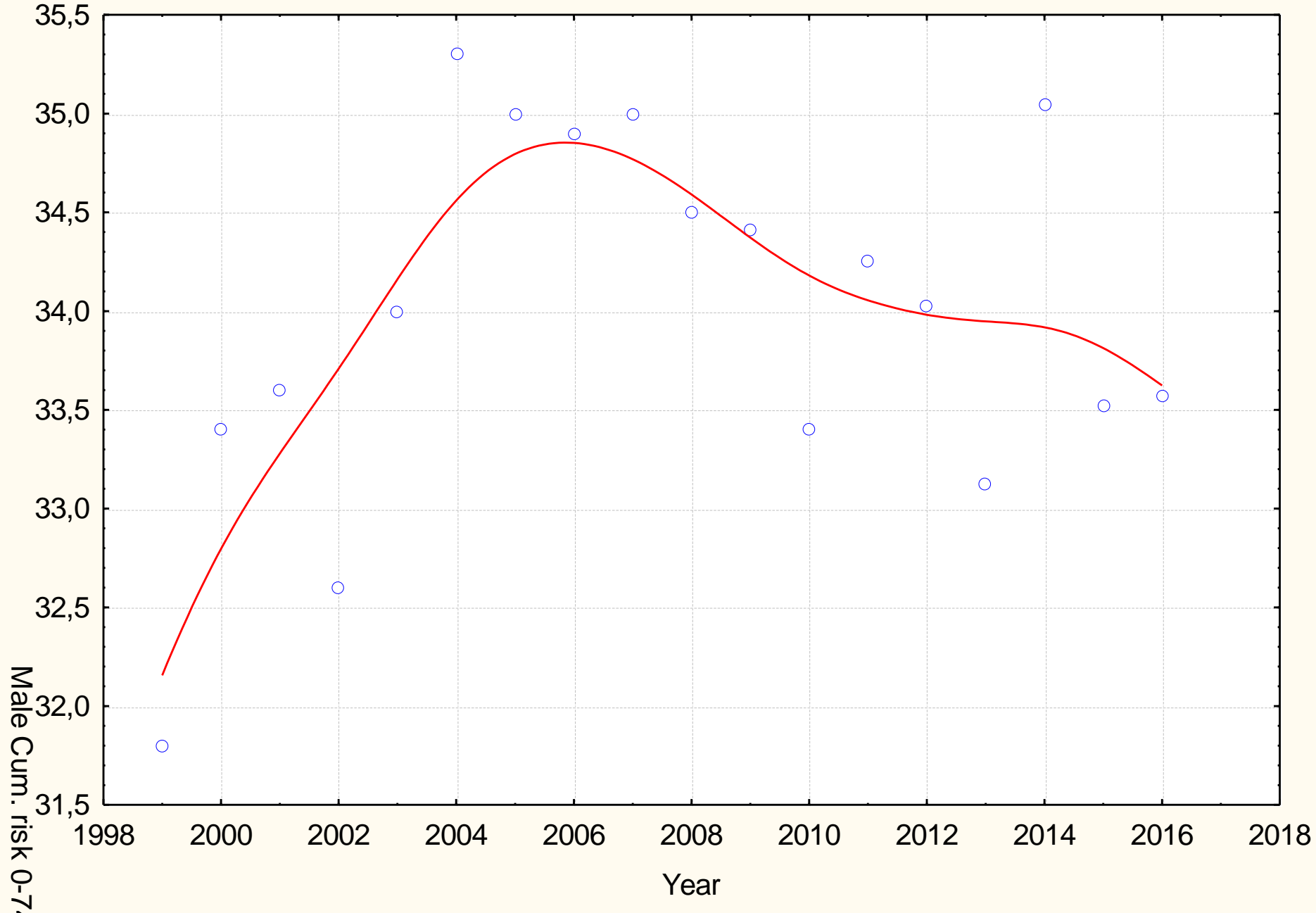
Scatterplot (Tijdstrend vrouw a excl nonmelanoma B 4v*19c)

Cum risk 0-74 non-melanoma = Distance Weighted Least Squares



Scatterplot (Tijdstrend vrouw a excl nonmelanoma B 4v*19c)

Male Cum. risk 0-74 excl nonmelanoma = Distance Weighted Least Squares



Cancer incidence

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Great Britain 1993 to 2015:

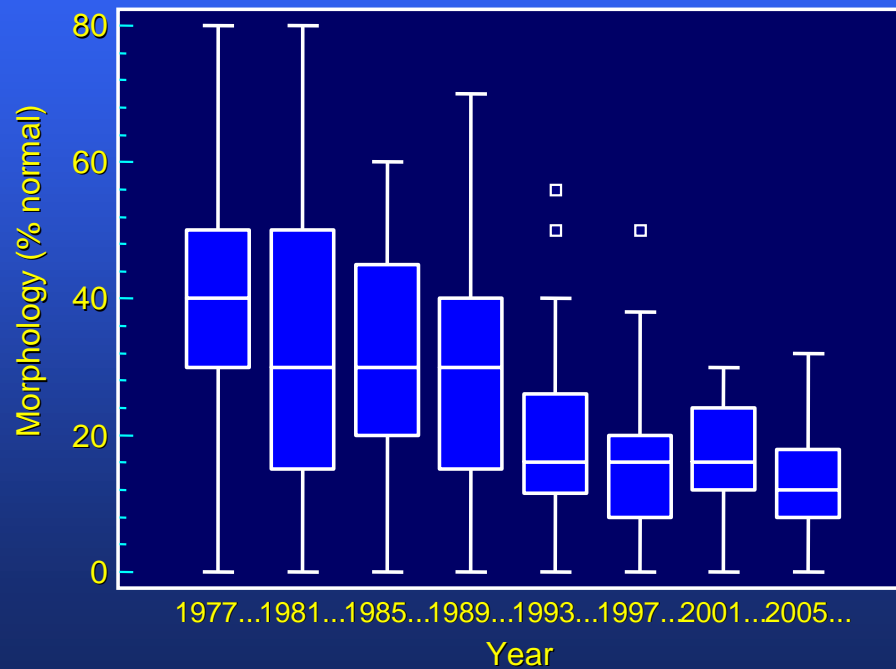
Age 0-24	+24%;
25-49	+20%;
50-59	+13%;
60-69	+ 15%;
70-79	+11%,
80 and over:	+9%



Candidate sperm donors Ghent University Comhaire et al (2007)

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Evolution of sperm morphology



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SHC tries to give at least a partial answer to questions:

Why this happened

Which type of agents are involved

What could be done to come to an effective prevention



Mechanistic insights and molecular-epidemiological data:

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Mutagenic agents, endocrine disruptors, substances binding to hormone receptors or to nuclear receptors functioning as transcription factors in pollutants and man-made products, contribute to the risk of:

Cardiovascular disease (CVD)

Cancer

Diabetes

Female Reproductive Dysfunction

Male Reproductive Dysfunction

Disorders of neurodevelopment and cognition

Immune system related diseases

Obesity

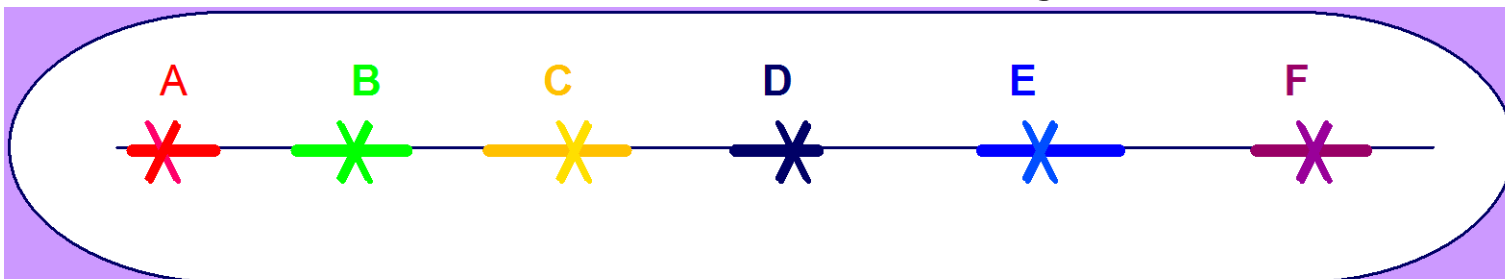


Early exposures (in utero, infancy adolescence) ⇒ important adverse effects on development of the brain and other organs, and can lead to a series of diseases in adult life.

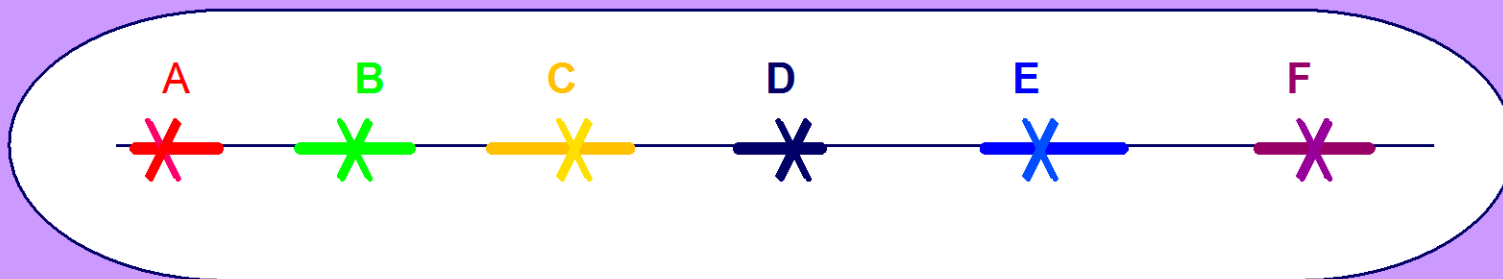
1. In utero: 10 times higher sensitivity to PAHs and mutagenic agents in general (< less detoxification and DNA repair)
2. In utero: high cell division rate. At birth 25% of all cell divisions and mutations already happened.
3. Development of organs steered by hormonal effects, gradients of signal molecules and cell-cell contacts, easily disturbed by exogenous, in particular receptor-binding, substances
4. Importance of time windows



A small increase in mutation rate causes a big increase in cancer



Kans op mutatie in generA en B en C en D en E en F:
 $1.10^{-5} \times 1.10^{-5} \times 1.10^{-5} \times 1.10^{-5} \times 1.10^{-5} \times 1.10^{-5} = 1.10^{-30}$



Kans op mutatie in generA en B en C en D en E en F:
 $2.10^{-5} \times 2.10^{-5} \times 2.10^{-5} \times 2.10^{-5} \times 2.10^{-5} \times 2.10^{-5} = 64.10^{-30}$

Real life exposure to a cocktail of chemicals. **Low dose effects, additive effects, synergistic interactions**

Mutagenic agents:

No critical treshold

Generally linear relation between dose and mutations

Very high doses can be more mutagenic per dose unit than lowed doses (when defense mechanisms overwhelmed)

Very low doses can be more mutagenic per dose unit than higher doses.

Lack of induction of DNA repair: Intense exposure induces mechanisms of DNA repair. Results in less and other mutations. A very low dose, or a dose administered over a long time, affects the cells while repair mechanisms are not fully active.

Bystander effect: also cells which are not touched by an agent show effects. Demonstrated for ionising radiation and gene therapy

Receptor binding Endocrine disrupting agents often have very low dose effects



Numerous substances are mutagenic, carcinogenic or endocrine disruptors.

The European union (ECHA) has listed 145,297 chemicals as pre-registered before 2008 (last updated 11 August 2017)

National Toxicology Program: 26 (20%) of 127 substances, selected because they were produced in huge quantities and/or because of the existence of an important human exposure, were carcinogenic (Huff, 1993). A large percentage of reactive chemical substances are genotoxic carcinogens (see Alberts et al., 1994, p 243; Huff & Hoel, 1992)

The Environmental Protection Agency considers 10.517 substances for testing related to endocrine disruption.

So far, 1,409 chemicals (last updated September 2017) have been listed as potential EDC based on data published in the peer-reviewed literature (TEDX, 2017)



Reach (since 2008): a very slow proces

October 2008 and June 2013: 52 substances SVHC (10/year)

December 2013 and July 2017: 42 substances SVHC, none phased out early 2018

Average 7-year between “substances of very high concern” (SVHC) and phased out.

This time span increases with time

