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

In this scientific advisory report, which offers guidance to public health policy-makers, the Superior Health Council of Belgium provides insights in the underlying causes of the high incidence of diseases of civilization in Western countries.

This report aims at providing both authorities and the public with recommendations contributing to an effective prevention of diseases of civilization.

This version was validated by the Board in May 2019

The Superior Health Council wants to dedicate this advisory report to the memory of Prof. Dr. Jean-Pierre Bourguignon who contributed importantly to this report and co-chaired the ad hoc working group.

EXECUTIVE SUMMARY

Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. Health can also be seen as the ability to adapt and to self-manage. As to risk, risk is inherently connected to societal developments.

That chronic non-communicable diseases are an important cause of human suffering is certain. In the last hundred years the socioeconomic conditions and the availability of many food items have improved markedly in the western countries. However, although life expectancy has risen, the incidence and prevalence of many diseases of civilization has increased after correction for ageing. In this advice the term "diseases of civilization" is used to designate cardiovascular diseases, cancer, diabetes, obesity, female and male reproductive dysfunction, disorders of neurodevelopment and cognition and immune system related diseases. The incidence of cancer and the prevalence of diabetes, the metabolic syndrome, obesity, allergies and problems with fertility have risen. Here the Superior Health Council (SHC) tries to give at least a partial answer to the question why this happened, which type of agents are involved and what could be done to come to an effective prevention. The Council is of the opinion that by now sufficient mechanistic insights and molecular-epidemiological data are available indicating that a series of agents contribute importantly to many diseases of civilization, even if definite epidemiological proof is not yet available. Prevention should be knowledge-based, and not merely evidence-based.

1 The Council reserves the right to make minor typographical amendments to this document at any time. On the other hand, amendments that alter its content are automatically included in an erratum. In this case, a new version of the advisory report is issued.
There is overwhelming evidence, part of it presented in the annexes to this advice, indicating that pollutants, man-made chemicals and physical factors linked to present day lifestyle and present day environmental conditions are important causal factors for several diseases of civilization. Mutagenic agents, endocrine disruptors, substances binding to hormone receptors, and substances binding to nuclear receptors functioning as transcription factors (which thus can affect gene expression and/or have epigenetic effects) are important, especially with relation to cancer, and contribute also to the risk of other diseases of civilization.

An important aspect of the problem is the huge number of chemical substances, among which probably a few percent have mutagenic, carcinogenic, endocrine disrupting or receptor binding properties. Many thousands of pollutants have been identified: the European Union has pre-registered 145,297 chemicals, the Toxic Substances Control Act Chemical Substances Control Inventory has listed (February 2017) more than 67,000 chemicals, the U.S. Environmental Protection Agency considers 10,517 substances for evaluation of endocrine disrupting properties, based on peer reviewed literature the Endocrine Disrupter Exchange has identified 1,409 chemicals as potential endocrine disrupting chemicals (EDCs). Assessing the toxicological properties for humans of a chemical is time consuming and costly, only about 1% of the chemicals have been studied so far. Through REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals), between October 2008 and June 2013, only 52 substances have been phased out, i.e. 10 per year, while since 2013 the decision on 42 substances is pending.

On the basis of the abundant available information indicating the importance of pollutants and man-made chemicals in the induction of several diseases of civilization and in view of the impossibility to correctly assess the toxic or endocrine disrupting potential of each of the many thousands of chemicals two recommendations are formulated in this report.

First, as carcinogenic, mutagenic and endocrine disrupting agents have a major impact on the risk of diseases of civilization and as their effects share common characteristics, a particular form of hygiene, here called "physical chemical environmental hygiene", is proposed. Its purpose is to decrease the number of such substances to which people are exposed and to decrease the intensity of exposure to such agents. Chemicals suspected to have endocrine disrupting or carcinogenic properties based on human or animal data, or showing, in tests that can be performed on numerous substances, mutagenic activity, binding to hormone receptors or to nuclear receptors, should be considered as potentially harmful to human health. Unrestricted exposure to such chemicals should only be allowed after more extensive evaluation indicating that the chemical in question does not cause adverse health effects in humans. In the absence of convincing data showing safety, human exposure should be restricted, in each particular case as much as reasonable, by regulation imposed by public authorities. Risks associated with carcinogenic, mutagenic and endocrine disrupting agents are often undesirable effects of societal developments. Management of these risks thus implies management of, in these cases, technological and societal developments. Implementation of physical chemical environmental hygiene can lead to, but should not be equated to, prohibiting products or technologies, and will probably more often lead to the imposition of a modified version of the ALARA (as low as reasonably achievable) approach. Modified in the sense that the exposures should not only be as low as possible, but also as late in life as possible, as short as possible and as few as possible, given the importance of exposures early in life and of low dose effects. If the agent or technology in question is important or is associated with substantial benefits, the implementation of physical chemical environmental hygiene should lead to the starting up of a strategy based on the precautionary principle, as proposed by the Dutch Health Council in “Voorzorg met Rede” (GR, 2008), leading, in a careful, reasonable and transparent fashion, to a decision in which risks and benefits are balanced. It is essential, as proposed by Passchier (2013), that policy making involves listening to concerned citizens, field experts, stakeholders, civil society organizations, but with the awareness that each of them is possibly blind to certain aspects of the problem. When implementing physical chemical environmental hygiene proper attention should be paid to the phenomenon of risk migration.
Indeed, sometimes preventive measures can, directly or indirectly, lead to the use of replacing methods or technologies that present substantial risks.

Secondly, a more focused approach is proposed with the following rationale in addition to the issues addressed above. Exposures early in life can interfere with an optimal development and can result in disease later in life; real life exposures do not occur to single agents but instead involve complex mixtures of many chemicals and other hazards, with possible interactions between them explaining adverse effects. Therefore a more holistic approach involving avoidance or reduction of exposure to many different agents is desirable along the precautionary principle. Though published studies on effects of individual chemicals justify environmental hygiene, its relevance and benefits as a global strategy reducing the harmful interactions among hazardous agents deserve further studies. In such studies "environmental hygiene" would be implemented on the level of the individual, involving young women intending to become pregnant and pregnant women as a priority. A list of implementable recommendations should be endorsed by an international panel of experts and would be applied by study participants as a package during pregnancy and lactation. Biomonitoring studies in the women and the children and follow up studies of health and developmental outcomes in children would then allow, at different points in time, to evaluate whether the holistic package of preventive measures indeed resulted in positive effects. This strategy is proposed in "Rationale for Environmental Hygiene towards global protection of fetuses and young children from adverse lifestyle factors" published in Environmental Health (Bourguignon et al., 2018).
Keywords and MeSH descriptor terms

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<th>Sleutelwoorden</th>
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<td>'cancer'</td>
<td>cancer</td>
<td>kanker</td>
<td>cancer</td>
<td>Krebs</td>
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<tr>
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<td>cardiovascular diseases</td>
<td>hart en vaatziekten</td>
<td>maladies cardiovasculaires</td>
<td>Herz-Kreislauf-Erkrankungen</td>
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<tr>
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<td>diabetes</td>
<td>suikerziekte</td>
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<td>'pollution'</td>
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<td>pollutie</td>
<td>pollution</td>
<td>Umweltverschmutzung</td>
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<td>scheikundige stoffen</td>
<td>substances chimiques</td>
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<td>'endocrine disruptors'</td>
<td>endocrine disruption</td>
<td>hormoonverstoring</td>
<td>perturbation endocrinienne</td>
<td>endokrine Störungen</td>
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<tr>
<td>'mutagens'</td>
<td>mutagens</td>
<td>mutagenen</td>
<td>mutagènes</td>
<td>Mutagenen</td>
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<tr>
<td>early exposure</td>
<td>early exposures</td>
<td>blootstellingen vroeg in het leven</td>
<td>expositions précoces</td>
<td>frühzeitigen Exposition</td>
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The Council wishes to clarify that the MeSH terms and keywords are used for referencing purposes as well as to provide an easy definition of the scope of the advisory report. For more information, see the section entitled "methodology".
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<tr>
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<td>aryl hydrocarbon receptor</td>
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<tr>
<td>ALARA</td>
<td>as low as reasonably achievable</td>
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<td>ALS</td>
<td>amyotrophic lateral sclerosis</td>
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<tr>
<td>AR</td>
<td>androgen receptor</td>
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<td>ATP</td>
<td>adenosine triphosphate</td>
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<tr>
<td>ATR</td>
<td>atrazine</td>
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<tr>
<td>BBP</td>
<td>benzyl butyl phthalate</td>
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<td>BDE-47</td>
<td>2,2',4,4'-tetrabromodiphenyl ether</td>
</tr>
<tr>
<td>BPA</td>
<td>bisphenol A</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
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<td>CVD</td>
<td>cardiovascular disease</td>
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<tr>
<td>DALYs</td>
<td>disability-adjusted life years</td>
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<tr>
<td>DBP</td>
<td>dibutyl phthalate</td>
</tr>
<tr>
<td>DDE</td>
<td>dichlorodiphenyldichloroethylene</td>
</tr>
<tr>
<td>DDT</td>
<td>dichlorodiphenyltrichloroethane</td>
</tr>
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<td>DEHP</td>
<td>bis(2-ethylhexyl) benzene-1,2-dicarboxylate</td>
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<td>diisononyl phthalate</td>
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<td>DNA</td>
<td>deoxyribonucleic acid</td>
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<tr>
<td>DOHaD</td>
<td>Developmental Origin of Health and Disease</td>
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<td>DSB</td>
<td>double strand DNA break</td>
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<td>ECHA</td>
<td>European Chemicals Agency</td>
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<td>EDCs</td>
<td>endocrine disrupting chemicals</td>
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<tr>
<td>EE2</td>
<td>17α-ethinylestradiol</td>
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<td>ER</td>
<td>estrogen receptor</td>
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<td>EU</td>
<td>Emissions, Exposure Patterns and Health Effects of Consumer Products in the EU</td>
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<td>EPHECT</td>
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<td>FP7</td>
<td>7th framework programme</td>
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<tr>
<td>FSH</td>
<td>follicle-stimulating hormone</td>
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<tr>
<td>Gy</td>
<td>gray</td>
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<tr>
<td>HCH</td>
<td>hexachlorocyclohexane</td>
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<tr>
<td>LET</td>
<td>linear energy transfer</td>
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<tr>
<td>LOAEL</td>
<td>lowest observed adverse effect level</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>MXC</td>
<td>methoxychlor</td>
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<td>NER</td>
<td>nucleotide excision repair</td>
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<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
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<td>NOAEL</td>
<td>no-observed-adverse-effect level</td>
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<td>NR</td>
<td>nuclear receptors</td>
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<td>NTP</td>
<td>USA National Toxicology Program</td>
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<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
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<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>PAH</td>
<td>polycyclic aromatic hydrocarbon</td>
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<tr>
<td>PCB</td>
<td>polychlorinated biphenyl</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>PFOA</td>
<td>perfluorooctanoic acid</td>
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<tr>
<td>PFOS</td>
<td>perfluorooctane sulfonate</td>
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<tr>
<td>PM</td>
<td>particulate matter</td>
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<tr>
<td>PM2.5</td>
<td>fine particles with a diameter of 2.5 μm or less</td>
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<tr>
<td>POP</td>
<td>persistent organic pollutant</td>
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<tr>
<td>PPAR</td>
<td>peroxisome proliferator-activated receptor</td>
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<tr>
<td>PXR</td>
<td>pregnane X receptor</td>
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<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
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<tr>
<td>REACH</td>
<td>Registration, Evaluation, Authorisation and Restriction of Chemicals</td>
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<tr>
<td>RXR</td>
<td>retinoid X receptor</td>
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<tr>
<td>SAhRM</td>
<td>selective AhR modulator</td>
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<tr>
<td>SHC</td>
<td>Superior Health Council</td>
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<tr>
<td>TBT</td>
<td>tributyl tin</td>
</tr>
<tr>
<td>TCA</td>
<td>trichloroacetic acid</td>
</tr>
<tr>
<td>TCDD</td>
<td>tetrachlorodibenzo-p-dioxin</td>
</tr>
<tr>
<td>TDS</td>
<td>testicular dysgenesis syndrome</td>
</tr>
<tr>
<td>TNC</td>
<td>trans-nonachlor</td>
</tr>
<tr>
<td>TPA</td>
<td>12-O-tetradecanoylphorbol-13-acetate</td>
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<tr>
<td>VMM</td>
<td>Flanders Environment Agency</td>
</tr>
<tr>
<td>XRE</td>
<td>xenobiotic responsive element</td>
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<td>ZIKV</td>
<td>zika virus</td>
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I. THE ISSUE: HIGH AND OFTEN INCREASING INCIDENCE OR PREVALENCE OF "DISEASES OF CIVILIZATION"

That chronic non-communicable diseases are an important cause of human suffering is certain. In the last hundred years the socioeconomic conditions and the availability of many food items have improved markedly in the western countries. However, although life expectancy has risen, the incidence and prevalence of many diseases of civilisation has increased after correction for ageing. In this advice the term "diseases of civilization" is used to designate cardiovascular diseases, cancer, diabetes, obesity, female and male reproductive dysfunction, disorders of neurodevelopment and cognition, and immune system related diseases. The incidence of cancer and the prevalence of diabetes, the metabolic syndrome, obesity, allergies and problems with fertility have risen. Here the Council tries to give at least a partial answer to the question why this happened, which type of agents are involved and what could be done to come to an effective prevention.

It is clear that the progress in medical science and techniques has allowed to limit the impact of diseases on mortality and severe morbidity, but the percentage of people in good health has not risen. In the Netherlands the life expectancy without chronic illness has decreased for men from 51.4 years in 1985 to 48.1 years in 2012 and for women from 48.8 in 1985 to 40.5 in 2012 (http://www.eengezondernederland.nl/Heden_en_verleden/Levensverwachting/Gezonde_levensverwachting, accessed 7/09/2018). Also in the Netherlands, there was a stable trend in the prevalence of poor self-rated health and severe disability, while the mean number of chronic diseases (1.3 - 1.8) and the prevalence of mild disability (20.5 - 32.1 %) increased between 1992 and 2009 (Galenkamp et al., 2013).

A world-wide increase in the incidence of cancer is observed (Sasco, 2008). In Flanders, the incidence of cancer has risen till recently (2004 for men, 2014 for women) (last figures are from 2015) and in 2015 the cumulative incidence of cancer for ages 0 - 74, after exclusion of non-melanoma skin cancer, amounted to 27.62 % in women and 33.52 % in men. See Annex 1 for additional data and considerations on time trends of cancer incidence.

Although age-adjusted atherosclerotic cardiovascular disease mortality rate trends decreased globally (Barquera et al., 2015), the leading cause of death, globally, remains cardiovascular diseases; their prevalence is incessantly progressing in both developed and developing nations according to the report of the World Health Organization (Balakumar et al., 2016). However, probably due to medical progress, the mortality from cardiovascular disease in Belgium diminished from 36.0 % of total mortality in 1998 to 28.4 % in 2015 (National Institute for Statistics).

The prevalence of obesity, diabetes, the metabolic syndrome have risen in the past decades. Overweight and obesity have increased markedly in the last 20 years in most OECD (Organisation for Economic Co-operation and Development) countries, not only in adults, but also in children, and an increase in children has also been observed in Belgium between 2000 - 2001 and 2013 - 2014 (https://www.oecd.org/els/health-systems/Obesity-Update-2017.pdf, accessed 26/9/2018).

From 2003 - 2004 to 2011 - 2012, overall prevalence of the metabolic syndrome increased in the USA from 32.9 % (95 % confidence interval (CI), 31.6 % - 34.2 %) in 2003 - 2004 to 34.7 % (95 % CI, 33.5 % - 36.0 %) in 2011 - 2012 (Aguilar et al., 2015).

In the second half of the 20th century it became obvious that a relentless increase in diabetes type 2 (diabetes mellitus (DM)) affecting the economically affluent countries, is gradually afflicting also the developing world (Ginter & Simko, 2010). The global prevalence of type 2 diabetes is estimated to have doubled over the past 30 years and now includes rapidly rising numbers of children and adolescents (The Lancet editorial, 2018). In the USA age-adjusted prevalence of type 2 diabetes for adults age 65+ increased at an average annual percentage change of 2.31 % between 1992 and 2012 (Akushevich et al., 2018). The incidence of childhood-onset type 1 diabetes has increased worldwide. Throughout Europe the reported annual increment varied between 2 % and
5% according to the observed population. In Belgium a secular trend of increasing incidence was noted in children, but a decreasing incidence in the age group 15-39 years was observed, indicating an earlier onset of diabetes type 1 (Gorus et al., 2004). According to the Belgian "Diabetes Liga" prevalence of diabetes has more than doubled in the past decades and the International Diabetes federation estimates that 8.0% of the Belgian population suffers from diabetes, predominantly (about 90%) from diabetes type 2 (https://www.diabetes.be/diabetes-cijfers, accessed 26/9/2018).

In Flanders (Comhaire et al., 2007) and many other regions in the world the incidence and prevalence of problems with male fertility has increased. A review by Sengupta et al. (2018) identified an overall 57% diminution in mean sperm concentration over the past 35 years (p = 0.0002), which, when analyzed for each geographical region, identified a significant decline in North America, Europe, Asia, and Africa.

According to the World Allergy report allergic diseases are increasing in prevalence worldwide (Pawankar et al., 2008). In the UK, the prevalence of allergic disorders has risen importantly over several decades, but rates have stabilized over the past decade (Gupta et al., 2007). In the UK admissions for some systemic allergic diseases have however risen sharply in the last decade which may indicate a rising incidence of these conditions (Gupta et al., 2007).

In most countries, the prevalence of asthma has been reported to increase in the last few decades (Eder et al., 2006).

Chronic obstructive pulmonary disease (COPD) is a leading cause of world-wide mortality and disability. On average about 5–15% of adults in industrialized countries have COPD defined by spirometry (Anto et al., 2001). The World Health Organisation has predicted that COPD will become the third most common cause of death in the world by 2030 (cited by Diaz-Guzman & Mannino, 2014). In recent years the COPD morbidity and mortality have however decreased in some developed countries (Diaz-Guzman & Mannino, 2014).

There are indications that since more than a decade, cognitive capacities have decreased in some Western countries (Teasdale & Owen, 2005; Dutton & Lynn, 2013), whereas these cognitive capacities had increased over the previous decades in the 20th century (Flynn, 1987; Pietschnig and Voracek, 2015). Moreover, the prevalence of neurodevelopmental disorders has increased during the past decades: autistic spectrum disorders and attention deficit hyperactivity disorders (Bellanger et al., 2015).

The prevalence of neurodegenerative diseases has increased. In the Netherlands, the incidence of Persistent Cognitive Decline increased among 65-88 year-olds from 2.5% to 3.4% between 1992/1993 and 2015/2016, and in Belgium the importance of Alzheimer disease as a cause of death has increased with 35.4% between 2005 and 2016 (healthdata.org).

Finally, it seems probable that the prevalence of certain types of behavioral problems has increased (Bor et al., 2014).
II. METHODOLOGICAL APPROACH

After analysing the project proposal, the Board and the chair of the area chemical agents and the chairs of the working group identified the necessary fields of expertise. An ad hoc working group was then set up which included experts in cancerology, endocrinology, epidemiology and molecular epidemiology, pediatrics, genetic toxicology, nutrition and ionizing and non-ionising radiation. The experts of this working group provided a general and an ad hoc declaration of interests and the Committee on Deontology assessed the potential risk of conflicts of interest.

The advice rests on the expert opinion of the members of the ad hoc working group and of Prof Dr. Jos C. S. Kleinjans, co-author of a scientific paper that is part of the advice (Bourguignon et al., 2018, see annex 4), and on a literature search aiming at:
- Documenting the high and often increasing incidence of some diseases of civilization.
- Studying the main lines of evidence indicating that pollutants and man-made products contribute to the risk of diseases of civilization.
- Studying some of the mechanisms involved in the induction of diseases of civilization.
- Studying the mechanistic characteristics of the dose-response relations, low dose effects and effects of combined exposures to genotoxic and endocrine disrupting agents.
- Studying the molecular epidemiological evidence for the impact of pollutants and man-made products to diseases of civilization.
- Studying the epidemiological evidence for the impact of exogenous influences (as opposed to inherited characteristics) on the incidence of cancer.
- Documenting the fact that there is credible evidence indicating the hazardous properties of a series of agents (mentioned in chapter 1.2 of the “Conclusions and recommendations”). However, no attempt was made to make a comprehensive study of each of the individual agents to demonstrate that the hazardous properties must be considered proven.

With the exception of citing a few figures from the Global Burden of Disease study (GBD 2015; Cohen et al., 2017) and the Lancet Commission on Pollution and Health (Landrigan et al., 2017), no attempt was made to estimate the precise impact of pollution and man-made products on the incidence of diseases of civilization, as the Council is of the opinion that this is at present not possible. This because of the importance of early life exposures, the lack of sensitivity of epidemiological studies, and the lack of unexposed control populations. This is in particular true for cancer, due to the long latency period and as epidemiological studies allow only seldom to detect a risk factor leading to a relative risk smaller than a factor 1.5 (Ehrenberg, 1996).

This advice concerns a wide ranging, difficult and controversial subject and is based on a comprehensive set of data and insights. For the sake of readability and clarity the main text is limited in size, and much of the underlying information on which the advice is based is presented in annexes or is contained in the references.

Once the advisory report was endorsed by the ad hoc working group and by the standing working group chemical agents it was ultimately validated by the Board.
III. ELABORATION AND ARGUMENTATION

1. Adverse effects observed in relation to exposure to pollutants and man-made products, in particular carcinogenic agents, mutagenic agents and endocrine disruptors

It is well known that the causes of diseases of civilization are multifactorial, and that inherited traits, nutrition (WHO technical staff, 2014) and behaviour, including the amount and regularity of physical exercise (American Cancer Society, Kushi et al., 2012), play an important role. This text is meant to present the main lines of evidence indicating that pollutants and man-made products contribute substantially to the risk of diseases of civilization. This item is developed in somewhat greater detail with relation to cancer but is also addressed in relation to other diseases. That pollution poses a serious threat to human health is increasingly recognized. The Global Burden of Disease study, a multinational study (WHO, World Bank, Harvard School of Public Health, 2015), estimates that pollution-related disease was responsible in 2015 for 16 % of total global mortality. According to the global burden of disease study, all forms of pollution combined were responsible in 2015 for 21 % of all deaths from cardiovascular disease, 26 % of deaths due to ischaemic heart disease, 23 % of deaths due to stroke, 51 % of deaths due to chronic obstructive pulmonary disease, and 43 % of deaths due to lung cancer.

Annex 2 summarizes data (according to Landrigan et al., 2017) from the Global Burden of Disease study on the health impact of air pollution, lead, toxic occupational risk factors and endocrine disruptors and on pollution related diseases in children.

1.1. Cardiovascular disease (CVD)

According to the Lancet commission on pollution and health (Landrigan et al., 2017) all forms of pollution combined were responsible, worldwide, in 2015, for 21 % of all deaths from cardiovascular disease.

There are now studies suggesting a direct link between EDCs and CVD, independently of those EDCs acting as obesogens or diabetogens (Gore et al., 2015.). Dioxin exposure (Humblet et al., 2008), organochlorine pesticides (Min et al., 2011) and dichlorodiphenyltrichloroethane (DDT) (La Merrill et al., 2013) were found to be associated with CVD in epidemiological studies. There is evidence that Bisphenol A (BPA) acts directly as a cardiovascular disruptor in rodents (Gore et al., 2015) and that internal exposure to BPA is associated with CVD in humans (Gore et al., 2015).

Carcinogenesis and atherosclerosis might have several fundamental biological mechanisms in common (Botto et al., 2001). So several of the pollutants contributing to the risk of cancer might also contribute to the risk of CVD. In accordance with this is, for instance, the fact that fine airborne particles increase risk of cardiovascular disease by inducing atherosclerosis (Landrigan et al., 2017). Also, fine particulate air pollution is associated with several risk factors for cardiovascular disease, including: hypertension, increased serum lipid concentrations, increasing oxidative stress, increasing insulin resistance, promoting endothelial dysfunction, and enhancing propensity to coagulation (Landrigan et al., 2017). Ionizing radiation is another example of an exogenous factor inducing, at low level exposures, as well cardiovascular diseases as cancer. A systematic review and meta-analysis has been performed to summarize information on circulatory disease risks associated with whole-body ionizing radiation exposures. This review supports an association between circulatory disease mortality and low and moderate doses of ionizing radiation (Little et al., 2012). Studies are ongoing to elucidate the mechanisms implicated in the genesis of these effects, such as epigenetic mechanisms and the role of the mitochondria. (EU, 2018).

Tumor suppressor molecules are activated in the complex environment of atherosclerotic plaque, and regulate growth arrest, cell senescence and the apoptosis of vascular smooth muscle cells, which may protect against the progression of atherosclerosis (Suzuki et al., 2014.).
1.2. Diabetes

Many EDCs produce insulin resistance and alter insulin production and secretion by directly acting on adipocytes, liver, and Beta-cells in the absence of overweight or obesity (Gore et al., 2015). There is substantial evidence, including prospective studies, linking some persistent organic pollutant (POP) exposure to type 2 diabetes in humans, including organochlorine pesticides such as trans-nonachlor, hexachlorobenzene, dichlorodiphenyldichloroethylene (DDE), polychlorinated biphenyls (PCBs), and dioxin-like chemicals. Notably, nonmonotonic relationships and low-dose effects (see 2.4 for a definition) appear in humans (Lee et al., 2014). Also internal exposure to bisphenol A, and exposure to arsenic and phthalates were found to be associated with the risk of type 2 diabetes (Gore et al., 2015).

Experiments in vitro and on animals have produced evidence for diabetogenic activity of several chemicals, including perfluorooctane sulfonate (PFOS) (Gore et al., 2015).

In a systematic review, Dimakakou et al. (2018) found a consistent positive association between ambient air pollution and type 2 diabetes.

More data on the link between pollution and diabetes are mentioned in annex 2.

1.3. Obesity

The origin of obesity is multifactorial and is influenced by both genetic and environmental factors. The “obesogen hypothesis” suggests that prenatal or early-life exposure to certain EDCs predisposes some individuals to gain fat mass and become obese. Bisphenol A, phthalates and persistent organic pollutants have been found to be associated with obesity in some epidemiological studies, but the evidence for this associations is limited (Gore et al., 2015).

In vitro experiments have shown that low concentrations of tributyl tin (TBT), some phthalates, parabens, 4-nonylphenol, the fungicide triflumizole, the pesticide tolylfluaniad, the brominated flame retardant 2,2',4,4'-tetrabromodiphenyl ether (BDE-47) and bisphenol A promote adipogenesis (Gore et al., 2015). Activation of peroxisome proliferator-activated receptor gamma (PPARgamma) and the retinoid X receptor (RXR) are an important mechanism that can lead to adipogenesis (Gore et al., 2015). But adipogenesis can also be stimulated through other mechanisms, involving estrogen receptors, a glucocorticoid receptor or the aryl hydrocarbon receptor (AhR) (Ingaray et al., 2006; Gore et al., 2015).

Animal studies show obesogenic effects of environmental estrogens, tributyltin, some phthalates, the flame retardant tetrabromobisphenol, the anti-stick chemical perfluoroctanoic acid, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), the polychlorobiphenyls 126 and 77, DDT and the organophosphate insecticides chlorpyrifos, diazinon and parathion (Gore et al., 2015).

1.4. Female reproductive dysfunction

Several studies indicate that EDCs can adversely affect the ovary, uterus, vagina, anterior pituitary, and/or steroid production, which can lead to reproductive disorders such as early puberty, infertility, abnormal cyclicity, premature ovarian failure/menopause, endometriosis, fibroids, and adverse pregnancy outcomes (Gore et al., 2015).

Bisphenol A, some phthalates, the pesticide methoxychlor (MXC) and the dioxin TCDD were reported to disturb ovarian development in animals (Gore et al., 2015).
Disturbance of ovarian function in animals was reported (Gore et al., 2015) for postnatal exposure to: bisphenol A, some phthalates, the pesticides MXC, endosulfan, malathion, chlorpyrifos, cypermethrin, imidaclorpid, fenvalerate, trifluralin, bifenthrin, diuron, and 2,4-dichlorophenoxyacetic acid; diethylstilbestrol; the dioxin TCDD, several PCB congeners (Gore et al., 2015). Multiple studies consistently show that a variety of pesticides alter ovarian steroidogenesis in laboratory animals (Gore et al., 2015). Bisphenol A, some phthalates, and the pesticide heptachlor were reported to disturb ovarian steroidogenesis in women (Gore et al., 2015).

Interestingly, the effects of EDCs on the ovary may be transgenerational in nature because studies indicate that both fetal and neonatal exposure to MXC caused epigenetic alterations in ovarian genes in adults (Zama & Uzumcu, 2009; Uzumcu et al., 2012).

Bisphenol A, some phthalates, several pesticides including a mixture of organophosphorus pesticides (dichlorvos, dimethoate, and malathion), endosulfan, fenvalerate, DDT, hexachlorocyclohexane, benomyl, carbendazim, the herbicide pendimethalin, the antibacterial agent triclosan, and the antistick chemical perfluorooctanoic acid (PFOA) all were reported to disturb uterine structure/function (Gore et al., 2015).

Diethylstilboestrol induces adenosis lesions in the cervix and vagina in women, and in utero exposure causes clear cell carcinoma of the vagina (Smith et al., 2012).

Bisphenol A, the phthalate DEHP (bis(2-ethylhexyl) benzene-1,2-dicarboxylate), the pesticide atrazine (ATR) and diethylstilbestrol adversely affected the function of the anterior pituitary gland in animals (Gore et al., 2015). Endocrine disrupting substances were reported to be associated with diverse effects on puberty, but the results of these studies are mixed (Gore et al., 2015).

Bisphenol A was observed as well in women as in animals to adversely affect fertility (Gore et al., 2015) and prenatal BPA exposure may have transgenerational effects on female fertility in mice (Ziv-Gal et al., 2015). Experimental studies show an association between phthalate exposure and reduced fertility in animals, but only limited information exists on phthalate exposure and fertility outcomes in women (Gore et al., 2015). Several studies indicated that pesticide exposures reduce fertility or cause infertility in animal models (Diamanti-Kandarakis et al., 2009; Gore et al., 2015) but the data on pesticide exposure and infertility in humans are equivocal (Gore et al., 2015).

Studies in women, including a prospective cohort study, showed that BPA exposure is associated with premature ovarian failure and early menopause in women (Yang et al., 2009; Souter et al., 2013). In a cross-sectional survey using the US National Health and Nutrition Examination Survey (NHANES), women with high levels of phthalate metabolites or with high levels of the pesticides β-hexachlorocyclohexane (β-HCH) and mirex had an earlier mean age at menopause compared to women with low levels (Grindler et al., 2015). Animal studies are consistent with the effect of the pesticides in the study of Grindler et al. because they indicated that exposure to pesticides may cause premature ovarian failure (Gore et al., 2015). In utero exposure to diethylstilbestrol was associated with an increased lifetime risk of early menopause in women (Gore et al., 2015).

DDE (a DDT metabolite), the dioxin TCDD and PCBs were shown to induce premature reproductive senescence in female animals, and for DDE this was also observed in women (Gore et al., 2015). Urinary levels of propylparaben (a preservative in personal care products) were associated with a trend toward lower antral follicle counts as well as higher day-3 follicle-stimulating hormone (FSH) levels (indicators of ovarian aging) (Smith et al., 2013).

The potential effects of EDCs on premature ovarian failure may be transgenerational in nature because developmental exposure to a pesticide mixture (permethrin and N,N-diethyl-m-toluamide) increased ovarian insufficiency in the F3 generation of rats (Manikkam, 2012a). Similarly, TCDD increased the incidence of ovarian insufficiency in the F3 generation of rats (Manikkam, 2012b).
Earlier studies showed that the dioxin TCDD was associated with an increased risk of endometriosis in nonhuman primates and women. A positive association between dioxin-like PCBs and an increased risk of endometriosis was also observed in women. Recent studies indicated that TCDD exposure disrupted cannabinoid signaling in the human endometrium, leading to increased inflammation in the endometrium and that it inhibited progesterone responsiveness in humans and animal models. Exposing mice to TCDD caused a progesterone-resistant phenotype in adults that persisted over multiple generations, suggesting that TCDD exposure had transgenerational effects on endometriosis (Gore et al., 2015).

1.5. Male reproductive dysfunction

Genetic mutations affecting androgen production or action cause testicular dysgenesis syndrome (TDS), including cryptorchidism, hypospadias, impaired semen quality, and markedly increased risk of testicular cancer (Skakkebaek et al., 2001).

Chemical compounds that disrupt androgen production or action can cause testicular dysgenesis symptoms such as hypospadias, cryptorchidism, and impaired spermatogenesis in experimental animals and cause structural alterations in the testis resembling the abnormalities seen in human testicular cancer (Fisher et al., 2003). Animal models show that antiandrogens can act in a dose-additive or even synergistic manner, which has challenged the current no adverse effect levels because the adverse outcomes have appeared when the animals have been exposed to a combination of chemicals far below their individual no-observed-adverse-effect levels (NOAELs) (Christiansen et al., 2009; 2012). In addition to antiandrogens, estrogens and dioxins cause similar effects, via their cognate estrogen receptors (ERs) and AhRs, respectively (Gore et al., 2015). Perfluorinated chemicals such as PFOS and PFOA have been associated with disruption of male fertility in as well animal experiments (Song et al., 2018) as in observations on humans (Di Nisio et al., 2018; 2019). In the Flemish biomonitoring program however no adverse effects on fertility were observed at the levels of internal exposure to perfluorinated chemicals measured in Flanders.

One meta-analysis suggested an increased risk of hypospadias in sons of parents exposed to pesticides, but in general results concerning the link between pesticides and hypospadias in men are rather inconsistent (Gore et al., 2015). In animal studies, hypospadias is a common outcome in male pups that have been exposed to antiandrogens in utero. Some of the chemicals inhibit testosterone production (e.g., phthalate esters [benzyl butyl phthalate (BBP), dibutyl phthalate (DBP), DEHP, diisononyl phthalate (DINP)]), whereas others block the androgen receptor (AR) (e.g. the pesticide DDE, and fungicides vinclozolin and procymidone). Despite their dissimilar mechanism of action, these chemicals act in a dose-additive manner, with increased likelihood of adverse effects of low intensity exposures to individual chemicals in the mixture (Gore et al., 2015).

1.6. Disorders of neurodevelopment and cognition

Many studies report an association between exposure to air pollution and disturbance of neurodevelopmental processes, neurodegeneration and impairment of cognitive development. A search in Pubmed on the seventh of September 2018 for articles published in the period 2015 - 2018 mentioning “air pollution” and one of the terms “cognition”, “cognitive”, “neurdegen*” or “neurodevelopm*” in the title or abstract resulted in a list of 175 articles.

Basagana et al. (2016) performed a longitudinal observational study on 2,618 schoolchildren (average age 8.5 years). Children completed computerized tests assessing working memory, superior working memory, and inattentiveness during four visits. An interquartile range increase in indoor traffic-related PM2.5 (particulate matter - fine particles with a diameter of 2.5 μm or less) was associated with reductions in cognitive growth equivalent to 22 % (95 % CI: 2 %, 42 %) of the annual change in working memory, 30 % (95 % CI: 6 %, 54 %) of the annual change in superior
working memory, and 11% (95% CI: 0%, 22%) of the annual change in the inattentiveness scale. Traffic was the only source of fine particles associated with a reduction in cognitive development.

In a systematic review, Dimakakou et al. (2018) found a consistent positive association between ambient air pollution and both type 2 diabetes and neurodegeneration risk, such as dementia and a general decline in cognition. Neuroimaging studies found cerebral white matter, cortical gray matter, and basal ganglia might be the targets of traffic-related air pollution (de Prado et al., 2018). Seelen et al. (2017) report, based on a case control study including 917 amyotrophic lateral sclerosis patients and 2,662 controls, that long-term exposure to traffic-related air pollution is associated with increased susceptibility to amyotrophic lateral sclerosis (ALS). Risk of ALS was significantly increased for individuals in the upper exposure quartile of PM2.5 absorbance [odds ratio (OR)=1.67; 95% confidence interval (CI): 1.27, 2.18], NO2 (OR=1.74; 95% CI: 1.32, 2.30), and NOx concentrations (OR=1.38; 95% CI: 1.07, 1.77).

The Lancet commission on pollution and health considered that air pollution is causally associated with decreased cognitive function, attention-deficit or hyperactivity disorder and autism in children and neurodegenerative disease, including dementia, in adults (Landrigan et al., 2017). Pollutants known to be toxic to the developing brain (in addition to lead) include mercury, combustion by-products such as polycyclic aromatic hydrocarbons and fine particulate matter, organophosphate pesticides, brominated flame retardants, phthalates, and polychlorinated biphenyls (Landrigan et al., 2017).

Decreased school performance and scoring on intelligence tests and even mental retardation were observed in individuals exposed in utero to the radioactive fallout of the atomic bombs in Hiroshima and Nagasaki, particularly when exposure occurred between weeks 8 and 15 of pregnancy (Otake et al., 1998; Schull et al., 1999). In the medical field, low doses of ionizing radiation to the brain in infancy have been shown to influence cognitive abilities in adulthood (Hall. et al., 2004). In order to increase the statistical power and to have more dosimetric and biological data allowing to understand the mechanisms of the cognitive and cerebrovascular effects after an exposure to low ionizing radiation doses, the project CEREBRAD was developed and supported by the EU Euratom 7th framework programme (FP7) with a multidisciplinary approach (human epidemiology, animal studies and mechanistic studies). This project unveiled effects at doses previously assumed to be harmless. Persistent effects (DNA (deoxyribonucleic acid) damages, inflammation) were observed in animal studies at low doses (20 and 100 mGy) several months after exposure (corresponding to years in humans) (Benotmane A., in EU 2018). Combined exposures to radiation and other environmental agents decreased significantly the dose at which brain effects are observed (Eriksson et al., 2010). Interestingly, compared to the offspring exposed to maternal alcohol intake or to infectious agents (zika virus (ZIKV)), the neuropsychological development and the transcriptomic modifications of those prenatally exposed to ionising radiation are highly similar, including induction of genes involved in premature neuron differentiation (Benotmane A., in EU 2018).

EDCs also contribute to impairment of intellectual development, increased risk of autistic spectrum disorders and attention deficit hyperactivity disorders (Trasande et al., 2015; Attina et al., 2016). According to Bellanger et al. (2015), polybrominated diphenyl ether and organophosphate exposures contribute to IQ loss in the European population. The mechanism is likely involving interaction with the developmental effects of thyroid hormones in the brain, particularly during prenatal and early postnatal life. The most harmful chemicals appear to be organophosphate pesticides in the EU and polybrominated flame retardants in the U.S.A. Importantly, the cost of EDC effects in the EU has been estimated by Trasande et al. (2015) to be 157 billion euros per year of which the vast majority (84%) is related to neurodevelopmental disorders.

1.7. Immune system related diseases

1.7.1. Endocrine disruption, risk of asthma, allergies and some autoimmune diseases
There are some indications that endocrine disrupting substances can increase the risk of asthma, allergies and some autoimmune diseases. Developmental exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) may increase the risk of autoimmune responses (Rooney et al., 2008). Prenatal exposure to the persistent environmental pollutant and model Ah receptor agonist, TCDD, has been shown to permanently suppress postnatal cell-mediated immunity (Rooney et al., 2008). More recently, skewing of select adult T and B cell responses toward enhanced inflammation has also been described in C57BL/6 mice after prenatal TCDD (Mustafa et al., 2011). Prenatal exposure to polychlorinated biphenyls showed a positive association with asthma, eczema/hay fever, and frequent ear infections (Parker-Lalomio et al., 2017).

1.7.2. Reactive substances directly interfering with immunological reactions

Many drugs but also environmental pollutants may cause adverse reactions in susceptible individuals that are reminiscent of autoimmune syndromes (Pieters, 2000; Pieters et al., 2001; 2003). Reactive chemicals or metabolites may provoke formation or release of immunosensitizing neo-antigens (a.o. hapten-carrier complexes or cryptic epitopes). Indeed, reactive chemicals, such as tetrachlorobenzoquinone, the reactive metabolite of hexachlorobenzene, can alter endogenous macromolecules through covalent or non-covalent binding, resulting in the formation of a novel antigen in which the chemical functions as hapten, leading to autoimmune reactions. Reactive chemicals can also alter the structure of an endogenous macromolecule, such that epitopes, that were previously hidden, become exposed (Ezendam et al., 2003). In addition reactive chemicals but also certain inert chemicals may trigger macrophages and other inflammatory cells to release proinflammatory products that, via elicitation of costimulatory help, support hapten- or neo-antigen-specific T cell activation. In addition, chemicals may influence immunoregulatory processes and modulate for instance the balance between type 1 and type 2 responses (Pieters, 2003).

Examples of pollutants that can induce autoimmune diseases are trichloroethylene (Cooper et al., 2009), hexachlorobenzene (Ezendam et al., 2003) and heavy metals (Chen et al., 2002).

1.8. Cancer

Cancer is a disease due to the clonal proliferation starting in a single cell due to a disturbance of the control of cell division. Cancer is a disease of the social organization of cells in tissues, and cancer cells divide when they should not, and move when they should not. During this clonal proliferation a process called tumor progression occurs and cancer cells acquire the capacity to invade surrounding tissues and to metastasize to other organs. Mutations, and genetic instability leading to further mutations form the basis of carcinogenesis, tumor progression and resistance to therapy (Alberts et al., 1994).

Under age 75 cancer (all cancers together) is the most frequent cause of mortality in the western world, before cardiovascular diseases (Belpomme et al., 2007; Clapp et al., 2006).

1.8.1. A small increase in mutation rate leads to important increase in cancer risk

It is known since the beginning of the 1970’s that cancer rests fundamentally on the accumulation of several mutations in the same cell, most often in a stem cell. The number of mutations necessary to the malignant tumoral transformation varies in function of the type of tumor (Renan, 1993; Alberts et al., 1994), but is generally between 3 (leukemia’s) and 7 (carcinoma’s). The fact that several mutations (in the same cell) are needed is in agreement with the increase of the risk with age (often with the 3rd, 4th or 5th power of age) and is the main line of defense against carcinogenesis, as the probability of accumulating several mutations in the same cell is very low. An important implication of the fact that multiple mutations in the same cell are a necessary condition for the malignant tumoral transformation is that the chance of this transformation occurring increases exponentially with the mutation rate. In a model where this transformation would depend on 6
mutations, a doubling of the mutation rate would lead to an increase of the likelihood of malignant tumoral transformation with a factor 64. So the important message is: a small increase in mutation rate already leads to an important increase in risk of cancer.

1.8.2. Carcinogenesis also rests on changes in gene expression

Not only mutations, but also changes in gene expression can contribute to carcinogenesis. The important impact of tumor promotion and of receptor binding and otherwise endocrine disrupting agents rests mainly on changes in gene expression.

As well genotoxic carcinogens (carcinogens acting primarily through causation of mutations) (Godderis et al., 2012) as non-genotoxic carcinogens (acting primarily through effects on gene expression) (Van Delft et al., 2004) affect expression of genes in human cells, but in different ways (Van Delft et al., 2004).

Prenatal low intensity exposures to bisphenol A, induced changes in the expression of genes that can contribute to carcinogenesis in the mammary gland tubes of mice (Vandenberg, 2008; Wadia et al., 2013; Wang, 2014). Diethylstilbestrol induces the precancerous condition vaginal adenosis by disrupting SMAD/RUNX1-mediated cell fate decision in the Müllerian duct epithelium through a downregulation of the RUNX1 gene (Laronda et al., 2013). Bisphenol A affected the gene expression in human prostate stem cells and stimulated their proliferation (Ho et al., 2015; Calderon-Gierszal & Prins, 2015). This is particularly relevant because lifetime cancer risk is strongly correlated with the total number of divisions of the stem cells (Tomasetti & Vogelstein, 2015).

Molecular epidemiology revealed that real life exposures have effects on gene expression that probably contribute to the risk of cancer (see section 2.4.4.).

1.8.3. Endocrine disrupting agents and cancer

Endocrine disrupting agents are substances that disrupt hormonal and homeostatic systems. They act through nuclear receptors, non-nuclear steroid receptors, non-steroid receptors (for instance receptors for neurotransmitters, "orphan" receptors such as the AhR), and through interference with enzymatic reactions related to the biosynthesis or metabolism of endogenous hormones. The most important endocrine disrupting substances are xenoestrogens, antiestrogens, antiandrogens and substances disrupting thyroid function and metabolism (De Coster & van Larebeke, 2012). Endocrine disruptors can have widely different chemical structures and comprise substances used as industrial liquids, plastic components, pesticides, medical drugs, pollutants arising from combustion processes and heavy metals such as cadmium and lead (De Coster & van Larebeke, 2012). There is substantial evidence indicating the importance of endocrine disruption in the causation of breast cancer, uterine cancer, ovarian cancer, cancer of the vagina, prostate cancer and testicular cancer (Gore et al., 2015).

1.8.4. Risk of cancer increases strongly with duration of exposure

That cancer is a disease affecting mainly older people is evident. The fundamental reason for this is that cancer rests on the accumulation of different mutations in the same cell, and this accumulation increases with time (Alberts et al., 1994). But through an experiment on a very large number of rats (4,080) Peto et al. (1991a, 1991b) could demonstrate that duration of exposure in itself, independent of age, is more important than intensity of exposure. Lung cancer risks depend far more strongly on the duration than on the daily dose-rate of cigarette smoking (Peto, 1986; Flanders et al., 2003). For example, a three-fold increase in the daily dose-rate may produce only about a three-fold increase in effect, while a three-fold increase in duration might produce about a 100-fold increase in effect (Peto, 1986) This implies that chronic exposures to environmental or life style factors have a more important impact on the risk of cancer than short term accidental exposures to the same dose.
2. Some characteristics of the effects of environmental agents

2.1. Epidemiology points to life style and occupational or environmental agents

Epidemiological data indicate that in the vast majority (probably about 80 %) of cases of cancer exogenous factors (life style, environment) play an essential role (Higginson & Muir, 1977; van Larebeke, 1997). Indeed, there are huge differences (generally a factor of 10 or more) in the age standardized incidence of each type of cancer between different geographical area's having good cancer registers. Not only between industrial countries and developing nations, but also between industrial nations. It is highly likely that these important differences cannot be explained by differences in diagnostic capabilities, and for some cancer types the highest incidences are recorded in third world countries.

Studies on migrants indicate that differences between populations inhabiting different geographical area's are not primarily due to genetic factors, as migrants and their descendants adopt, with time, the cancer incidence pattern of the area in which they immigrated (Thomas & Karagas, 1987). Also important changes in cancer incidence in function of time, in the same population, have been described (Devesa et al., 1995; Tominaga, 1995).

Parents of children suffering of cancer do not, themselves, show an increased risk of cancer (Olsen et al.,1995).

The Finish twin study (Verkasalo et al., 1999) and the Swedish family cancer data base (Hemminki & Vahttinen, 1997) both point to a limited impact of inherited genetic factors on the incidence of cancers, also concerning breast cancer. Even for BRCA mutant carriers external factors are important in determining the eventual occurrence of breast cancer. The cumulative incidence at age 50 amounts to 24 % for such women if born before 1940, and to 67 % if born after 1940 (King et al., 2003). In Iceland the cumulative incidence at age 70 in women carrying the BRCA mutation was 18.6 % (95 % CI = 11.0 % to 29.5 %) in 1920 and 71.9 % (95 % CI = 45.9 % to 100 %) in 2002 (Tryggvadottir et al. 2006).

There is substantial epidemiological evidence for the link between air pollution and cancer, mainly lung cancer. The risk of lung cancer is clearly increased by exposure to polluted air (Cislaghi & Nimis, 1997; Raaschou-Nielsen et al., 2010; Katanoda et al., 2011; Allen et al., 2013; Heinrich et al., 2013). Air pollution, assessed in terms of biological activity by the limitation of lichen diversity, was, for men, clearly associated with mortality due to lung cancer (Cislaghi & Nimis, 1997). According to the Global Burden of Disease study in 2015, all forms of pollution combined were, in 2015, responsible for 43 % of deaths due to lung cancer.

Possibly, as one would expect on mechanistic basis, also the risk of other forms of cancer might be increased by exposure to polluted air, including breast cancer (Crouse et al., 2010), bladder cancer (Liu et al., 2009) and kidney cancer (Soll-Johanning et al., 1998).

A recent prospective cohort study found an increase in the risk of breast cancer in women in association with a more frequent use of beauty or skincare products (Taylor et al., 2018).

A recent prospective cohort study on 94,668 French adults found that a higher frequency of organic food consumption was associated with a reduced overall risk of cancer (hazard ratio for quartile 4 vs quartile 1, 0.75; 95 % CI, 0.63 – 0.88, P for trend = 0.001) (Baudry et al., 2018).

The International Agency for Research on Cancer has published lists of risk factors it considers to be proven, probable or possible human carcinogens. These lists are available on the website of the IARC (http://www.cancer-environnement.fr/478-Classification-des-substances-cancerogenes.ce.aspx). Also there are thousands of publications in the international scientific
literature describing associations between risk factors and an increase in the incidence or mortality from cancer. An (incomplete) oversight of chemical or physical agents and complex exposures associated with an increase in the risk of cancer is provided in a report to the Flemish Administration by van Larebeke & De Coster (2008), mainly based on articles by Clapp et al., (2005 and 2007), report that can be obtained from the Secretariat of the Superior Health Council.

2.2. Numerous substances are mutagenic, carcinogenic or endocrine disruptors

For about four decades, the human population has been exposed to an increasingly large array of synthetic chemicals. Only about 1% of those chemicals have been studied so far since scientific research is time-consuming and costly (Trasande et al., 2016), or because testing was simply not requested or not deemed necessary.

Animal tests with 127 substances, selected because they were produced in huge quantities and/or because of the existence of an important human exposure, showed that 26 (20%) of these substances were carcinogenic (Huff, 1993). It is probable that a large percentage of reactive chemical substances are genotoxic carcinogens (see Alberts et al., 1994, p 243; Huff & Hoel, 1992). According to a report by Dhooge et al (1998) two to three percent of the substances with a high production volume might have an oestrogenic activity. 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). Some 82,000 chemicals are registered for commercial use in the USA alone (Duncan, 2006), and in Europe almost more than 140,000 chemicals were preregistered for a later full registration within REACH (Backhaus et al., 2010). The European Union (European Chemicals Agency (ECHA)) has listed 145,297 chemicals as pre-registered before 2008 (last updated 11 August 2017). An estimated 2,000 new chemicals are introduced annually for applications in everyday items such as foods, personal care products, prescription drugs, household cleaners, and lawn care products (Duncan, 2006). In the European Union there are about 100,000 substances on the market and about 2,000 chemical substances are produced or imported in large quantities. The Toxic Substances Control Act Chemical Substances Inventory contained in February 2017 more than 67,000 chemicals (https://www.epa.gov/tsca-inventory/about-tsca-chemical-substance-inventory#howare). In polluted air or in emissions to environmental air more than 2,800 different chemical substances were already identified in 1992 (Lewtas, 1993). The US Environmental Protection Agency considers 10,517 substances for testing related to endocrine disruption. The literature contains data on testing for endocrine disruption of 1,036 substances (http://endocrinedisruption.org/).

As to carcinogens, important insights are:

1° The large majority of carcinogenic substances has not been identified at present.
2° Carcinogenic potency of carcinogenic substances can differ widely. For only a few substances the carcinogenic potency at low, environmentally relevant exposures, is known with a precision better than a factor 10. For most of the identified carcinogens there is still a huge uncertainty concerning the potency exposures of low intensity. The 95% confidence interval of the relative risk associated, in the USA, with consumption of pindas contaminated with aflatoxin or with drinking apple juice containing the agricultural substance ALAR amounted to a factor of 10,000 (Finkel, 1995).
3° Knowledge on the carcinogenic potency of exposure to complex mixtures, as is occurring in real life, is very limited (see 2.3).
4° The existence, for some genotoxic carcinogens, of low dose effects (see sections 2.4 and 2.4.1 and annex 3).

For some important insights as to endocrine disrupting agents, see sections 2.4.3 and 2.5.

2.3. Exposure to a combination of chemicals. Cocktail effects
Another concern is the exposure to combinations of chemicals, which is the dominant way of exposure in everyday life. More than 300 chemicals have been measured in cord blood samples at birth (Woodruff et al., 2011; Rosofsky et al., 2017; Koppen et al., 2009). As analytical techniques improve, it is expected that many more environmental chemicals will be identified in human fluids and tissues. It is not known how these chemicals interact and at what exposure levels these combinations may cause biological effects that pose health risks. To study the effects of combined exposures of chemicals by empirical methods is not possible due to the large number of possible combinations.

That man-made chemicals and pollutants can have synergistic effects through the activation of nuclear receptors has by now been proven. Ligands of the RXR receptor and ligands of the partner receptors (which form active heterodimers with the RXR receptor) can act synergistically to activate heterodimers (Germain et al., 2002). This regulatory control of nuclear signaling pathways by multiple RXR heterodimers allows environmental RXR ligands to potentially trigger a multitude of adverse effects on human health (Balaguer et al., 2017). Delfosse et al. (2015) recently demonstrated that a pharmaceutical estrogen (the contraceptive 17α-ethinylestradiol EE2)) and a persistent organochlorine pesticide (trans-nonachlor (TNC)), both exhibiting low efficacy when studied separately, cooperatively bind to the Pregnane X Receptor (PXR), leading to synergistic activation. Both biophysical and cell-based analyses showed that each ligand enhances the binding affinity of the other one, so the binary mixture binds 100-fold more avidly to PXR than TNC and EE2 alone, and induces a substantial biological response at doses at which each chemical individually is inactive (Balaguer et al., 2017). This study provided the first detailed mechanistic explanation and a proof of concept for the synergistic action of a mixture (cocktail) of compounds via their simultaneous interaction with a nuclear receptor (Balaguer et al., 2017).

A major problem in relation to the effect of combined exposures is the possibility of synergistic interactions between substances with different modes of actions. An example of this, important in carcinogenesis, is tumor promotion, an important topic in the early research on carcinogenesis, abundantly studied through in vivo experiments (Slaga, 1983). Tumor promoters such as the phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA) have a very strong synergistic effect on carcinogenesis when given after an initiating (genotoxic) carcinogen. Exposure to tumor promoters leads to the fact that even a low dose of a carcinogen can induce cancers (Burns et al., 1983; Ehrenberg et al., 1996). Dioxins and some other substances binding on the AhR receptor probably have a tumor promoting activity. Tumor promotion might well be responsible for the human cancer risk in association with exposure to dioxins and dioxin-like substances, as these might act on cells already initiated for carcinogenesis by endogenous or environmental mutagens (McGregor et al. 1998; Schwarz and Appel, 2005; Van Larebeke et al., 2015).

2.4. Effects of real life exposures, low dose effects

According to the Global Burden of Disease study 2015, exposure-response curves of health effects versus air pollution (annual mean PM2.5 concentration) show, for ischaemic heart disease, cerebrovascular disease, lung cancer and chronic obstructive pulmonary disease, a general trend towards relatively higher effects per unit of exposure at low intensity exposures (Cohen et al., 2017). Below an overview is given of the mechanistic basis on which low dose health effects rest.

In 2001 the USA National Toxicology Program (NTP) defined low-dose effects as any biological changes 1) occurring in the range of typical human exposures or 2) occurring at doses lower than those typically used in standard testing protocols, i.e. doses below those tested in traditional toxicology assessments. Other definitions of low dose include 3) a dose below the lowest dose at which a biological change (or damage) for a specific chemical has been measured in the past, i.e. any dose below the lowest observed effect level or lowest observed adverse effect level (LOAEL), or 4) a dose administered to an animal that produces blood concentrations of that chemical in the range of what has been measured in the general human population (i.e. not exposed occupationally, and often referred to as an environmentally relevant dose because it creates an
2.4.1. Low dose effects of genotoxic agents

It is evidently very difficult to collect data on the link between exposures and mutations in human beings. Experiments are ethically unacceptable. The structure, replication and repair of DNA and the interactions of DNA with exogenous agents that can disturb the structure of DNA have, however, been conserved to a high degree throughout the phylogenetic evolution. So, for instance, a given mutagen induces the same primary class of base pair changes in the Ames test strain Salmonella TA100 and in the bacterium E. coli as in mammalian cells in vitro, in rodents in vivo and in the p53 tumor suppressor gene in human cancers associated with exposure to the same mutagen (DeMarini, 2000).

For genotoxic agents there is no critical threshold under which there is no mutagenic effect at all. Generally an approximately linear relation is observed between the dose of a genotoxic substance and the amount of DNA adducts (Phillips et al., 1988; Lutz, 1990). For the induction of double strand breaks by X-rays a strictly linear dose effect relation has been observed between 100 gray (Gy) and 1 mGy (Rothkam & Lobrich, 2003). According to the International Commission for Protection against Environmental Mutagens and Carcinogens (Ehrenberg et al., 1982) and according to Lutz (1990) a linear relation is also generally observed between the dose of a mutagenic chemical and the number of induced mutations (for low doses and for most, but not for all, chemicals, see also Ehrenberg et al., 1996).

In some cases higher doses can have a proportionally larger effect than low doses, especially when the agent in question has, on itself, two different but synergistically acting effects, such as a mutagenic effect and a cell division stimulating effect, or when the dose is very high so that the DNA repair mechanism cannot cope any more (Lutz, 1990).

However, for ionizing radiation very low exposures could be, also in human beings, relatively more mutagenic (per unit of dose) than more intensive exposures (Simonsson et al., 2008; Vandevoorde et al., 2015). This relative increase in mutagenicity at very low doses is however not generally accepted as there are few studies, and a potential bias is explored in a recent publication (Harbron et al., 2017). A relative increase in mutagenicity at very low doses could occur when an exposure occurs in the absence of full expression of the corresponding DNA repair mechanisms. Induction, by environmental carcinogens such as benzo(a)pyrene and by anti-cancer drugs, of the nucleotide excision repair (NER) system, repairing the DNA damage of most environmental and man-made carcinogens, has been observed (Christmann & Kaina, 2013). So it seems likely that low dose hypersensitivity could also occur in relation to exposure to genotoxic chemicals. Also non-targeted effects, effects shown by cells who did not receive a direct hit, including bystander effects (probably mediated through intercellular communication) and induced genetic instability (through the activation of endogenic mutagenic mechanisms) could contribute to larger mutagenic effects per unit of dose at very low doses (Kadhim et al., 2013).

Annex 3 contains additional information on the biological basis of low dose effects of genotoxic agents.

2.4.2. Genotoxic effects of real life exposures

There is a convincing amount of evidence indicating that internal exposures to a series of substances, as occurring in the general population, are associated with mutagenic or genotoxic effects (Bolognesi, 2003; Farmer et al., 2003; Perera & Vineis, 2011; DeMarini, 2013). In the Flemish human biomonitoring on the general population, internal exposure to metabolites of benzene, toluene and phthalates, internal exposure to cadmium, lead, chromium, arsenicum, thallium, dichlorophenol, dioxin-like substances and perfluorooctanoic acid were associated with
genotoxic effects (van Larebeke et al., 2004; Koppen et al., 2007; De Coster et al., 2008; Franken et al., 2017; De Craemer et al., 2016). In the New Generis study on neonates, transplacental exposure to oxidative fat metabolites, dioxins and PCBs was associated with mutagenic effects (Kleijnjans et al., 2015). In the Environage study on 463 Flemish mother-neonate pairs, prenatal exposure to particulate air pollution with median PM2.5 and black carbon levels of respectively 13.61 µg/m³ (far below the European Air Quality standard of 25 µg/m³) and 0.90 µg/m³ was associated with significant increases in the placenta in mutation rate, methylation of DNA repair genes and methylation of the p53 tumor suppressor gene. Alu mutation rate was associated with greater exposure to PM 2.5 (r=0.26, p<0.0001) and black carbon (r=0.33, p<0.0001). (Neven et al., 2018). The Flemish biomonitoring studies suggested that persons with more unfavorable genetic traits concerning genotoxic agents have less chance of surviving until age 50 - 65, probably because they are at a higher risk of morbidity and mortality from chronic diseases (Ketelslegers et al., 2011).

2.4.3. Low dose and non-monotonic effects of endocrine disrupting agents

Even infinitesimally low levels of exposure - indeed, any level of exposure at all - may cause endocrine or reproductive abnormalities, particularly if exposure occurs during a critical developmental window (Sheehan et al., 1999). Balaguer et al. (2017) describe three mechanisms explaining high-affinity interactions (and so possible low dose effects) between EDCs and nuclear receptors. The mycoestrogen α-zearanol, although structurally different from 17β-estradiol, displays a similar interaction with the ligand binding pocket of the estrogen receptor α. In contrast, organotins such as TBT do not recapitulate any of the specific interactions made by the classical ligands, but use a Sn–S covalent interaction to bind to and modulate the transcriptional activity of the Retinoid X Receptor - peroxisome proliferator-activated receptor (RXR-PPAR) heterodimer at nanomolar concentrations. In the third reported mechanism, a pesticide and a pharmaceutical compound were found to interact with each other in the Pregnane X Receptor Ligand binding pocket, forming a ‘supramolecular ligand’ that is a more potent activator than either of the two chemicals alone.

Surprisingly, low doses may even exert more potent effects than higher doses. Second, EDCs may exert non-traditional-dose-response curves, such as inverted-U or U-shaped curves (vom Saal et al., 2007). Both of these concepts have been known for hormone and neurotransmitter actions, but only in the past decade have they begun to be appreciated for EDCs. Non-monotonic responses and low-dose effects are remarkably common in studies of natural hormones and EDCs (Vandenberg et al., 2012; Vandenberg, 2014).

Whether low doses of EDCs influence certain human disorders is no longer conjecture, because epidemiological studies show that environmental exposures to EDCs are associated with human diseases and disabilities (Diamanti-Kandarakis et al., 2009; Gore et al., 2015). When nonmonotonic dose-response curves occur, the effects of low doses cannot be predicted by the effects observed at high doses. Furthermore, endocrine disruption can have opposite effects in function of the developmental stage considered (Parent et al., 2016). Thus, fundamental changes in chemical testing and safety determination are needed to protect human health (Vandenberg et al., 2016).

2.4.4. Effects on gene expression of real life exposures

The Flemish biomonitoring produced a substantial amount of evidence indicating that internal exposures occurring in the general population can be associated with changes in gene expression that could be relevant in terms of risk of cancer. Among a random sample of Flemish adults an association was observed between the expression of a number of genes related to carcinogenesis and internal exposure to pollutants (Van Leeuwen et al., 2008). Internal exposure to pollutants showed an association with tumor-associated protein levels in adults: positive exposure-effect relationships were found for carcinoembryonic antigen (urinary cadmium, t,t' muconic acid, 1-hydroxypyrene, blood lead, serum levels of p,p'-DDE above the p90), prostate specific antigen above p90 (urinary cadmium), values of p53 above the p90 (higher serum levels of p,p'-DDE,
hexachlorobenzene and marker (De Coster et al., 2008). Among Flemish adults De Coster et al. (2013) found significant changes in the expression of a series of genes in association with cadmium, lead, PCBs, dioxin, hexachlorobenzene, p,p'-DDE, benzene, and polycyclic aromatic hydrocarbons. Among Flemish adolescents Croes et al. (2014) observed associations between internal exposure to mercury and a series of genes some of which are linked to the functioning of the nervous system and/or cancer. Among 134 Flemish adults aged 50 - 65, substantial associations, in persons carrying certain genetic polymorphisms, between combined internal exposure to carcinogenic substances (cadmium, lead, polychlorinated biphenyls, p,p'-dichlorodiphenyl dichloroethylene, hexachlorobenzene and 1-OH-pyrene) and changes in expression of genes which are known to have a direct link with carcinogenesis were found (Espin-Perez et al., 2015). In Flemish middle-aged men and women sex-specific associations were observed between particulate matter exposure and the expression of genes, some of which featured in pathways related to carcinogenesis such as cell-cell communication, signaling by Type 1 Insulin-like Growth Factor, Insulin receptor signaling cascade, packaging of telomere ends and telomere maintenance (Vrijens et al., 2017).

In the context of the Norwegian BraMat cohort, internal exposure in utero to as well genotoxic as non-genotoxic carcinogens affected expression of genes relevant for carcinogenesis (Hochstenbach et al., 2012).

Ember et al. (2002) proposed that measuring the expression of oncogenes and of oncosuppressor genes is a proper and early molecular epidemiological biomarker of carcinogen exposure and a tool for risk assessment. Measurement of the expression of such genes could also contribute to the development of a more personalised treatment of cancer (Duffy et al., 2016; Kamel & Al-Almoudi, 2017; Yang & West, 2018).

2.5. Ligand specific effects of exogenous substances binding to nuclear receptors: pollutants might cause adverse health effects which are unrelated to the effects of the endogenous ligands

The superfamily of nuclear receptors (NR) is a group of 48 ligand-activated transcription factors that play important roles in metabolism, homeostasis, reproduction and normal development. They are additionally often linked to pathologies such as neurodegenerative and metabolic diseases, inflammation and cancer (Lee et al., 2008; Skerrett et al., 2014; Schulman et al., 2010; Balaguer et al., 2017; Dhiman et al., 2018; Sala & Ampe, 2018). Recently, there is growing evidence supporting the involvement of multiple nuclear receptors other than the estrogen and progesterone receptors, in the regulation of various processes important to the initiation and progression of breast cancer (Doan et al., 2017). Nuclear receptors have evolved throughout the fylgenetic evolution as proteins specially selected for binding to DNA. By binding a ligand they acquire, after additional association with co-activators or corepressors, the capacity to bind to specific DNA sequences (Alberts et al., 1994). But the binding of the ligand is not the only interaction that determines the genomic action of nuclear receptors, coregulators, which are either coactivators or corepressors, also play a role (Dasgupta et al., 2014). The ligand can also intervene in determining which coregulators are bound to the receptor (Li et al., 2018).

Quite recently it has been shown that the type of the ligand (thus the detailed chemical structure of the ligand) is determining to which DNA sequences the ligand-bound receptor binds. For instance, the participation of alternative xenobiotic responsive elements (XREs) (specific DNA sequences) in the AhR transcriptional response suggests that the binding of a particular ligand might adapt the structure of the AhR to permit binding to a particular XRE sequence (Guyot et al., 2013). The model hypothesizes that the AhR-mediated transcriptional response is modulated by selective ligands of the receptor (Guyot et al., 2013), in accord with the selective AhR modulator (SAhRM) concept that was initially described by Safe and McDougal (2002). Selective modulation of sex hormone receptors has been studied for some time (Cappelletti et al., 2003; Shanle & Xu, 2011).
Ligand specific effects could be exploited for therapeutic aims, for instance in the development of hormone replacement therapy without carcinogenic side effects (breast cancer) (Diamanti-Kandarakis et al., 2003). Carbidopa, a drug used for treating Parkinson's disease, is also a SAhRM and inhibits pancreatic cancer cell and tumor growth (Safe, 2017).

However, ligand specific effects were also described for xenoestrogens (Routledge et al., 2000; Watanabe et al., 2003; Shanle & Xu, 2011). Bisphenol AF and bisphenol S, used as replacements for bisphenol A, have also agonistic activity for estrogen receptors. However, bisphenol A, bisphenol AF and bisphenol S differentially recruit coregulators and so have different biological effects (Li et al., 2018).

So it seems likely that the many chemicals that bind to receptors with transcription factor functions might have effects that differ from the effects of the physiological ligands and hormones. These effects cannot easily be predicted and might lead to adverse health effects.

2.6. Epigenetic and transgenerational effects

Gene expression is not only regulated by transcription factors, but is also influenced, in a longer term, by epigenetic changes including methylation of cytosine residues on DNA, post-translational modification of histones, nucleosome remodeling by “nucleosome remodeling” ATPases (adenosine triphosphatases) and altered microRNA (micro ribonucleic acid) expression. Epigenetic changes can lead to transgenerational effects (Gore et al., 2015).

Much direct experimental evidence now shows that disruption of epigenetic processes by chemicals is a carcinogenic mode of action that leads to altered gene functions playing causal roles in cancer initiation and progression (Parfett & Desaulniers, 2017). Four causal mechanisms participating in pathways to persistent epigenetic gene silencing (of tumor suppressor genes) were considered: covalent histone modification, nucleosome remodeling, non-coding RNA interaction and DNA methylation. Within these four interacting mechanisms, 25 epigenetic toxicity pathway components (SET1, MLL1, KDM5, G9A, SUV39H1, SETDB1, EZH2, JMJD3, CBX7, CBX8, BMI, SUZ12, HP1, MPP8, DNMT1, DNMT3A, DNMT3B, TET1, MeCP2, SETDB2, BAZ2A, UHRF1, CTCF, HOTAIR and ANRIL) were found to have experimental evidence showing that functional perturbations played “driver” roles in human cellular transformation (Parfett & Desaulniers, 2017). A systematic review by Dik et al. (2012) found changes in histone modifications and hence gene expression in association with exposure to xenobiotic stressors, mainly heavy metals. For several environmental exposures including metals (cadmium, arsenic, nickel, chromium, and methylmercury), peroxisome proliferators (trichloroethylene, dichloroacetic acid, and trichloroacetic acid (TCA)), air pollutants (particulate matter, black carbon, and benzene), and endocrine-disrupting/reproductive toxicants (diethylstilbestrol, bisphenol A, persistent organic pollutants, and dioxin), it has been proved that chemicals can alter epigenetic marks, and that the same or similar epigenetic alterations can be found in patients with the disease of concern or in diseased tissues (Baccarelli & Bollati, 2009). Baccarelli et al (2009) found decreased repeated-element methylation after exposure to traffic particles. In a study on 78 gas station attendants, 77 traffic police officers, and 58 unexposed referents in Milan, hypermethylation in tumor suppressor p15 and hypomethylation in Melanoma-associated Antigen 1 MAGE-1 genes were associated with increasing airborne benzene levels (Bollati et al., 2007). In this study altered DNA methylation, reproducing the aberrant epigenetic patterns found in malignant cells, was linked to low-level carcinogen exposure (Bollati et al., 2007).

In a Swedish study children had an increased risk of asthma in the first 6 years of life if their grandmothers smoked during early pregnancy, independent of maternal smoking. Importantly, this exhibited a exposure-response relationship and was associated with a persistent childhood asthma phenotype. These findings support possible epigenetic transmission of risk from environmental exposures in previous generations (Lodge et al., 2018).
Ionizing radiation-induced transgenerational effects have been demonstrated in animals, but there is currently in the available literature no consistent picture of the potential impact of transgenerational instability in humans. Current data suggest that the phenomenon of transgenerational instability is most probably attributed to high-dose paternal acute exposure (Little et al., 2013).

The impact of epigenetics will be part of a SHC advisory report on omics technologies (in preparation).

2.7. Exposures in early life are of critical importance (according to Bourguignon et al., 2018)

Mutagens, EDCs, carcinogens and teratogens may cause lifelong harm depending on life period and level of exposure among other factors (UNEP/WHO, 2013). Past findings and derived concepts indicate that several adult diseases represent late onset consequences of early exposures (Herbst et al., 1971; Skakkebaek et al., 2001; Kleinjans et al., 2015; Martens et al., 2016). A pioneering dramatic illustration was the occurrence of vaginal cancer and reproductive disorders in the offspring of mothers treated with diethylstilbestrol during pregnancy (Herbst et al., 1971; Hoover et al., 2011). Here, transgenerational and other studies point toward involvement of epigenetic mechanisms (Ho et al., 2017). Another pioneering observation was the possible fetal origin of testicular cancer (Nielsen et al., 1974; Skakkebaek et al., 1987). This provided the basis of the Testicular Dysgenesis Syndrome linking delay in differentiation of fetal testes with lifelong consequences including reduced sperm quality and testicular cancer (Skakkebaek et al., 2001). Early exposures to EDCs can have huge impact on development and on the risk of diseases such as adult reproductive failure, cancer, obesity, diabetes and metabolic syndrome, and neurodevelopmental disorders among others (Gore et al., 2015). Fetal exposure to dietary carcinogens seems to induce molecular events that indicate increased cancer risks together with other adverse health effects such as reduced birth weight and head circumference (Kleinjans et al., 2015). Childhood cancer, in particular leukemia among boys, can be causally related to the maternal dietary intake of carcinogenic substances during pregnancy (Kleinjans et al., 2015). Fetal exposure to mutagens such as polycyclic aromatic hydrocarbons also increases the risk of cancer and neurodevelopmental disorders (Perera et al., 2011). Telomeres, markers of biological ageing are highly variable at birth and it has been identified recently that maternal exposures to air pollution is associated with telomere length of the next generation (Martens et al., 2017). Taken together, those data demonstrate some causal mechanisms linking early life exposures and later health.

Besides these examples of early disorganization of health for the rest of life, fetal life is also a critical period due to occurrence of unique processes such as brain development. As an example, disruption of thyroid hormone promotion of brain development during fetal and early postnatal life has detrimental consequences on lifelong intellectual abilities (Bellanger et al., 2015).

Overall, a robust set of data concurs to support prioritization of pregnancy and early postnatal life for a healthy environment (Sutton et al., 2012; Grandjean et al., 2015). All those findings are consistent with the concept of Developmental Origin of Health and Disease (DOHaD) (Gluckman et al., 2007). This concept was promoted by the observation that impaired fetal growth, a reflection of intra-uterine exposure to adverse conditions in the maternal environment, can be predictive of adult metabolic malfunctioning (Barker et al., 1986; 1993).
IV. CONCLUSIONS AND RECOMMENDATIONS

1. Physical-chemical environmental hygiene on the collective (regulation) and the individual level: a necessary condition for an effective prevention of diseases of civilization

Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. Health can also be seen as the ability to adapt and to self manage. As to risk, risk is inherently connected to societal developments. That chronic non-communicable diseases are an important cause of human suffering is certain.

As argued in "Elaboration and Argumentation", mechanistic insights and also data from molecular epidemiology and epidemiological studies indicate that carcinogenic, mutagenic or endocrine disrupting agents contribute importantly to the risk of diseases of civilization. Taking into account some common characteristics of their effects a particular form of hygiene, here called "physical chemical environmental hygiene", is proposed. Indeed, prevention should be knowledge-based, and not merely evidence-based. This proposition should be viewed as a signal to authorities and society that protection against mutagens and endocrine disrupting chemicals should be put on the agenda, and that development of appropriate policies is desirable.

Physical chemical environmental hygiene refers to a global change in collective (regulation) and individual (consumer and citizen) behavior that should result in a limitation of the exposure to health damaging, in particular carcinogenic, mutagenic, receptor binding, or endocrine disrupting agents.

At the end of the 19th and in the beginning of the 20th century the introduction of the anti-microbial hygiene has permitted, together with improved nutrition, to decrease the incidence and the impact of infectious diseases to a large extent, long before the identification of the most important pathogenic microorganisms and long before the introduction of the antibiotics and vaccination (Centers for Disease Control and Prevention, 1999). Because we are exposed to a very large number of carcinogenic, mutagenic, receptor binding, or endocrine disrupting agents, each in low or even very low doses, because our capacity to make a detailed assessment of their potency is very limited, and because our capacity to set priorities is largely insufficient, the introduction of a physical chemical environmental hygiene is a necessary condition for an effective prevention of diseases of civilization. This new aspect of hygiene consists of limiting, to the extent that this is reasonably possible, exposure to substances and physical agents that have mutagenic or endocrine disrupting properties or that can bind to hormone receptors or to nuclear receptors functioning as transcription factors. The introduction of physical chemical environmental hygiene is, together with an increase in the consumption of fruit and vegetables (WHO technical staff, 2014), avoiding overnutrition and having sufficient physical activity as proposed by the American Cancer Society (Kushi et al., 2012), a necessary measure if we want to obtain a clear decrease in the incidence and prevalence of cancer and other diseases of civilisation. This physical chemical environmental hygiene applies as well with regard to regulation and public health as with regard to personal individual behaviour. For instance, on the individual level it implies closing the intake of outside air in a car in a tunnel, wearing a mask during certain do it yourself activities, avoiding passive smoking.

1.1. On the collective, regulatory, level

On the collective, regulatory, level, physical chemical environmental hygiene implies the recognition of the fact that agents known to have, at least in certain circumstances or systems, mutagenic or endocrine disrupting properties or that can bind to hormone receptors or to nuclear receptors functioning as transcription factors, have a rather high probability of having adverse health effects on humans. These agents might have health effects, also at very low, environmental exposures. Proving the existence of such effects might be painstakingly difficult and could take a very long time. As to receptor binding, the chemicals of most concern are those that bind to receptors, such as nuclear receptors and the AhR, that function as a transcription factor, because
of their essential role and of the existence of ligand-specific effects as discussed under point 2.5 of the “Elaboration and argumentation” chapter.

On the collective, regulatory, level, physical chemical environmental hygiene rests on limiting, to the extent that this is reasonably possible, exposure to substances and physical agents that are mutagenic or genotoxic in simple (in vitro or in vivo) tests, that are endocrine disruptors in in vitro or in animal tests, that are carcinogenic in in vitro tests or that bind, in in vitro tests that can be performed on many substances, to a receptor that functions as a transcription factor. As mentionned by Parfett & Desaulniers (2017) in vitro assays will probably assume a leading role in testing for chemical hazards in the 21st century. A more intensive exposure to such an agent is only acceptable if thorough investigation (in vivo) indicates that the agent is not hazardous. So, in terms of physical chemical environmental hygiene, the burden of proof changes side in the case of agents that show hazardous properties in simple tests and intensive exposure to such an agent is only deemed acceptable if it can be shown that it is extremely unlikely to be hazardous. Risks associated with carcinogenic, mutagenic and endocrine disrupting agents are often undesirable effects of societal developments. Management of these risks thus implies management of, in these cases, societal and especially technological developments. So implementation of physical chemical environmental hygiene can lead, but should not be equated to, the prohibition of a product or technology. In cases where the product or technology brings no significant benefit or when less hazardous alternatives exist prohibition can be desirable. In other instances the implementation of physical chemical environmental hygiene could lead to the imposition of a modified version of the ALARA approach. Modified in the sense that the exposures should not only be as low as possible, but also as late in life as possible, as short as possible and as few as possible, given the importance of exposures early in life and of low dose effects. If the product or technology in question is important or is associated with substantial benefits, physical chemical hygiene should lead to the starting up of a strategy based on the precautionary principle, leading, in a carefull, reasonable and transparent fashion, to a decision in which risks and benefits are balanced. Due attention should also be paid to the toxicity of adjuvants (coformulants) in commercial mixtures (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5786549/). It is essential, as proposed by Passchier (2013), that policy making involves listening to concerned citizens, field experts, stakeholders, civil society organizations, but with the awareness that each of them is possibly blind to certain aspects of the problem. When implementing physical chemical environmental hygiene proper attention should be paid to the phenomenon of risk migration. Indeed, sometimes preventive measures can, directly or indirectly, lead to the use of replacing methods or technologies that present substantial risks.

1.2. The range of measures available to the individual and collective levels (Good Consumer Practices)

In practical terms, the individual is only rarely in a position to limit his/her exposure to single chemicals. Exposure is almost always to complex mixtures. But the individual can engage in a limitation of his/her exposure to a series of products and conditions that are likely to be associated with an increase in risk of adverse health effects. This approach might be considered to be part of "Good Consumer Practices". What is sought here is a more global approach of potentially hazardous factors. The idea is to try to limit exposure to a factor that is likely to be hazardous, even if there is no definite proof of a hazardous property. In table 1 measures are proposed that can diminish exposure to one or to a series of agents for which there is evidence that they contribute to the risk of diseases of civilization. For some agents, such as ionizing radiation or certain solvents, hazardous properties are known with certainty, but for other agents there might still be some uncertainty and the Superior Health Council does not formally speak out about the hazardous properties of the agents mentioned in table1. For illustrative purposes a non-exhaustive list of references is included below and in table 1.

This approach is discussed in greater detail in the document "Rationale for environmental hygiene towards global protection of fetuses and young children from adverse lifestyle factors", associated
with this advice (annex 4) and which is published in the scientific journal "Environmental Health" (Bourguignon et al., 2018).

It is evident that certain risk factors are really avoidable at the level of the individual (e.g. the use of cosmetics or the use of certain food items) and that certain risk factors are more important or established with more certainty than others. It should be noted that children have often less control of their exposures than adults. Exposure to other risk factors can only partially be avoided at the level of the individual and requires regulation by public authorities (e.g. air pollution, pesticides in food items). Many risk factors concern everyone, while some risk factors are especially of concern to a subset of the population (e.g. pregnant women, young children).

An individual wishing to protect him/herself and, mainly for the women, his/her descendants, should consider a range of measures (table 1) relating to:

**Smoking and passive smoking**
Smoking tobacco and passive smoking are a well established and important risk factor for many diseases (Jones et al., 2013; Onor et al., 2017; Macacu et al., 2015; Masaoka et al., 2016; Shaper et al., 2003). Maternal smoking and maternal passive smoking were shown to be associated with an increased risk of central nervous system tumors and disordered child neurodevelopment (Fillipini et al., 2000; Julvez et al., 2007; Irner, 2012; Polanska et al., 2015; Evlampidou et al., 2015). There is consistent evidence for a moderate increase in the risk of breast cancer in women who smoke tobacco. The evidence for a moderate increase in risk with passive smoking is more substantial than a few years ago (Macacu et al., 2015). In a meta-analysis passive smoking was associated with an increased risk of colorectal cancer (Yang et al., 2016).

**Consumption of alcohol**
Alcohol is a well established and important risk factor for some cancers and maternal alcohol consumption was associated with disturbances of child and adolescent neurodevelopment (Irner, 2012; Polanska et al., 2015).

**Nutrition, food, drinks, plastic recipients and metal cans**

*Well established important risk factors:*
Consumption of charred meat and darkened bread was associated with an increased risk of cancer (Fu et al., 2011; Kleinjans et al., 2015). Consumption of processed meat, especially nitrite-treated, was also reported to be associated with some types of cancer (Bouvard et al., 2015). Consumption of organic food is linked with a reduced overall risk of cancer (Baudry et al., 2018).

*Other risk factors:*
There is some evidence that prenatal exposure to bisphenols and phthalates is followed by increased risk of behavioral and respiratory disorders in childhood (Philippat et al., 2017; Vernet et al., 2017) as well as possible adverse outcomes in adulthood involving male reproductive and cardio-metabolic disorders (Bonde et al., 2016; Philips et al., 2017). The presence of agricultural chemicals and arsenic in drinking water is linked with increased occurrence of birth defects (Brender and Weyer, 2016). Prenatal exposure to persistent organic pollutants is known to be associated with adverse neurodevelopmental effects (Kyriklaki et al., 2016). Consumption of organic food during pregnancy is linked with a reduced risk of maternal obesity and diabetes (Simões-Wüst et al., 2017) and may decrease the prevalence of hypospadias in the offspring (Brantsæter et al., 2016).

**Air pollution, transport**
Air pollution is a well established and important risk factor for several diseases. Long-term exposure to air pollution PM2.5 was associated with non-accidental cardiovascular mortality, lung cancer and chronic obstructive pulmonary disease in a recent Chinese study, with risks being higher than estimated from previous cohort studies in western Europe and North
America (Yin et al., 2017). Mice exposed to traffic in a highway tunnel showed, in the brain, an increased expression of genes involved in inflammatory response (Bos et al., 2012). Although exercising is important to health, it is preferable to do so in less polluted air (Giles & Koehle, 2014). Interestingly, the number of particles downwind of traffic decreases exponentially with the distance and is substantially lower at a distance of 200 meter, and was, at 300 meter, indistinguishable from upwind background concentration (Zhu et al., 2002, 2006). Urban cycling, such as commuting to work by bicycle in London is associated with increased long-term inhaled dose of black carbon (Nwokoro et al., 2012).

**Exposure to ionizing radiation**

Ionizing radiation is a well established and important carcinogen and also induces cardiovascular diseases. Diagnostic X-ray examinations increase the risk of cancer (Mulvihill et al., 2017; Bhatti et al., 2010; Vandevoorde et al., 2015). Prenatal exposure to diagnostic X-rays is associated with increased prevalence of childhood cancer (Doll and Wakeford, 1997; Wakeford and Little, 2003; Wakeford, 2008). Risk associated with medical exposure to ionizing radiation can be limited by restricting use to situations where a real indication exists, and is principally of concern to certain target groups. Apart from medical exposures, there are also exposures to ionizing radiation coming from many other sources, including natural or man-made environmental sources (post-accidental situations, building materials, radon in dwellings, etc.). The Council refers also to the joint advice with the Health Council of the Netherlands on childhood leukemia (SHC, 2012).

**Exposure to the sun and artificial sources of ultraviolet light**

Exposure to ultraviolet light is a well established and important risk factor for non-melanoma and melanoma skin cancers (Mancebo & Wang, 2014). However, it must be kept in mind that a reasonable exposure to sunlight has also positive effects on health.

**Housing and maintenance**

Home care also deserves some recommendations.

*Well established important risk factors:*

Some organic solvents are known to cause cancer and maternal exposure to solvents is associated with childhood leukaemia and lymphoma (Lynge et al., 1997; McKinney et al., 2008). A registry based case control study in Scandinavian countries (n cases/controls: 8,112/26,264) showed a small but significant increase in testicular germ cell tumors of sons when the mother was exposed to toluene one year prior to birth (Le Cornet et al., 2017).

*Other risk factors:*

During pregnancy, parents often redecorate their homes. Especially changing floor materials, has been shown to increase exposure to hazardous chemicals and increases the risk for respiratory diseases in early childhood especially in families with a history of atopic diseases (Franck et al., 2014). Air fresheners emit hazardous components such as benzene, phthalates and limonene and may form secondary pollutants due to reaction with ozone. Health risks include damage to the central nervous system and alteration of hormone levels (Kim et al., 2015). The EU EPHECT project (Emissions, Exposure Patterns and Health Effects of Consumer Products in the EU) showed irritating and respiratory effects associated with consumer products used indoors. Combinations of purpose/kitchen/floor cleaning agents, furniture/floor polish, combustible/electric air fresheners, and perfume contributed considerably to formaldehyde emissions (Trantallidi et al., 2015). House dust carries chemicals such as phthalates, flame retardants, synthetic fragrances (Mitro et al., 2016) and also lead, cadmium, pesticides, polycyclic aromatic hydrocarbons (PAHs), bacteria, allergens. Babies are much more exposed than adults and are much more sensitive to the health effects of dust making it important to reduce indoor dust by efficient cleaning practices (Roberts et al., 2009). Ventilation has been shown to be important for reduction of the indoor concentrations of semi-volatile organic compounds such as formaldehyde (Liu et al., 2015). A prospective study in
Sweden reported low ventilation rates in the home as one of the significant risk factors for autism spectrum disorders among others (Larsson et al., 2009).

**Personal care, cosmetics, tattoos**
Chemicals such as triclosan (preservative), polycyclic musks (fragrances), diethyl phthalate (vehicle), benzophenone-3 (UV screen) or dibutyl phthalate (plasticiser in nail polish) are added to cosmetics. Also nanoparticles are frequently added for protection against UV light. Their metabolites can be measured in urine samples of all members of the general population including children and the levels are associated with the reported use of personal care products (Den Hond et al., 2013; Frederiksen et al., 2013). These compounds are considered endocrine disruptors and most pass also the placenta. Synthetic fragrances are ubiquitous components of personal care and household cleaning products, they contain constituents such as phthalates, paraben, glutaraldehyde, hydroperoxides, oil of turpentine, metals, nitro musks, and essential oils, among others (Patel, 2017). These compounds have endocrine properties and are easily taken up by dermal contact as well as inhalation of contaminated dust and volatilized fragrances. Tattooing might contribute to the risk of cancer as modern tattoos cause high skin concentrations of hazardous azo pigments, some being carcinogenic (Engel et al., 2008; Chung et al., 2016). Some cosmetics contain nanoparticles, which can be toxic in function of their surface reactivity inducing oxidative stress (Hattori et al., 2017) or of their form, resembling asbestos (Sinis et al., 2018).

**Textiles, artificial dyes**
In a recent study of the Swedish Chemical Agency, 2,400 substances of health concern were linked to textiles (Swedish Chemical Agency, 2016). More than 200 substances, as for example acid-type dyes, may contribute substantially to allergic skin reactions. Of major concern are azo dyes that are associated with increased risk of cancer and developmental effects. Reproductive toxicity has mainly been associated with flame retardants, phthalates, highly fluorinated water and stain repellants, and biocide treated textiles. Laundering will release some of the chemicals depending on how they are bound to textiles (Avagyan et al., 2015; Limpiteeprakan et al., 2016). Some textiles contain nanoparticles, which can be toxic in function of their surface reactivity inducing oxidative stress (Hattori et al., 2017) or of their form, resembling asbestos (Sinis et al., 2018).

**Exposure to herbicides and insecticides**
Exposure to insecticide spraying during pregnancy was found to be associated with a decrement in psychomotor development in Spain i.e. a country where prevention of malaria is not needed (Llop et al., 2015). Herbicides were observed to be associated with an increase in Non-Hodgkin lymphoma, and glyphosate, the most used herbicide, was classified by the International Agency for Research on Cancer as probably carcinogenic to humans (IARC, 2015; Myers et al., 2016).

**Plastic or rubber toys**
Anti-androgenic activity was observed to leach out from the surface of toys and baby products in contact with liquids with a composition corresponding to that of human bodily fluids (artificial sweat and saliva) (Szczepanska et al., 2016).

**Exposure to non-ionising radiation linked to power lines, communication and electronics**
Close exposure to power lines was found to be associated with childhood leukemia (Tabrizi et al., 2015; Schuz, 2011). Microwave non-ionising radiation was shown to act through voltage-gated calcium channel activation to induce biological impacts at non-thermal levels (Anghileri et al., 2006; Pall et al., 2015). Maternal exposure to mobile phone frequency electromagnetic fields was associated with behavioral and speech problems in children (Birks et al., 2017; Zarei et al., 2015). Use of mobile phone and cordless phones was observed to be associated with increased risk for glioma and acoustic neuroma (Hardell et al., 2013). According to Levis et al. (2011) blind protocols, free from errors, bias, and financial
conditioning factors, give positive results that reveal a cause-effect relationship between long-term mobile phone use or latency and statistically significant increase of ipsilateral head tumor risk, with biological plausibility. The meta-analyses (included that of Levis et al., 2011), examining only data on ipsilateral tumors in subjects using mobile phones since or for at least 10 years, show large and statistically significant increases in risk of ipsilateral brain gliomas and acoustic neuromas (Levis et al., 2011).

Table 1. Some recommendations aiming at reduced exposure to health hazards.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Targeted hazards</th>
<th>References*</th>
<th>EDCs</th>
<th>Mutagen</th>
<th>Others</th>
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<tbody>
<tr>
<td><strong>Everywhere</strong></td>
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<tr>
<td>Concerning well established and important risk factors:</td>
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<td>Stop smoking tobacco and drinking alcohol</td>
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<td>x</td>
<td>x</td>
<td>Julvez et al., 2007; Irner, 2012; Polanska et al., 2015</td>
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<tr>
<td>Limit as much as possible passive smoking</td>
<td>x</td>
<td>x</td>
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<td>Filippini et al., 2000; Evlampilidou et al., 2015</td>
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<tr>
<td>Concerning other risk factors:</td>
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<tr>
<td>Avoid frequent close presence to power lines; limit the use of cell phones</td>
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<td></td>
<td>x</td>
<td>Tabrizi et al., 2015; Schuz, 2011; Birks et al., 2017; Zarei et al., 2015; Carlberg &amp; Hardell, 2017; Bortkiewicz et al., 2017</td>
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<td>applied against the head or cordless mobile phones</td>
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<td>For small children:</td>
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<td></td>
<td>x</td>
<td>Szczepańska et al, 2016; Hashemipour et al., 2018; Andaluri et al., 2018; Liao et al., 2018</td>
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<tr>
<td>Limit the use of plastic or rubber toys and prefer products declared to be free</td>
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<td>of bisphenol A or phthalates</td>
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<td>For pregnant women:</td>
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<td></td>
<td>x</td>
<td>Zhang et al, 2017</td>
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<tr>
<td>Stay in a cool place in case of heat &gt; 30°C</td>
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<tr>
<td><strong>Personal care</strong></td>
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<tr>
<td>Avoid tattoos</td>
<td></td>
<td></td>
<td>x</td>
<td>Engel et al., 2008; Chung, 2016</td>
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<tr>
<td>Restrict the use of hair dyes and nail polish</td>
<td>x</td>
<td></td>
<td></td>
<td>Marie et al., 2016; Towle et al., 2017; Stiel et al., 2016</td>
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<tr>
<td>Restrict the use of cosmetics and lotions as much as possible</td>
<td>x</td>
<td></td>
<td></td>
<td>Den Hond et al, 2013; Frederiksen et al., 2013; Penninklampi and Eslick, 2018; Chow &amp; Mahalingaiah, 2016; Darbre, 2016; Grande &amp; Tucci, 2016; Nicolopoulou-Stamati et al., 2016; Cerna et al., 2015</td>
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<tr>
<td>Prioritize unscented products and restrict the use of perfumes</td>
<td>x</td>
<td></td>
<td></td>
<td>Patel, 2017</td>
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<tr>
<td><strong>Food and drinks</strong></td>
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<tr>
<td>Concerning well established and important risk factors:</td>
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<td></td>
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<tr>
<td>Avoid charred meat and consumption of bread or other cereal products that are</td>
<td>x</td>
<td></td>
<td></td>
<td>Fu et al., 2011; Kleijnaans et al., 2015; Ngoan et al., 2009; Figg, 2012</td>
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<td>darkened due to high temperature treatment</td>
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<tr>
<td>Avoid processed, especially nitrite treated, meat</td>
<td>x</td>
<td></td>
<td></td>
<td>Bouvard et al., 2015; Rohrmann &amp; Linseisen, 2016</td>
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</tbody>
</table>
### Concerning other risk factors:

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Authors 2016</th>
<th>Authors 2017</th>
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</thead>
<tbody>
<tr>
<td>Prioritize food and drinks from glass containers instead of plastic bottles or metal cans</td>
<td>Bonde et al.</td>
<td>Philips et al.</td>
</tr>
<tr>
<td>Do not microwave food in plastic recipients</td>
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<tr>
<td>Avoid use of non-stick pans; cast-iron and ceramic are probably preferrable</td>
<td>Kontou et al.</td>
<td>Schlummer et al.</td>
</tr>
<tr>
<td>Limit to once a week the consumption of predator fishes (such as tuna, swordfish)</td>
<td></td>
<td>Mergler et al.</td>
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<tr>
<td>Use quality-controlled water in glass bottles</td>
<td>Brender and Weyer, Komulainen, Wigle.</td>
<td></td>
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<tr>
<td>Prioritize organic food whenever possible</td>
<td>Kyriklaki et al.</td>
<td>Brantsæter et al.</td>
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</tbody>
</table>

### Home care

#### Concerning well established and important risk factors:

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Authors 1997</th>
<th>Authors 2008</th>
<th>Authors 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid or limit exposure to organic solvents</td>
<td></td>
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<tr>
<td>Avoid or limit the use of insecticides</td>
<td>Llo et al.</td>
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<tr>
<td>Avoid scented cleaning products, air fresheners and fragrances</td>
<td>Kim et al.</td>
<td></td>
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<tr>
<td>When pregnant, avoid as much as possible painting or coating (walls, doors, floors, etc.)</td>
<td>Franck et al.</td>
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<tr>
<td>Wash new clothes before wearing them</td>
<td>Avagyan et al.</td>
<td></td>
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<tr>
<td>Clean inside the house using damp clothes and reduce dust</td>
<td>Roberts et al.</td>
<td>Mitro et al.</td>
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<tr>
<td>Ventilate the bedrooms and living rooms at home for 10 min, 1-2 times a day</td>
<td>Larsson et al., Liu et al.</td>
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</table>

#### Concerning other risk factors:

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Authors 2012</th>
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<tbody>
<tr>
<td>Avoid or limit the use of herbicides or pesticides</td>
<td></td>
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<tr>
<td>Avoid exposure to medical x-rays unless really necessary</td>
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</table>

### Outdoor

#### Concerning well established and important risk factors:

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Authors 2002</th>
<th>Authors 2006</th>
<th>Authors 2012</th>
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</thead>
<tbody>
<tr>
<td>Close the car windows and recycle air while driving on highways, in tunnels and in heavy traffic</td>
<td>Zhu et al.</td>
<td></td>
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<tr>
<td>Prefer exercising in green areas and avoid heavily polluted air such as within 200 meters of heavy traffic</td>
<td></td>
<td>Giles &amp; Koehle, Yin et al., Zhu et al.</td>
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</table>

#### Concerning other risk factors:

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Authors 2015</th>
<th>Authors 2016</th>
<th>Authors 2017</th>
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</thead>
<tbody>
<tr>
<td>Avoid or limit the use of herbicides or pesticides</td>
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</table>

### Medical

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Authors 1997</th>
<th>Authors 2003</th>
<th>Authors 2008</th>
<th>Authors 2017</th>
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<tbody>
<tr>
<td>Avoid exposure to medical x-rays unless really necessary</td>
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2. Physical chemical environmental hygiene towards global protection from adverse lifestyle factors starting from preconception over the embryo to young children
In view of the critical importance of exposures early in life for both an optimal development and good health later in life, implementation of physical chemical environmental hygiene is of special importance in the case of young women and pregnant women. Real life exposures, also those occurring early in life, do not occur to single agents but instead involve complex mixtures of many chemicals and other hazards, with possible interactions between them explaining adverse effects. Therefore a more holistic approach involving avoidance or reduction of exposure to many different agents is desirable along the precautionary principle. Published studies on effects of individual chemicals justify physical chemical environmental hygiene, and the harmful interactions among hazardous agents probably add to its relevance and benefits as a global strategy. In such studies "physical chemical environmental hygiene" would be implemented on the level of the individual, involving young women intending to become pregnant and pregnant women as a priority. A list of implementable recommendations should be endorsed by an international panel of experts and would be applied by study participants as a package during pregnancy and lactation. Biomonitoring studies in the women and the children and follow up studies of health and developmental outcomes in children would then allow, at different points in time, to evaluate whether the holistic package of preventive measures indeed resulted in positive effects.

This strategy is explained and justified in greater detail in "Rationale for Environmental Hygiene towards global protection of fetuses and young children from adverse lifestyle factors", a scientific publication written in the context of this advice, published in Environmental Health (Bourguignon et al., 2018), and presented in annex 4.

3. Science and technology can contribute to physical chemical environmental hygiene

Although, as described above, the incidence and/or prevalence of diseases of civilization has increased over the last hundred years, recent evolutions and the possibilities offered by science and technology point away from doom! Recent regulations concerning emissions to the environment have led to improvements in the quality of outdoor air and surface water. According to the Flanders Environment Agency (VMM), the air quality in Flanders improved markedly between 2004 and 2015 (https://www.milieurapport.be/milieuthemas/luchtkwaliteit/fijn-stof/jaargemiddelde-pm2-5-concentratie/jaargemiddelde-pm2-5-concentratie-per-typegebied) and the quality of surface water, as assessed in terms of fish, improved slightly (https://www.milieurapport.be/milieuthemas/waterkwaliteit/ecologisch-toestand/vissen). Probably in relation to changes in the use of pesticides, the number of birds of prey has increased markedly in our regions, e.g. according to "waarnemingen.be", over the last 25 years, the number of buzzards has increased, in the Netherlands, from 2.000 pairs to 10.000 pairs (https://waarnemingen.be/soort/info/82). The Flemish biomonitoring program showed that concentrations of well-regulated chemicals especially traditional POPs such as polychlorinated biphenyls (PCBs), dichlorodiphenyldichloroethylene (p,p'-DDE), the major metabolite of dichlorodiphenyltrichloroethane (DDT), and hexachlorobenzene (HCB) and cadmium and lead are decreasing in the population of Flanders. Response to regulatory measures seems to happen rapid, since concentrations in humans of specific regulated perfluorinated compounds and phthalates were significantly reduced in five years of time (Schoeters et al., 2017). In terms of the increase in risk of disease, the increase in the risk of cancer stopped in the USA about 20 years ago, and in Flanders the increase in the risk of cancer stopped, for men, a few years ago.

New technological developments, e.g. the widespread implementation of hydrogen technology, may help to solve the air pollution problem to an important extent. Interestingly, Belgium accommodates, in industrial terms as well as in scientific terms, world leaders in hydrogen technology.

Further development of the omics technologies (genomics, epigenomics, transcriptomics, proteomics, metabolomics, glycomics, lipidomics, microbiomics, exposomics) in combination with fast improvements in bioinformatics and data management using supercomputers and the systematic deployment of these technologies in real green chemistry and medicine can lead to
great progress. Green chemistry could lead to the production of safer chemical substances, avoiding, thanks to the omics technologies, the introduction into the market of substances with hidden toxic properties. The use of the omics technologies in medicine could lead to a personalized treatment adapted to the individual patient, possibly even leading to an effective treatment for most cases of cancer.

4. Physical chemical environmental hygiene and measures proposed to curb the impact of early life exposures confronted to the considerations formulated in the document “Voorzorg met Rede” issued by the “Gezondheidsraad” of the Netherlands (GR, 2008)

Physical chemical environmental hygiene is similar to the classical anti-microbial hygiene in that both these concepts are intended to protect humans from exposure to a class of agents among which quite many have hazardous properties that are however not necessarily well characterized. Physical chemical environmental hygiene is also relevant in terms of technologies and technological developments. Physical chemical enviromental hygiene is a concept that is related to, but clearly different, from the ALARA concept, the precautionary principle and the concept of prevention. The ALARA concept is relevant in relation to issues in which the existence of benefits renders prohibition undesirable. Prevention applies to issues where hazards (to humans, to the environment, to society) are considered proven and not only assumed to be existent on the basis of mechanistical and experimental data. The precautionary principle is a very broad concept that can be applied to serious, plausible threats, where uncertainty exists concerning the nature, the extent and the probability of damage. The European Environmental Agency describes the precautionary principle as follows: “The precautionary principle provides justification for public policy actions in situations of scientific complexity, uncertainty and ignorance, where there may be a need to act in order to avoid, or reduce, potentially serious or irreversible threats to health or the environment, using an appropriate level of scientific evidence, and taking into account the likely pros and cons of action and inaction” (Gee, 2008). However there are no sharp boundaries between these concepts and in fact there is a continuüm. So the physical chemical enviromental hygiene will probably often lead to application of a modified version of the ALARA approach and to the implementation of the precautionary principle as a strategy for dealing with uncertainty in an alert, careful, reasonable and transparent fashion, which takes account of the particular situation, as proposed in “Voorzorg met Rede” (GR, 2008).

Critics of the precautionary principle argue that the precautionary principle is vague and unscientific, promotes arbitrary decision-making and inhibits technological development and progress. The Dutch "Gezondheidsraad" believes that, if the precautionary principle is applied as a strategy as described in “Voorzorg met Rede” (GR, 2008), the criticisms that have been levelled at it cease to be valid.

The physical chemical enviromental hygiene is a more limited and more precise concept than the precautionary principle. The physical chemical enviromental hygiene is a concept that rests on a clear scientific, largely mechanistic, basis for which there is overwhelming evidence and it applies only to certain types of agents. Plausibility cannot be an issue concerning physical chemical enviromental hygiene and the concept is rather irreconcilable with arbitrary decision-making. Importantly, the implementation of physical chemical enviromental hygiene is likely to stimulate innovation, in particular in the field of “green chemistry”, like restrictive regulatory policies concerning climate change have already stimulated innovation (Rubin, 2011). The American Chemical Association declared in a Public Policy Statement 2009 - 2012 (https://www.acs.org/content/dam/acsorg/policy/publicpolicies/sustainability/endocrinedisruptors/endorcrine-disruption.pdf) to be favourable to the development of “green chemistry”.

In Belgium the implementation of the precautionary principle was first introduced in the legislation in a decree of the Flemish region of 5 April 1995, which stated that: “Environmental policy shall seek to achieve a high level of protection … it shall be based on, inter alia: - the precautionary principle” (De Sadeleer, 2000). Also, rulings underpinned by a precautionary stance are not
exceptional in litigation, under Belgian law use of the precautionary principle is implicit in two judgments of the Belgian constitutional “Cour d’arbitrage” (De Sadeleer, 2000). Also, certain judgments of the Belgian Conseil d’Etat similarly draw inspiration from the precautionary principle. For instance, the Conseil d’Etat determined that a polluting industry could be closed down even if it had not been proven that it endangered the environment, since the mere existence of risk was sufficient basis for action (De Sadeleer, 2000).

Implementation of the physical chemical enviromental hygiene should or can lead to the prohibition of a product or technology in cases where the product or technology brings no significant benefit or when less hazardous alternatives exist. In other instances the implementation of physical chemical enviromental hygiene could lead to the imposition of a modified version of the ALARA approach. If the product or technology in question is important or is associated with substantial benefits, physical chemical enviromental hygiene can be considered as the first step, the ”specification” step, in a full-blown strategy (as proposed by the Dutch Health Council in the document "Voorzorg met Rede" (GR, 2008)) for implementation of the precautionary principle. This strategy then leads, through an approach referred to as risk governance, to a well-defined policy that is transparent, in which risks and benefits are balanced, that takes into account that foregoing benefits in order to avoid a particular risk can itself introduce other risks (risk migration) and allows for monitoring of the effects of measures and their reassessment and adjustment. It is essential, as proposed by Passchier (2013), that policy making involves listening to concerned citizens, field experts, stakeholders, civil society organizations, but with the awareness that each of them is possibly blind to certain aspects of the problem.

The measures, here designated as physical chemical environmental hygiene, proposed to curb the impact of early life exposures, have to be viewed essentially as an answer to the huge complexity and uncertainties surrounding the impact of exposures during early life. These complexity and uncertainties stem from the exposure to very many agents with unknown interactions. The proposed approach particularly takes into account the fact that overwhelming evidence indicates that the impact of early life exposures is very important, and that much more is to be gained than to be lost from measures protecting early life. In that "environmental hygiene" is related to the application of the precautionary principle to an issue in which the potential risks far outweigh the benefits associated with not taking any restrictive measures. Also, "environmental hygiene" can be viewed as relating to an issue characterized by serious uncertainty in which more weight should be attached to the potential negative consequences of human behavior than to its potential (or in this case perceived) positive consequences.
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VI. APPENDICES

Annex 1 - Additional data on the time-trends of diseases of civilization (Landrigan et al., 2017)

In Great Britain, all cancers combined incidence rates have increased overall in all broad age groups in males and females combined between 1993 and 2015. Incidence rates have increased more in young people than in older people: rates in 0-24s have increased by 24 %, in 25-49s by 20 %, in 50-59s by 13 %, in 60-69s by 15 %, in 70-79s by 11 %, and in 80+s by 9 % (https://www.cancerresearchuk.org/health-professional/cancer statistics/incidence/age?_ga=2.262144332.1566422954.1536335611-508569465.1536335611#heading-Three, accessed 7/9/2018). In the USA, cancer incidence has risen by 85.9 % (yearly increase 1.5 %) between 1950 and 2001. Life time risk of cancer in the USA is about 1/2 for men and 1/3 for women. Encouraging is that, in the USA, the incidence of cancer has decreased slightly after 1992 in men and has remained stable in women since 1998 (https://seer.cancer.gov/csr/1975_2014/results_merged/sect_02_all_sites.pdf accessed 14/01/2018). In the United Kingdom, total cancer incidence rates are projected to decrease by 0.03 % in males and increase by 0.11 % in females yearly between 2015 and 2035 (Smittenaar et al., 2016). Generally, however, a world-wide increase in the incidence of cancer has been observed in the recent past (Sasco, 2008). Under age 75 cancer (all cancers together) is the most frequent cause of mortality in the western world, before cardiovascular diseases (Belpomme et al., 2007; Clapp et al., 2006). This increase cannot be explained totally, nor by differences in effectiveness of correct diagnosis, nor by improvement of registration. It has to be emphasized that not all types of cancer increase in incidence. The incidence of some cancers such as stomach and cervix cancer decreases, while this of breast, prostate, testis, colon, lung, thyroid and brain cancer and also this of non-Hodgkin lymphoma increases, (Sasco, 2008). Importantly, the time trends in different countries can be quite different (see data from the International Association of Cancer Registers, http://ci5.iarc.fr/CI5plus/Pages/graph4_sel.aspx). In fact, the registered incidence of some rather difficult to diagnose cancers decreases in many places, where one would rather expect that they would increase due to improved diagnostic methods. Furthermore the incidence of cancer rises more steeply in young people than in older people (see above) and also the incidence of cancer in children has increased (Steliarova-Foucher et al., 2004; Kaatsch et al., 2006; Dreifaldt et al., 2004), whereas the diagnosis of cancer in children is less difficult than in older people. That the observed increase in the incidence of cancer is due to the finding, through early screening, of small tumors who would never have developed into invasive cancer, has been contradicted by the experience with prostate screening. Prostate cancers detected through screening showed the same Gleason scores as non-screened cases, indicating that screened and non-screened cases of prostate cancer probably have a similar histoprognosis (Crawford, 2003).
Annex 2 - Data from the Global Burden of Disease study on the health impact of air pollution, lead, toxic occupational risk factors and endocrine disruptors and on pollution related diseases in children (according to Landrigan et al., 2017)

Specific causal associations have been established between PM2.5 pollution and myocardial infarction (Wang et al., 2015; Su et al., 2016; Weichenthal et al., 2016; Milojevic et al., 2014; Brook et al., 2004; Mustafic et al., 2012; Gardner et al., 2014), hypertension (Chan et al., 2015), congestive heart failure, arrhythmias (Link et al., 2010) and cardiovascular mortality (Krewski et al., 2009; Gold & Samet, 2013; Newby et al., 2015; Beelen et al., 2014; Kaufman et al., 2016). Causal associations have also been established between PM2.5 pollution and chronic obstructive pulmonary disease and lung cancer (GBD, 2015). The International Agency for Research on Cancer has reported that airborne particulate matter and ambient air pollution are proven group 1 human carcinogens (Loomis et al., 2013; Burnett et al., 2014; Hamra et al., 2014). Fine particulate air pollution is associated with several risk factors or items related to cardiovascular disease, including: hypertension (Chan et al., 2015), increased serum lipid concentrations (Franklin et al., 2015), accelerated progression of atherosclerosis (Kaufman et al., 2012; Benziger et al., 2016; Claeyts et al., 2017), increased prevalence of cardiac arrhythmias (Link et al., 2010), increased numbers of visits to emergency departments for cardiac conditions (Su et al., 2016; Weichenthal et al., 2016), increased risk of acute myocardial infarction (Wang et al., 2015), and increased mortality from cardiovascular disease (Beelen et al., 2014) and stroke (Stafoggia et al., 2014). Clinical and experimental studies suggest that fine airborne particles increase risk of cardiovascular disease by inducing atherosclerosis, increasing oxidative stress, increasing insulin resistance, promoting endothelial dysfunction, and enhancing propensity to coagulation.

Emerging evidence suggests that additional causal associations may exist between PM2.5 pollution and several highly prevalent non-communicable diseases. These include diabetes (Meo et al., 2015), decreased cognitive function, attention-deficit or hyperactivity disorder and autism in children (Heusinkveld et al., 2016; Casanova et al., 2016; Block et al., 2012; Volk et al., 2013) and neurodegenerative disease, including dementia, in adults (Chen et al., 2017; Cacciottolo et al., 2017; Kioumourtzoglou et al., 2016). PM2.5 pollution may also be linked to increased occurrence of premature birth and low birthweight (Malley et al., 2017; Amegah et al., 2014; Smith et al., 2014; Van Vliet et al., 2013; Gao et al., 2014; Ha et al., 2014; Shah et al., 2011; Glinianaia et al., 2004).

Cardiovascular diseases, including hypertension, coronary artery disease, stroke, cardiac arrhythmias, and peripheral arterial disease, account for the overwhelming majority of deaths attributable to lead in adults (Cosselman et al., 2015; Schober et al., 2006). These associations are evident at blood lead concentrations as low as 5 μg/dL (Schober et al., 2006; Aoki et al., 2016). The GBD study (GBD, 2015) estimates that lead exposure accounts for 2.5% of the global burden of ischaemic heart disease. Lead is also estimated to account for 12.4% of the global burden of idiopathic intellectual disability. The GBD analysis indicates that deaths in 2015 that were attributable to lead are as follows: cardiovascular disease (465,000 deaths), ischaemic heart disease (240,000), cerebrovascular disease (155,000), ischaemic stroke (68,000), haemorrhagic stroke (87,000), hypertensive heart disease (47,000), and chronic kidney disease (28,000). WHO estimates that, in 2012, lead was responsible for 13.9 million disability-adjusted life years (DALYs) and that childhood lead exposure is responsible for mild to moderate mental retardation of 0.6 million children annually (Fewtrell et al., 2004). Based on data from the Blacksmith Institute/Pure Earth Toxic Sites Identification programme, we estimate that about 61 million people in the 49 countries surveyed to date are exposed to heavy metals and toxic chemicals at contaminated sites (Landrigan et al., 2017).

The GBD study (GBD, 2015) estimates that, in 2015, toxic occupational risk factors (not including occupational injuries or ergonomic factors) were responsible for 0.88 million deaths globally and for 18.6 million DALYs. Carcinogens were responsible for 0.49 million (55%) of the deaths from occupational exposures to toxicants and for 9.8 million DALYs. Asbestos was responsible for nearly 40% (0.18 million) of all deaths caused by occupational carcinogens.
Examples of pollution related diseases in children that have been identified through prospective studies are: cognitive impairment, with decreased IQ in children exposed prenatally to PCBs (Jacobson & Jacobson, 1996); reduced IQ and shortening of attention span in children exposed prenatally to methyl mercury (Grandjean & Landrigan, 2014); microcephaly at birth, anatomical and functional delays in brain development, and autistic behaviours in children exposed prenatally to the organophosphate pesticide chlorpyrifos (Rauh et al., 2012; Bouchard et al., 2011), autistic behaviours in children exposed prenatally to phthalates (Engel et al., 2010); cognitive impairment, shortened attention span, and disruptive behaviour in children exposed prenatally to brominated flame retardants (Herbstman et al., 2010), and neurodevelopmental delays in children exposed prenatally to polycyclic aromatic hydrocarbons (Perera et al., 2014; Jedrychowski et al., 2015).

Endocrine disruptors are chemical pollutants that mimic, block, or alter the actions of normal hormones (WHO, 2017; Bergman et al., 2013; Roen et al., 2015; Gore et al., 2015). They include phthalates, bisphenol A, perchlorate, several pesticides, such as the orthophosphates, brominated flame retardants, and dioxins. Many endocrine disruptors are also developmental neurotoxicants. The organophosphate insecticides are a large and widely used class of pesticides. Members of this class of chemicals are powerful developmental neurotoxicants, and prenatal exposures are associated with persistent deleterious effects on children’s cognitive and behavioural function and with long-term, potentially irreversible, changes to brain structure that are evident on magnetic resonance imaging (MRI) (Rauh et al., 2012).
Annex 3 - Additional information on the biological basis of low dose effects of genotoxic agents

Repair of damage to DNA is of crucial importance to living organisms. More than 130 different DNA repair proteins have been identified (Christman & Kaina, 2013), and many of them are inducible (Ames et al., 1993). It is, in terms of competition and evolution, in the interest of living organisms to produce only proteins and enzymes which are useful in the given circumstances (Alberts et al., 1994). Moreover, DNA repair mechanisms comprise nucleases, which by themselves represent a danger to the genome. Therefore, DNA repair has to be tightly regulated in unexposed cells and, in case of genotoxic insults, has to be appropriately activated. The regulation of DNA repair is a very complex system and proteins are phosphorylated on more than 900 sites encompassing over 700 proteins in response to damage to DNA (Matsuoka et al., 2007).

Some forms of endogenous DNA damage are permanently present in large quantities in mammalian or human cells (up to dozens of adducts per million nucleotides) (De Bont & van Larebeke, 2004). In comparison, one Gy of low linear energy transfer (LET) ionising radiation produces less than 1 base damage per ten million nucleotides (UNSCEAR 2000 Report to the General Assembly, Volume II: Effects (UNSCEAR, 2000)) and smoking increases the amount of 3,5 benzo(a)pyrenediolopoxide adducts in human cervical epithelial cells from 1.9 per 100 million cells to 3.5 per 100 million cells, which is then associated with an increase in the incidence of cervical cancer (Melikian et al., 1999). Probably the repair mechanisms relevant for endogenous DNA damage are permanently active. So for instance the repair of 7,8-dihydro-8-oxoguanine (8-oxoG), an endogenously highly prevalent DNA adduct, by the “Base Excision Repair” system cannot be induced by oxidative or alkylation damage (Bercht et al., 2007).

The repair of damage which occurs only rarely under physiological conditions, such as double strand DNA breaks (DSB) (of the order of 0.05 per cell in human fibroblasts in vitro), is however only effective after induction by exposure of sufficient intensity causing that type of damage (Rothkamm & Lobrich, 2003). The very low number of DSB induced by 1,2mGy of X-rays is barely repaired and no induction of repair activity can be detected after irradiation with 1,2mGy. X-rays induce between 35 and 29 DSB per cell, and Gamma-H2AX foci due to phosphorylated H2AX histones are already detectable after 3 minutes, and the repair is largely completed after 24 hours. Repair is however never 100 % complete, and even after 14 days almost 0.1 DSB per cell remain, corresponding to the amount of DSB induced by 1,2mGy. So it seems that more than 0.1 DSB per cell must be present to induce the relevant repair mechanism.

Xue et al. (2009) observed that for "high LET" ionising radiation HPRT mutations are more frequent per dose unit in the absence of activation of ATM, activation which leads to the formation of Gamma-H2AX foci starting the repair of DSB. Probably doses of the order of 200 mGy are necessary for activation of ATM (Marples & Collis, 2008).

DNA adducts from environmental carcinogens such as polycyclic aromatic hydrocarbons are also subject of inducible repair (Christman & Kaina, 2013). Induction, in human cells, of ddb2, xpc, xpf and xpg repair genes gives rise to an increase in Nucleotide Excision Repair (NER) activity and an adaptive response, that is a decrease in lethal and mutagenic effects. Transcriptional activation of the NER system is of high biological relevance, as most environmental and man-made carcinogens induce DNA damage that is repaired by NER (Christman & Kaina, 2013), so it seems likely that low dose hypersensitivity could also occur in relation to exposure to genotoxic chemicals. In human cells the "global genomic repair" system is induced after activation of the p53 tumor suppressor (Hanawalt, 2002), and activated p53 also decreases the relative importance of error prone "Non Homologous End Joining" repair (Sasaki et al., 2002). Activation of the p53 tumorsuppressor will however only occur after exposure to an exogenous agent at a certain intensity, and will not occur after exposure at very low intensity. How much benzo(a)pyrene- like adducts are needed for activation of p53 is not known with precision, estimates vary from 10 to 250 per 100 million nucleotides, but these numbers are much higher than the number of adducts detected in lymphocytes of non-smoking policemen in the city of Prague (Topinka et al., 2007).
But also non-targeted effects, effects shown by cells who did not receive a direct hit, including bystander effects and induced genetic instability, could contribute to larger effects per unit of dose at very low doses (Kadhim et al., 2013).

Bystander effects on cells in vitro were demonstrated by Nagasawa and Little (1992) and are probably mediated through intercellular communication (Zhou et al., 2000). According to Vandevenoorde et al. (2015) bystander effects could explain the low dose hypermutagenicity observed, in terms of γ-H2AX foci for pediatric patients exposed to diagnostic X-rays. (Vandevenoorde et al., 2015). This relative increase in mutagenicity at very low doses is however not generally accepted as there are few studies, and a potential bias is explored in a recent publication (Harbron et al., 2017). However, the existence of a relative increase in mutagenicity at very low doses is consistent with the frequently observed linear relationship between induction of cancer and dose of ionizing radiation, as an exponential increase in induced cases of cancer is expected with rising mutation frequency due to the fact that generally several mutations are required in the same cell for induction of cancer (Alberts et al., 1994).

Some exposures can induce a state of genetical instability in which mutations occur with high frequency without any relation with the intensity of the exposure and continue to occur many cell divisions after the exposure has come to an end. Rather than through a genetic mutation, instability might arise through the activation of endogenic mutagenic mechanisms, through epigenetically induced expression of a mutator gene.

Epigenetic mechanisms might also explain the persistently elevated mutation rates in the non-exposed progeny of irradiated cells, reviewed by Morgan (2003) and the transgenerational genomic instability reviewed by Dubrova (2003).
Annex 4 - Rationale for Environmental Hygiene towards global protection of fetuses and young children from adverse lifestyle factors (Bourguignon et al., 2018)

Rationale for Environmental Hygiene towards global protection of fetuses and young children from adverse lifestyle factors

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Abstract

Background: The regulatory management of chemicals and toxicants in the EU addresses hundreds of different chemicals and health hazards individually, one by one. An issue is that, so far, the possible interactions among chemicals or hazards are not considered as such. Another issue is the anticipated delay of several decades before effective protection of public health by regulatory decisions due to a time-consuming process. Prenatal and early postnatal life is highly vulnerable to environmental health hazards with lifelong consequences, and a priority period for reduction of exposure. There are some initiatives regarding recommendations for pregnant women aiming at protection against one or another category of health hazard, however not validated by intervention studies.

Hypothesis: Here, we aim at strengthening the management of exposure to individual health hazards during pregnancy and lactation, with protective measures in a global strategy of Environmental Hygiene. We hypothesize that such a strategy could reduce both the individual effects of harmful agents in complex mixtures and the possible interactions among them. A panel of experts should develop and endorse implementable measures towards a protective behavior.

Their application is meant to be preferably as a package of measures in order to maximize protection and minimize interactions in causing adverse effects. Testing our hypothesis requires biomonitoring studies and longitudinal evaluation of health endpoints in the offspring. Favorable effects would legitimate further action towards equal opportunity access to improved environmental health.

Conclusion: Environmental Hygiene is proposed as a global strategy aiming at effective protection of pregnant women, unborn children and infants against lifelong consequences of exposure to combinations of adverse lifestyle factors.

Keywords: Pregnancy, Mutagens, Endocrine disrupting chemicals, Carcinogens, Precautionary principle, Public health, Developmental origin of health and disease

Background

Prenatal/neonatal exposures and lifelong consequences

For about four decades, the human population has been exposed to an increasingly large array of synthetic chemicals. Only about 1% of these chemicals have been studied so far since scientific research is time-consuming and costly [1]. They include mutagens, Endocrine Disrupting Chemicals (EDCs), carcinogens and teratogens that may cause lifelong harm depending on life period and level of exposure among other factors [2]. Past findings and derived concepts indicate that several adult diseases represent late onset consequences of early exposures [3–6]. A pioneering dramatic illustration was the occurrence of vaginal cancer and reproductive disorders in the offspring of mothers treated with diethylstilbestrol during pregnancy [3, 7]. Here, transgenerational and other studies point toward involvement of epigenetic mechanisms [8]. Another pioneering observation

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was the possible fetal origin of testicular cancer [9, 10]. This provided the basis of the Testicular Dysgenesis Syndrome linking delay in differentiation of fetal testes with lifelong consequences including reduced sperm quality and testicular cancer [4]. Early exposures to EDCs can have huge impact on development and on the risk of diseases such as adult reproductive failure, cancer, obesity, diabetes and metabolic syndrome, and neurodevelopmental disorders among others [11]. Fetal exposure to dietary carcinogens seems to induce molecular events that indicate increased cancer risks together with other adverse health effects such as reduced birth weight and head circumference [5]. Childhood cancer, in particular leukemia among boys, can be causally related to the maternal dietary intake of carcinogenic substances during pregnancy [5]. Fetal exposure to mutagens such as polycyclic aromatic hydrocarbons also increases the risk of cancer and neurodevelopmental disorders [12]. Telomeres, markers of biological ageing are highly variable at birth and it has been identified recently that maternal exposures to air pollution is associated with telomere length of the next generation [13]. Taken together, those data demonstrate some causal mechanisms linking early life exposures and later health. Besides these examples of early dysfunction of health for the rest of life, fetal life is also a critical period due to occurrence of unique processes such as brain development. As an example, disruption of thyroid hormone promotion of brain development during fetal and early postnatal life has detrimental consequences on lifelong intellectual abilities [14]. Overall, a robust set of data concurs to support prioritization of pregnancy and early postnatal life for a healthy environment [15, 16]. All those findings are consistent with the concept of Developmental Origin of Health and Disease (DOHaD) [17]. This concept was promoted by the observation that impaired fetal growth, a reflection of intra-uterine exposure to adverse conditions in the maternal environment, can be predictive of adult metabolic malfunctioning [18, 19]. However, behind the different observations discussed here along the DOHaD concept, different mechanisms can possibly be involved and deserve studies in each specific condition.

Regulatory management of hazardous chemicals in the European Union

The development of a regulatory framework for the management of chemical substances in the European Union (EU) has been rightly viewed as a progress, hopefully contributing to reduced exposures including in early life. For example, REACH in 2006 [20] and the more recent regulations for plant protection products in 2009 [21] and biocidal products in 2012 [22] have provided the tools for chemicals risk management. While the health risk is a function of exposure, the first step in a strategy of limiting exposure is the identification of the hazard. The REACH regulation, which applies since 2008, allows action under its authorization regime: a hazardous substance can be included in the candidate list, i.e. identified as of very high concern (SVHC) and subsequently included in the so-called "authorization" list, i.e. banned as of a sunset date [23]. The data on these two regulatory actions [24, 25] indicate that there is on average a 7-year time span between the moment a substance has been identified as a SVHC and the moment it is being phased out. This time span however appears to increase with time (Fig. 1) as indicated by the slopes of the regression lines which are significantly different (Fig test, p < 0.0001). The time span is longer (Fig test, p < 0.001) for substances identified as SVHCs in the period 2011–2013 (7.67 ± 1.61 yrs, mean ± SD) than 2008–2010 (6.46 ± 0.69 yrs). Between October 2008 and June 2015, 52 substances have been regulated as SVHC accounting for 10 chemicals regulated each year. The regulatory decision about those 52 chemicals refers most frequently to carcinogenicity (n = 28) and toxicity for reproduction (n = 14), not excluding associated endocrine disrupting properties such as observed with phthalates [11]. Also shown in Fig. 1, there are 42 substances that have been identified as SVHCs between December 2013 and July 2017 [25] but no decision to phase them out has been taken so far [24]. Time since registration was not considered in this analysis since the data of registration was biased by differences in both the criteria for registration and time since marketing the substance.

The EU laws for identification and regulation of chemicals have set a new scene for long debates between stakeholders including industry, public authorities, non-governmental organizations (NGOs) and scientists, among others. A recent illustration is provided by the scientific criteria for identification of EDCs [26, 27]. While the current paradigm of management of individual hazardous factors is a requirement and must be pursued, it is a very slow process. So far, 1469 chemicals (last updated September 2017) have been listed as potential EDCs based on data published in the peer-reviewed literature [28]. Since this estimate does not include carcinogens and mutagens, we hypothesize a likely underestimated figure of 1–5% hazardous chemicals among the 145297 chemicals listed by ECHA as pre-registered before 2008 (last updated 11 August 2017). Based on the observed regulation of 10 chemicals per year under REACH and assuming a similar figure for the chemicals not falling under REACH, several generations would likely be needed before the possible carcinogens, mutagens, reprotoxic and EDCs are effectively regulated.

Presentation of the hypothesis

During the first half of the twentieth century, the implementation of a global anti-microbial hygiene led to an important decrease in the morbidity and mortality of infectious diseases, before the identification of most
pathogenic microbial agents and the advent of antibiotics [29]. An analogous strategy, Environmental Hygiene, a physical-chemical hygiene aiming at limitation of exposure to hazardous agents, in particular mutagenic agents and EDCs, is proposed here to reduce the burden of those factors present in environment. We hypothesise that, during prenatal and early postnatal life as a priority period for intervention, a global protective approach (Environmental Hygiene) could effectively reduce some complex exposures. Consequently, adverse health effects resulting from action of individual agents as well as interactions among them could also be reduced. It is hoped that such a global strategy will save time and protect health while awaiting that a healthy environment becomes a reality through the regulatory measures. The suggested approach is consistent with the precautionary principle and should involve regulatory authorities and industry in information of the public and the professionals towards equal opportunity access to improved environmental health.

In Fig. 2, the sequence of events is schematically illustrated and compared in the current regulatory approach of individual health hazards (Fig. 2, panel a) and in the proposed strategy of Environmental Hygiene (Fig. 2, panel b). As shown in panel a (Fig. 2), regulation identifies different categories of health hazards e.g. mutagens, EDCs, carcinogens and teratogens. In each category, compounds or toxicants (D, E, F, ...) are considered individually through their effects on a given system (X, Y, Z, ...) e.g. reproductive, thyroid/neurodevelopmental, metabolic/obesogenic, as recommended by OECD [30]. A compound or toxicant can affect different systems through involvement of different endpoints in each system. The critical demonstration of causality is provided by the study of one effect caused by one toxicant on one endpoint in one system, individually. When sufficient evidence has accumulated, risk assessment and management of each particular compound or toxicant are performed. Along the strategy of Environmental Hygiene (Fig. 2, panel b), the hazardous factors, the adverse effects, the intervention and the causality are addressed globally. Considering exposure to health hazards as a global condition is consistent with the exposure to environmentally relevant mixture of chemicals and the resulting interaction between chemicals and categories of hazards e.g. chemicals and psychosocial stress. Evaluation of the adverse effects as a whole can integrate immediate and delayed effects in different systems together. Here, the demonstration of causality is not a prerequisite to a preventive intervention as a whole. The concept is development of Environmental Hygiene for global reduction of exposure to hazards. It is suggested that an international panel of experts should develop and endorse relevant and implementable protective measures. Their application is intended to be preferably as a package of measures in order to maximize protection from exposures and to minimize interactions among hazards in causing adverse effects. The demonstration of causality is meant to be a global and retroactive process. Intervention studies are warranted with biomonitoring.
Fig. 2 Two complementary paradigms for the management of factors hazardous to human health are illustrated. The current paradigm (panel a) and the proposed additional paradigm (panel b) are schematically illustrated. Along the current strategy, the dashed arrows indicate that, based on a single hazardous factor (b), different systems and adverse effects are considered (X, Y, Z, ...), each desiring demonstration of causality before risk is assessed and the hazardous factor managed. The approach of the issue as a whole is meant to reduce interactions among hazardous factors, save time before hazard reduction and contribute to equal opportunity access to environmental health.

and longitudinal evaluation of health endpoints in the offspring. Based on the evidence obtained, the issue of equal opportunity access to improved environmental health will have to be addressed by authorities to make health protection available to all pregnant women and unborn children through action such as training of health professionals and consumer information.

Implications of the hypothesis

Number of hazardous compounds and factors

The rating number of compounds to be evaluated in each category of hazardous factors vastly outpace scientific studies about those compounds [1]. Despite efforts towards development of high throughput tests for mutagenicity and interaction of individual chemicals with different endocrine axes (e.g., reproduction, thyroid, energy balance), data about many chemicals are completely missing. Also, an approach "chemical by chemical" is not consistent with the environmentally relevant exposure to low-dose mixtures that account for complex effects [31, 32]. Incorporation of those findings in the decision-making process is challenging since the management of chemicals is meant to be one by one. An emerging issue is also that different factors with different modes of action can synergize and interact in causing adverse effects [32]. An example is tumor promotion, abundantly studied through in vivo experiments [33] and possibly responsible for the human cancer risk after multiple exposure involving dioxins and dioxin-like substances [34–36]. The concern of exposure to combination of chemicals raises several issues. At the very beginning of life, synthetic chemicals from different classes can be quantified already in cord blood and in samples from pregnant women or of reproductive age [37–39]. Overall, the fetus can be exposed to more than 300 chemicals. As analytical techniques improve, it is expected that many more environmental chemicals will be identified in human fluids and tissues. It is not known how these chemicals interact and at what exposure levels these combinations may pose health risks. Risk assessment of combined exposures is on the agenda of the European Commission who asked the European Food Safety Authority (EFSA) to develop a strategy for assessing health risks related to combined exposures [40]. One strategy is to group chemicals that belong to the same chemical class such as PCB congeners or dioxins. Chemicals can be grouped because they act on the same target and form a cumulative assessment group as proposed for pesticides by EFSA [41]. Alternatively exposures may be concurrent when chemicals are present in the same products. A more holistic approach is that specific lifestyle, behaviors and environmental settings may also lead to high exposures to a number of pollutants and high risks in vulnerable groups such as the
unborn, children or socio economic deprived subpopula-
tions. Possible combinations of adverse lifestyle factors
involve non-chemical hazards. For instance, exposure to
a stressful event during pregnancy can have cumulative
effects with chemicals [42, 43]. Thus, studies addressing
each factor one by one will often underestimate both
hazard and risk, signalling the requirement of more stud-
eys evaluating the effects of different factors together.

The proposed global strategy addresses different com-
ounds or factors as a whole. This approach is likely to
involve various hazardous chemicals or factors identified
in the environment (air, drinking water) and in consumer
products (e.g. food, drinks, home care and personal care).
Work environment should also be taken into account.
Identification of hazardous factors in relation with prod-
ucts and environmental conditions aims at building simple
recommendations that probably reduce exposure. This ap-
proach will address the issue of low-dose mixtures and
combination of different health hazards since application
of several protective measures as a package will likely
reduce the mechanistic interaction among the agents or
hazards. Chemical hygiene may be efficient to reduce mul-
tiple exposures in vulnerable groups.

Evaluation of adverse effects
The classical evaluation of adverse effects (as recom-
manded by OECD) considers the different systems sepa-
rateiy i.e. male hormones (androgens), female hormone
(estrogens), thyroid hormones, hormones controlling
weight and glucose metabolism, etc. [30]. However, many
hazardous chemicals lack specificity of interaction and can
 affect different parts of the endocrine system [11]. The
neuroendocrine effects of Bisphenol A provide an illus-
tration of the complexity and non-specificity of
adverse effects [44]. Importantly, the action of a
given hazardous factor on a given hormone in vivo
results in reactive changes in the same hormonal
system or axis (e.g. feedback mechanisms) and cross-
talking between different axes, e.g. leptin and
reproduction [45, 46]. Such mechanistic components
can be missed when addressing adverse effects using
components of the endocrine system one by one.

Along the proposed strategy, the adverse effects will be
addressed as a whole. This kind of approach is including
together different endpoints or outcomes that belong to
different systems. This multi system approach emanci-
pates scientists and regulators from linking a single
chemical exposure to a single adverse outcome, and is
consistent with the reality of involvement of different
systems in the in vivo conditions of exposure to mix-
tures of hazardous factors. This includes the interaction
between hazardous factors in causing some effects as
well as the interaction between systems in explaining an
effect or a reaction to an effect.

Preventive intervention against hazardous factors
The central and original component in the proposed
global approach is preventive intervention against haz-
ardous factors as a whole that is not subordinate to thor-
ough demonstration of causal involvement of each
individual factor in adverse effects. Environmental
Hygiene aims at global reduction of exposure to hazards,
especially in pregnancy and early postnatal life. Imple-
mentation of Environmental Hygiene should start as
early as possible in pregnancy. Starting before pregnancy
would have been a preferable option because pre-
pregnancy health weighs significantly on pregnancy out-
comes and clearance of persisting pollutants. While such
an extension is worth being implemented in the future,
we have considered that the pregnant status is associated
with increased likelihood of changing consumer behaviors
in an initial phase and that focusing on pregnant women
would improve feasibility. Recommendations aiming at
pregnancy have been published by Governmental agencies
e.g. the Danish Environmental Protection Agency [47]
or non-governmental organizations. We suggest that an
international panel of experts should develop and endorse
the protective measures. The panel should be multidisci-
plinary including gynecology, pediatrics, endocrinology,
toxicology, public health and epidemiology among others.
Environmental Hygiene is meant to provide guidelines
validated by experts based on our current knowledge of
effects of individual hazardous factors. Preliminary studies
will have to show that they are implementable. Examples
of such measures are provided in Table 1. Specific com-
ments and references to each recommendation can be
found in the Additional file 1.

Demonstration of causality
In the regulatory management of chemicals one by one,
science is expected to provide the demonstration of
causal involvement of a given chemical before any meas-
ure is considered. Carrying the burden of proof is chal-
lenging since most human health disorders that are
possibly involving adverse effects of chemicals are multi-
factorial [11]. This, together with the exposure to chemi-
cals as mixtures, explains why only a limited fraction of
a given effect can be attributed to a given chemical. At-
tribution of a given effect to a mixture and elucidation
of the respective contribution of agents in the mixture
effect is even more challenging given the number of
compounds and the variety of mechanisms. Moreover,
for ubiquitous compounds, there is no unexpressed popu-
lation that can provide an estimate of the "baseline"
prevalence of disease to which chemicals may contribute
an additional burden. Human epidemiology plays a crit-
ical role but carries severe limitations due to exposure to
mixtures, possibly long latency to effects, variability in
unintended level of exposure and negative confounding
Table 1 Some recommendations aiming at reduced exposure to health hazards during pregnancy and early postnatal life

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Targeted hazards</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Everywhere</strong></td>
<td>EDCs</td>
</tr>
<tr>
<td>Stop smoking tobacco and drinking alcohol</td>
<td>x</td>
</tr>
<tr>
<td>Limit as much as possible passive smoking</td>
<td>x</td>
</tr>
<tr>
<td>Avoid frequent close presence to power lines; limit the use of cell phones or cordless mobile phones</td>
<td>x</td>
</tr>
<tr>
<td>Limit the use of plastic or rubber toys and prefer products declared to be free of bisphenol A or phthalates</td>
<td>x</td>
</tr>
<tr>
<td>Stay in a cool place in case of heat &gt; 30 °C</td>
<td></td>
</tr>
<tr>
<td><strong>Personal care</strong></td>
<td>x</td>
</tr>
<tr>
<td>Restrict the use of cosmetics and lotions as much as possible</td>
<td></td>
</tr>
<tr>
<td>Prioritize unscented products and stop using perfumes</td>
<td>x</td>
</tr>
<tr>
<td>Do not color your hair; do not polish your nails</td>
<td>x</td>
</tr>
<tr>
<td>Avoid tattoos</td>
<td></td>
</tr>
<tr>
<td><strong>Food and drinks</strong></td>
<td>x</td>
</tr>
<tr>
<td>Prioritize food and drinks from glass container instead of plastic bottles or metal cans</td>
<td></td>
</tr>
<tr>
<td>Do not microwave food in plastic recipients</td>
<td>x</td>
</tr>
<tr>
<td>Use quality-controlled water in glass bottles</td>
<td>x</td>
</tr>
<tr>
<td>Prioritize organic food whenever possible</td>
<td>x</td>
</tr>
<tr>
<td>Avoid processed, especially nitrite treated, meet</td>
<td></td>
</tr>
<tr>
<td>Avoid charred meet and consumption of bread or other cereal products that are darkened due to high temperature treatment</td>
<td></td>
</tr>
<tr>
<td>Limit (once a week) consumption of predator fish ( tuna, swordfish, ... )</td>
<td>x</td>
</tr>
<tr>
<td><strong>Home care</strong></td>
<td>x</td>
</tr>
<tr>
<td>Wash new clothes before wearing them</td>
<td></td>
</tr>
<tr>
<td>Avoid exposure to organic solvents</td>
<td>x</td>
</tr>
<tr>
<td>Avoid as much as possible painting or coating (walls, doors, floor, ...)</td>
<td>x</td>
</tr>
<tr>
<td>Avoid scented cleaning products, air fresheners and fragrances</td>
<td>x</td>
</tr>
<tr>
<td>Clean inside the house, using damp clothes and reduce dust</td>
<td>x</td>
</tr>
<tr>
<td>Avoid use of insecticides</td>
<td>x</td>
</tr>
<tr>
<td>Ventilate the bedrooms and living rooms at home for 10 min, 1-2 times a day</td>
<td>x</td>
</tr>
<tr>
<td><strong>Outdoor</strong></td>
<td>x</td>
</tr>
<tr>
<td>Avoid the use of herbicides or pesticides</td>
<td>x</td>
</tr>
<tr>
<td>Close the car windows and recycle air while driving on highways, in tunnels and in heavy traffic</td>
<td>x</td>
</tr>
<tr>
<td>Prefer exercising in green areas and avoid heavily polluted air such as within 200 m of heavy traffic</td>
<td>x</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>x</td>
</tr>
<tr>
<td>Avoid exposure to medical x-rays unless really necessary</td>
<td></td>
</tr>
</tbody>
</table>

due to exposure of the control population to other factors having the same effects, among other reasons. While the generally agreed-upon WHO definition of EDC [2, 11] states that the adverse effect is a consequence of altered function of the endocrine system following exposure to the chemical (or mixture), the EU Commission has introduced in the scientific criteria a focus on the endocrine mode of action of which the adverse effect is a consequence [48]. These requirements undoubtedly will add to the delay in decision — making. Diethylstilbestrol and PCBs were banned several decades ago while our understanding of their mode of action was minimal as compared to nowadays.

Along our proposed strategy, the demonstration of causality is meant to be a retroactive process. Namely, the proof of the causal role of the hazardous factors is not a prerequisite to the global reduction of exposure. Instead, demonstration of the favorable impact of the global protective measures on the level of mother and offspring exposure studied by biomonitoring together with the effects on a number of health indicators will provide evidence of global causality. An intervention is substantiated by the numerous studies on the causal link between a given factor and a given adverse effect. Intervention studies are rather scarce such as a recent study on the effect of dietary recommendations on exposure of pregnant women to methyl mercury in Denmark [49]. While available studies on causal involvement of individual hazardous chemicals legitimate the global approach, development of more intervention studies is desirable though limited by ethical reasons and other factors such as possible latency of decades between exposure and
effects. The mode of action does not appear to be a pre-requisite in the global approach. Also, the intervention does not aim at a given product from a given company and intervention is not contingent upon demonstration of causal involvement of a given chemical. However, the possible demonstration of favorable effects on health outcomes after reduced exposure to some hazards through Environmental Hygiene will challenge industry to demonstrate that chemicals that they produce are not involved.

Risk assessment and management
A final step in the classical management of hazardous chemicals is risk assessment. Here, the dose is meant to be critical in an attempt to define a so-called safe dose. This approach is raising several issues including the possible gaps between in vitro models and in vivo conditions, variations in sensitivity to chemicals depending on endpoints and life periods as well as possible non-monotonic dose-response relationship [26, 50]. All those factors complicate the evaluation of risk and account for additional time needed before regulatory decision.

Involvement of stakeholders towards the pregnant woman as ultimate actor
The perspective and the implementation of Environmental Hygiene could unduly pressureize pregnant women. A mother should not blame herself for poor outcomes that must be attributed to collective negligence of industry, policymakers and others. Conversely, safer outcomes should result from mobilization of many stakeholders providing support and action towards women in pregnancy as the ultimate actors. A strategy is proposed in Fig. 3. We suggest that a task force binds together the different stakeholders in developing support to the initiative. This includes financial and technical means as well as empowerment of the different stakeholders in the different actions required for implementation of Environmental Hygiene. The next step consists in testing the hypothesis through validation of the recommendations and studies aiming at evidence that Environmental Hygiene can reduce exposure and protect health. These issues are addressed in the next section. The proposed strategy will then lead to action towards equal opportunity access to improved environmental health. The article 2 of the Treaty on European Union [51] states « The Union is founded on the values of respect for human dignity, freedom, democracy, equality, the rule of law and respect for human rights, including the rights of persons belonging to minorities. These values are common to the Member States in a society in which pluralism, non-discrimination, tolerance, justice, solidarity and equality between women and men prevail ». This substantiates action towards equal opportunity access to improved environmental health. Provided that scientific studies validate the benefits of a global approach, policymakers will have to ensure that access to

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**TASK FORCE for ENVIRONMENTAL HYGIENE IN PREGNANCY AND LACTATION**

<table>
<thead>
<tr>
<th>Citizen groups</th>
<th>Health Care Providers</th>
<th>Scientists, Academics</th>
<th>Regulatory Authorities</th>
<th>NGOs</th>
<th>Industry</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUPPORT (financial, technical, empowerment,…)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VALIDATION of recommendations</td>
<td>STUDIES: evidence of reduced exposure</td>
<td>STUDIES: evidence of health protection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENFORCEMENT / ENFORCEMENT</td>
<td>of equal opportunity access to Environmental Hygiene</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professional EDUCATION</td>
<td>Consumer INFORMATION</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnant and lactating mother, life circle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implementation of global protective measures</td>
<td></td>
<td></td>
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</table>

**Fig. 3** Implementation of Environmental Hygiene. A task force involving the different stakeholders is proposed and provides support to the initiative including financial, technical and any other aspects. The task force clarifies the role of stakeholders in subsequent action including validation of recommendations aiming at protection of pregnant and lactating mothers from environmental hazards and setting up studies aiming at evidence of reduced exposure and health protection in the offspring. Based on these studies, the task force endorses and enforces the strategy of Environmental Hygiene that must be made available to all. The next steps are professional education of health care providers and consumer information, with pregnant women and their life circle as ultimate actor.
Environmental Hygiene is not limited by educational, socio-economic or any other characteristic of subpopulations [52]. For instance, proper information of consumers about the composition of products will be critical. This is a regulatory issue implying that labeling is consistent with composition, readable and understandable. Moreover, education of health care providers, particularly those taking care of pregnant women and young children, should be developed in terms of both content and information tools [53]. The key of that management proposal is the individual citizen i.e. the individual pregnant woman and young parents who deliberately become players for the protection of their offspring and possibly next generations.

Environmental Hygiene will be conducted in conjunction with the current management of individual hazardous chemicals by regulatory authorities. This process aims at banning or restricting the use of a given chemical. The resulting benefits can take decades due to data gaps required to prove causation, time consuming experimental or epidemiological work, debates between stakeholders and persistence of some chemicals in the environment among other reasons. The regulatory evaluation of chemicals remains however a keystone in the management of hazards and risks threatening public health. It is therefore critical that policymakers take any suitable measures that can speed up the process of chemical safety assessment and management. The regulatory process is beyond the control of individual citizens and health care providers and may dismiss preventive management, a feeling reinforced by discordant information about the impact of chemicals on human health, and insufficient education. Industry also has a crucial role in the quality of raw materials used in the preparation of consumer products. This is essential for the presence or absence of hazardous chemicals [5]. This issue is beyond the awareness of consumers including pregnant women and advisers such as health care professionals. Awareness requires transparent and readable information about constituents in consumer products. Therefore, industry has a very important initial role that must be implemented and monitored by authorities.

The issues of Environmental Hygiene far transcend Europe. They have been addressed globally by WHO in a recent publication [54]. WHO points to emerging environmental hazards including chemicals as a threat to children's health and proposes a precautionary approach to protecting children from the effects of chemicals. This important work is symbiotic with our hypothesis and legitimizes extension of the efforts to a global scale.

**Testing the hypothesis and concluding remarks**

Environmental Hygiene is proposed as a global strategy aiming at protection of pregnant women, unborn children and infants against hazardous factors as a whole. Three research questions can be identified about the proposed strategy and must be addressed by scientists with financial support from public authorities: 1. What could be consensual and implementable protective measures in pregnancy and lactation? 2. What is the evidence that those protective measures reduce exposure to hazardous chemicals? 3. What is the evidence that those protective measures improve health? Implementation of such studies will have to address several issues including selection of recommendations, monitoring of exposure to hazards and health outcomes. The panel of experts will have to identify the criteria used for selection of the relevant recommendations. These criteria should incorporate the likelihood of reduced exposure through the proposed measure as well as the applicability based on the psychosocial characteristics of the study population. Questionnaires and interviews will be crucial for assessment of consumer behaviours before and during the study. The parameters selected for biomonitoring of exposure before and during the study will depend on baseline consumer behaviours, access to biological material and reliability of measurements among other factors. Inevitably, the studied population will be heterogeneous as far as the baseline consumer behaviours and exposure. Information on the efficacy of individual protective measures can come out of well-designed observational studies in a population of pregnant women. They could be stratified for specific lifestyles that they plan before or in early pregnancy and that they effectively embrace during pregnancy. These data could be used for the purpose of comparison with an intervention study using Environmental Hygiene as a package of measures. Inclusion of a control group is likely not feasible because everyone is exposed to some hazards and for ethical reasons. Some questions arise from the likely differences in risk awareness and health impact among the consumer behaviors. For example, the very serious consequences of fetal exposure to mother smoking and drinking alcohol and the public awareness about those issues may justify that refraining from smoking and drinking alcohol is an inclusion criterion in all the study groups. The inclusion criteria should be selected to maximize the chance of demonstrating the effects on exposure and health outcomes. An example is a short term intervention study of exposure to BPA and phthalates where the selected subjects were those reporting the most frequent use of canned foods [55]. The recruitment of subjects is challenging as shown in a study on reduction of mercury exposure in pregnant women [56]. These authors were able to enrol 8% or 36% of the women contacted by mail or directly approached on the ward before a scan, respectively. The investigators will have to motivate the participants, for instance through the feedback on exposures before and after implementation of Environmental Hygiene. Over the past 10 years, birth cohorts embraced the wave of new omics technologies to
allow and understand the molecular pathways from exposure towards disease prevention. Environmental Hygiene in early life will benefit from omics as a tool to address causality along with the aforementioned classical concepts, even on the basis of observations. Based on the results of such studies, all stakeholders could endorse Environmental Hygiene and the strategy should become accessible to all. Such an objective will need joint action of academicians, regulatory authorities and NGOs towards education of health care providers and consumer information.

The production of many environmental hazards arises out of economic activity, and the consequences of Environmental Hygiene cannot be ignored. While government inaction is often justified out of a concern that regulatory measures can stunt economic growth, the economic benefits are likely to be great, given the substantial disease burden that can be prevented by reducing exposure. Endocrine disruptor-related diseases are well known to contribute costs on the order of 1.2 and 2.3% of Gross Domestic Products in Europe and the US, respectively [57]. Among these costs, mixtures of EDCs were identified as contributors to disease-related costs, and a global approach is likely to maximize the economic impacts. Relevant exposures are also known to cluster by routes and categories of exposure (e.g., food packaging, pesticides), and a single contaminant approach is less likely to maximize effects on hormonal pathways (e.g., thyroid) that are particularly important.

Environmental hygiene can be by no means substitute for regulatory management restricting or banning chemical use. Such a regulatory approach is indispensable to protect public health in the long term and to reduce detrimental effects of chemicals on animal and plant biodiversity. However, Environmental hygiene calls for additional involvement of regulatory authorities in information and education of consumers and professionals towards global protective behaviors and equal opportunity access to improved environmental health.

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The authors acknowledge the helpful suggestions made by NE Stukelbaek (Rigshospitalet, University of Copenhagen, Denmark), J. Tsiang (New York University, New York, NY, USA) and RT Zlotter (University of Massachusetts, Amherst, MA, USA).

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Availability of data and materials
Data sharing is not applicable to this article as no personal datasets were generated or analyzed during the current study. For the ICHA data quoted in the manuscript, the web addresses wherein the data were retrieved are stated in the text (referenced and the legend (Fig. 1).

Authors’ contributions
JPH and NW developed together the concept of this manuscript. JPH wrote the first draft manuscript. ASP, JCK, TSN and GS provided comments, amendments and additions to the draft manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References
VII. COMPOSITION OF THE WORKING GROUP

The composition of the Committee and that of the Board as well as the list of experts appointed by Royal Decree are available on the following website: About us.

All experts joined the working group in a private capacity. Their general declarations of interests as well as those of the members of the Committee and the Board can be viewed on the SHC website (site: conflicts of interest).

The following experts were involved in drawing up and endorsing this advisory report. The working group was chaired by Jean-Pierre BOURGUIGNON and Nicolas VAN LAREBEKE; the scientific secretary was Marleen VAN DEN BRANDE.

<table>
<thead>
<tr>
<th>Name</th>
<th>Field</th>
<th>Institution</th>
</tr>
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<tbody>
<tr>
<td>ADANG Dirk</td>
<td>Human ecology</td>
<td>Universiteit Hasselt</td>
</tr>
<tr>
<td>BOULAND Catherine</td>
<td>Environmental &amp; occupational health</td>
<td>ULB</td>
</tr>
<tr>
<td>BOURGUIGNON Jean-Pierre</td>
<td>Pediatric endocrinology</td>
<td>ULiège</td>
</tr>
<tr>
<td>DEN HOND Elly</td>
<td>Environment and health</td>
<td>PIH Antwerpen</td>
</tr>
<tr>
<td>GODDERIS Lode</td>
<td>Occupational and environmental medicine</td>
<td>KULeuven</td>
</tr>
<tr>
<td>NAWROT Tim</td>
<td>Environment and health</td>
<td>Universiteit Hasselt</td>
</tr>
<tr>
<td>SCHOETERS Greet</td>
<td>Environmental toxicology</td>
<td>UA/VITO</td>
</tr>
<tr>
<td>SMEESTERS Patrick</td>
<td>Radiological protection &amp; radiobiology</td>
<td>FANC/UCL</td>
</tr>
<tr>
<td>VAN LAREBEKE Nicolas</td>
<td>Toxicology</td>
<td>UGent/VUB</td>
</tr>
</tbody>
</table>

The standing working group on chemical agents has endorsed the advisory report. The standing working group was chaired by Luc HENS; the scientific secretary was Marleen VAN DEN BRANDE.

<table>
<thead>
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<td>Toxicology and environmental toxicology</td>
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<td>HEILIER Jean-François</td>
<td>Toxicology</td>
<td>SPAQUE</td>
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<td>HENS Luc</td>
<td>Human ecology</td>
<td>VITO</td>
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<tr>
<td>HOLSEBECK Ludo</td>
<td>Risk assessment, pesticides</td>
<td>LNE</td>
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<td>STEURBAUT Walter</td>
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The following administrations and/or ministerial cabinets were heard:

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>CASTELAIN Philippe</td>
<td>DGAPF – Pesticides and fertilizers</td>
<td>FPS Health, Food Chain Safety and Environment</td>
</tr>
<tr>
<td>DE BOOSERE Isabel</td>
<td>DVZ - Health and environment</td>
<td>FPS Health, Food Chain Safety and Environment</td>
</tr>
<tr>
<td>DUSSART Aurelie</td>
<td>DGEM – MRB - Chemicals</td>
<td>FPS Health, Food Chain Safety and Environment</td>
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<tr>
<td>ROHL Martine</td>
<td>DGEM – MRB - Chemicals</td>
<td>FPS Health, Food Chain Safety and Environment</td>
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