"The Environmental Burden of Disease" International Expert Workshop

REPORT

Thursday April 13th, 2006

Amazone Centre, 1210 Brussels

Programme and organisation by WECF, the Netherlands.

Chaired by Prof. Dr. Jacqueline Cramer (Sustainable Entrepreneurship, Utrecht University).

This workshop is part of the WECF project on Eco Efficiency and is held in the framework of the Lisbon Agenda and the review of the EU Sustainable Development Strategy (SDS).

The workshop was sponsored by the Dutch Ministry of VROM.

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Women in Europe for a Common Future (WECF)

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June 2006

Summary

Women in Europe for a Common Future (WECF) is a network of more than 70 organisations working to improve the protection of human health and the environment. Our international network consists of members and partners in Western and Eastern Europe, the Caucasus, and Central Asia. Activities range from practical health and environment issues in partnership projects to advocacy projects, bringing issues to international fora.

WECF has a growing concern about the environmental burden of disease (EBD). WECF focuses in the first place on the health effects on new generations: effects can be transferred from mother to child. WECF also recognizes that the health of the population contributes to a healthy workforce, a key element in a competitive Europe.

To learn more about the environmental impact on health, WECF organised an International Expert Workshop on the EBD in Brussels on 13th of April, chaired by **Prof. Jacqueline Cramer (Sustainable Entrepreneurship, Utrecht University)**.

Marie Kranendonk, president of WECF, argued that policymakers still base policies on the assumption that the proven causal relationship between health and environment is only 2 to 6 %, but that methods of assessment are not suited to the current complexity of contamination and effects. A multi-causality approach, combined with studies on effects of mixtures of substances, human bio-monitoring, and progressive cohort studies, amongst other things, will result in completely different percentages.

Professor Dr. Nic van Larebeke, Cancer Specialist from Ghent University, showed some problems of epidemiological studies that lead to an underestimation of cancer risks, including low sensitivity for relative risks smaller than 1.5 to 2, negative confounding; a follow up time which is too short compared to latency of cancer; and inaccuracies in assessing exposure, including exposure to air pollutants through food. He also showed how important the timing of the dose exposure is: early exposure is far more important than later in life, and exposure in the womb is extremely important. ”Small” environmental causes can be very important. 25% of all cell divisions and mutations occur before birth. A person who has more mutations from early life will be more vulnerable. We need to give more attention to these very early affects.

According to **Professor Dominique Belpomme, Oncologist, University of Paris, Chairman of ARTAC, European Georges Pompidou Hospital**, two out of three or even three out of four cancers are caused by the environment. 25% is caused by smoking. For fatal cancers, the first step occurs during pregnancy. But there is societal refusal to accept the scientific proof. In Europe, environmental factors cause ⅓ of diseases among children and adolescents. There is a 1% yearly increase of incidence of child cancers in Europe and in the USA. Leukaemia in children has doubled over the past 20 years. Congenital malformations of the reproductive tract have tripled in agricultural areas polluted by pesticides. Asthma increased over the last 15-20 years. Carcinogenesis needs a critical number of mutations (3-6). A mutation is always induced by environmental factors. Lifestyle, apart from smoking, is a necessary but not sufficient factor for carcinogenesis.

Philippe Irigaray, PhD, Biochemist from CNRS-ARTAC added that a certain dose intensity is not required, but multiple repetition of doses, i.e. duration of exposure, is important to induce carcinogenesis. His research was done in cooperation with Boston University. The conclusion is that complementary action of lifestyle and environmental factors are accountable for co-carcinogenesis promotion probably in a 50-50 ratio. Smoking and environmental factors are accountable for mutations in a 25-75 ratio respectively. This leads to the hypothesis that one out of two cancers is caused by environmental factors. These results will be published by Belpomme D., Irigaray P. et al. “Increased cancer incidence: the environmental impact on carcinogenesis.”

The **Paris Appeal** is an international declaration on diseases due to chemical pollution. It has been signed by, amongst others, the Standing Committee of European Doctors (representing around 2

million doctors), more than 1000 scientists from all over the world, and several medicine Nobel Prize winners.

Dr. Ludwine Casteleyn, leader of the Human Biomonitoring Expert Group working for the EU Commission, and adviser to the Flemish Government, pointed out that human biomonitoring can be confronting; makes the issues more personal and brings them closer to politicians and the public. But member states need to take a consistent approach. The question is: should it be a European or an international approach?

In the debate it was pointed out that the Commission should ensure that leading scientists are involved in these issues. The working group in January with **Professor Brunekreef** and others on air pollution is a good example. Also in the thematic strategy on pesticides the precautionary principle is needed. In the REACH debate NGOs proposed that uncertainties need to be communicated to policymakers. Impact assessments are not including health impacts, per se. Meta-analysis needs to be promoted instead of repeating studies.

Professor Dr. Nic van Larebeke from Ghent University presented some examples of low dose mechanisms. For example, low doses of radiation are relatively more efficient when mutation frequency is compared to exposure intensity. This is due to an increase in repair capacity at higher doses. Another example is from Columbia University who found, unexpectedly, that irradiation of 10% or 100% of cell nuclei has the same result. This is explained by communication between cells. The BPA hormone (Bisphenol A, a xenoestrogen) increases cell proliferation in prostate cancer only in low doses. The possible explanation is that in higher doses the effect of binding to specific receptors might disappear.

John A. Newby from the University of Liverpool presented the study "Environmental Influences in Cancer Aetiology", done with **Dr. C. Vyvyan Howard from the University of Ulster**. Their findings are that the environment is implicated in the majority of cancers, building on several recent studies, for example a cohort study of identical twins. His findings support the idea of conceptual shifts in toxicology as put forward by **John Peterson Myers, Ph.D.**, who points to the relevance of low level contamination; impacts of 'background' levels; the sensitivity of the prenatal and youth phase; long latencies being common rather than an exception; and the effect of mixtures being stronger than the sum of the single chemicals.

John Newby explained that there are critically sensitive periods during organogenesis and environmental exposure to chemicals may have differing or no adverse effects on a developing foetus, depending on precise time of exposure. Several examples related to testicular cancer were presented. He also concluded that the mixture of xenochemicals in environments consisting of tens of thousands of congeners, enantiomers and metabolites, is beyond the current ability of toxicologists to analyse. Elucidating cause/effect relationships by epidemiology to specific environmental contaminants is improbable. Therefore, we should not wait for an unobtainable certainty before action is taken

Professor Klea Katsouyanni, Department of Hygiene and Epidemiology, University of Athens Medical School, explained how conceptual shifts took place in the effects of air pollution on health. From about 1970 to 1990, the prevailing opinion among scientists and decision makers was that current air pollution levels did not have important adverse health effects. Since roughly 1990, it became evident that the current, relatively lower, air pollution levels (mainly ambient particles) had adverse, short-term and long-term health effects including an increase in mortality. The findings came mainly from epidemiological studies. Recently, experimental findings support the epidemiology. These results had an impact on setting guidelines and standards, in the U.S. (Environmental Protection Agency (EPA), the European Union, and the World Health Organisation (WHO). However, the EU is still reluctant to impose stricter and legally binding measures on fine particulate matter (PM), despite adequate recognition of the health effects.

Fintan Hurley from the Institute of Occupational Medicine (IOM) in Edinburgh (UK), underlined the importance of the paradigm shifts in our understanding of air pollution and health. Firstly, health effects are not restricted to air pollution episodes but rather occur at 'normal' levels of air pollution ('daily variations' in air pollution). Second, long term effects are more serious than accumulated short

term effects. He explained the usefulness of the CAFE (Clean Air For Europe) approach. Health Impact Assessment in CAFE was part of a Cost-Benefit Analysis of policy options and scenarios. This included a high level peer review done by a group of U.S. scientists. The Cost-Benefit Analysis showed that benefits of a 20% reduction in $PM_{2.5}$ across the EU-25 outweigh the cost by a factor 6 - 23. Despite the evidence, the final recommendations from the European Commission on regulating PM are not adequate. Apart from scientific uncertainties, additional uncertainties were 'created' by opponents of regulation. This was referred to as 'manufactured uncertainty'.

Dr. Med. Stephan Böse O'Reilly of the German Network – Children's Health and Environment, is working on the financial burden to the German health care system caused by environmental hazards for children in Germany. He gave a first presentation of ongoing work with, primarily, Dr. Andreas Gerber (Institute of Health Oeconomics) at the University of Cologne.They looked especially at environmental tobacco smoke and traffic accidents. 25% pregnant women smoke and 50% of children are exposed to tobacco smoke at home. The estimated annual health costs for German children in million Euros for the smoke connected diseases are: asthma bronchiale 490, otitis media (ear infection) 90, lower respiratory tract infections 389, preterms 1,157 and low birth weight 84 million euro per year. Traffic accidents with children cost 1,022 million Euro per year. They recently calculated that the costs of environment-related asthma and PM10 could be 100 million Euros. Other diseases such as Sudden Infant Death Syndrome (SIDS), cancer, and developmental disorders were not taken into account. Therefore this study presents a very conservative estimation. Could it be that up to 10 % of all the health costs for children per year are related to the environment?

Discussion and conclusions
Finally, the WECF draft recommendations were discussed. They will later be finalised under the responsibility of WECF.

WECF concluded from the workshop:

A new paradigm - or conceptual shift - is evolving in science in the field of environmental effects on health. Low doses and multiple causes have been underestimated in the past. The new paradigm is based on a multi-causality approach and research that looks at complex interactions from multiple exposures and long-term effects of low dose contaminations, taking into account vulnerable periods, and shows a much stronger relation between environmental factors and health effects.

Although it is difficult to get hard proof of the health effects of environmental pollution and of the low-dose and long-term effects, and there is a lot of discussion on how to estimate the health costs, we should draw the attention of politicians and policymakers on the EBD. We should ask them to go beyond the uncertainties, not to wait for more proof, but to choose for the precautionary principle and to be cognizant of manufactured uncertainties from interest groups like industry. There are urgent measures to be taken. Because we believe that a healthy Europe is a prerequisite for long-term competitiveness.

Scientist and NGO's should try to inform and convince the scientific community, policy makers, the general public and also industry. We should offer them scientific data; formulate clear, consistent, and convincing messages and adapt them to the particular audience; emphasise effects on children and other vulnerable groups; not just focus on the problems but also propose solutions; show the costs and benefits of the environmental health.

WECF will use the recommendations and conclusions as input for the scheduled High-Level Roundtable with European politicians and policymakers in the autumn of 2006.

Introduction to the WECF Expert Workshop "The Environmental Burden of Disease"

Goals

Women in Europe for a Common Future (WECF), a network of 70 member organisations all over Europe, has started the project "Eco-efficiency and sustainable development; Women promoting the environmental pillar of the Lisbon Strategy and the EU Sustainable Development Strategy (SDS)". It is our belief that competitiveness is, in the long term, unthinkable when not based on a healthy environment and a healthy population. Our goal is to make the link between environmental pollution and health (the environmental burden of disease) and its effect on Europe's competitiveness. Therefore, in this project WECF wants to engage citizens, particularly women, in the debate on how to advocate with convincing arguments that the SDS and protection of environment and health should be overarching goals to economic competitiveness in the Lisbon strategy.

WECF organised an international Expert Workshop on the Environmental Burden of Disease Workshop on 13th of April in Brussels, as a preparation for a High-Level Roundtable on these issues. At that occasion, scientists presented new findings and insights into the role and importance of environmental factors in causing a range of diseases. Important new findings into the low dose, long-term effects of early childhood and prenatal exposure are evolving.

The outcome of this workshop and the highlights of the debate will be presented at a High-Level Roundtable, to be organised by WECF in October this year. The aim of the High-Level Roundtable is to discuss with politicians and opinion leaders from business and civil society how the Lisbon strategy and policy development can incorporate reduction and prevention of environmental pollution so as to decrease the environmental burden of disease and lower the societal costs of illness and health damage.

Programme

Date: Thursday 13 April 2006
Location: Amazone Centre, Rue du Méridien 10, 1210 Brussels
Chair: Prof. Dr. Jacqueline Cramer (Sustainable Entrepreneurship, Utrecht University)

Morning session:

10.00 Marie Kranendonk (WECF): Welcome, introduction to workshop and Jacqueline Cramer

10.15 Prof. Dr. Nic van Larebeke (Ghent University): Environmental Burden of Disease, including input from David Gee

10.30 Prof. Dominique Belpomme (ARTAC): Paris Appeal as example of successful strategy used by scientific community to convince policy makers

10.45 Response by Prof. Ludwine Casteleyn (Human Biomonitoring Group)

10.55 Prof. Dr. Jacqueline Cramer: inventory response participants

11.00 Coffee/tea break

11.10 Prof. Dr. Jacqueline Cramer: discussion responses and concluding remarks morning session

12.30 Lunch break

Afternoon session:

Case 1: Cancer and environmental links

13.30 Brief presentations by Prof. Dominique Belpomme (ARTAC), Prof. Dr. Nic van Larebeke (Ghent University) and John Newby (University of Liverpool)

14.00 Group discussion

Case 2: Health effects of air pollution

14.30 Brief presentations by Fintan Hurley (Institute of Occupational Medicine), Prof. Klea Katsouyanni (University of Athens Medical School) and Dr. Stephan Böse o'Reilly (die Kinderärzte)

15.00 Group discussion

15.30 Coffee/tea break

15.45 Prof. Dr. Jacqueline Cramer: concluding session: using arguments and supporting cases to draw policy recommendations

16.45 WECF: follow-up (High-Level Roundtable and proposal follow-up project)

17.00 End

List of participants

Organisation	Participants	Function
Utrecht University	Prof. Dr. Jacqueline Cramer	Professor Sustainable Entrepreneurship Chair workshop
ARTAC	Prof. Dominique Belpomme	President
ARTAC	Marie Vigorie	Director general
ARTAC	Philippe Irigaray	Research coordinator
European Academy for Environmental Medicine	Dr. Hans-Peter Donate	Vice-president
EPHA Environment Network (EEN)	Christian Farrar-Hockley	Policy Officer
EU DG Environment	Scott Brockett	Extended Impact Assessment
European Women's Lobby (EWL)	Mary McPhail	General secretary
Ghent University	Prof. Dr. Nic van Larebeke	Radiotherapy and nuclear medicine
Human Biomonitoring Group	Ludwine Casteleyn	Chair
Observatoire Regionale de Sante d' Ile de France (Regional Health Observatory, France)	Agnès Lefranc	Epidemiologist
Institute of Occupational Medicine	Fintan Hurley	Scientific Director
Die Kinderärzte	Dr. Stephan Böse-O'Reilly	Paediatrician
Pesticides Action Network (PAN) Europe	Dr. Sc. Catherine Wattiez	Campaign coordinator
University of Athens Medical School	Prof. Klea Katsouyanni	Coordinator of APHEA studies
University of Liverpool, Dept. of Human Anatomy and Cell Biology	John Newby	Developmental Toxico-Pathology Research Group
Westfries Gasthuis	Gavin ten Tusscher, M.D., Ph.D	Paediatrician
WECF	Marie Kranendonk	President of the board
WECF	Yvette Bellens	Project manager
WECF	Irma Thijssen	New project manager
WECF	Sonja Haider	Director German office
WECF	Jasmine Osorio	Project assistant
Ecostrategy	Maria Buitenkamp	Project consultant

Morning session

Marie Kranendonk, president of WECF: Welcome and introduction to workshop

Marie Kranendonk gives a warm welcome to all participants. WECF is very grateful that all participants could come, even if for some it is now their holidays. We regret that David Gee is seriously ill and cannot make his presentation, but he sent us some Powerpoint sheets. We are grateful that Professor Belpomme and Professor Van Larebeke were able to prepare an alternate presentation on such a short notice. We highly appreciate that Professor Dr. Jacqueline Cramer will chair this meeting. She also assisted WECF in developing this program. Professor Cramer is teaching Sustainable Entrepreneurship at the University of Utrecht.

Marie Kranendonk

About WECF

WECF is a network of more than 70 organisations working to improve the protection of human health and the environment. The international network consists of members and partners in Western and Eastern Europe, the Caucasus and Central Asia. Activities range from practical health and environment issues in partnership projects through advocacy projects, bringing issues to international fora.

WECF has working groups on:

- Health & Environment (including Chemicals)
- Water & Sanitation
- Agriculture & Sustainable Development
- Energy & Climate Change
- Gender & Sustainable Development

The Environmental Burden of Disease

We have a growing concern about the environmental burden of disease (EBD). We focus in the first place on the health effects on new generations. Effects can be transferred from mother to child. Scientists have opened our eyes on the issue of prenatal contamination, an issue also to be discussed today. Contaminants are passed on from mother to foetus and infant in the most vulnerable phase of development. Risks include cancer, neurodevelopment disorders with lifelong effects, endocrine disruption, and effects on fertility. Women are most affected as they usually suffer an extra burden as

caretakers when there is disease in the family. There are other gender aspects of EBD for example the vulnerability of the reproductive system.

We see scientists and health professionals as our allies: they can raise awareness about health effects and help with the development of policy and research demands. They provide us with arguments to strengthen our appeals to policymakers.

Integrating health effects in Lisbon Agenda and SDS

This workshop is held in the framework of the Lisbon Agenda and the review of the EU Sustainable Development Strategy (SDS).

The political reality of this moment is a high priority on economic development and competitiveness, while neglecting environment and health protection as prerequisites. The Lisbon Agenda added an environmental pillar in 2001 after the launch of the SDS. But it does not integrate health aspects. There is a strong focus on eco-innovation and efficient use of resources, however, so called eco-efficient technology choices can still be harmful for health (e.g. nuclear energy, recycling of toxic waste in wood preservatives) if these concerns are not integrated in all policies from the outset.

The full extent of related health effects should be made visible, as well as the costs and benefits of health protection. This will provide an incentive for policymakers to strengthen the environmental pillar of the Lisbon Agenda and the SDS.

Input from David Gee, European Environment Agency (EEA)

David Gee discussed with us the following points:

- Policymakers still base policies on the assumption that the proven causal relations between health and environment (H&E) are only 2 - 6 %. Why? Methods of assessment are not suited to the current complexity of contamination and effects.
- A multi-causality approach, combined with human bio-monitoring, progressive cohort studies, etc. will result in completely different percentages.
- Better assessment of cost and benefit aspects of environmental health protection, precaution and prevention measures is needed.
- How can health experts convince policy makers?

Discussion points

Essential views from WECF, which we would like to discuss with you this afternoon, are:

- Assuring a clean environment is a prerequisite for a healthy development of every new human being.
- Priority setting in policy should not be based primarily on economic considerations, cost-benefit, win-win.
- A healthy environment is necessary for a good quality of life; it is arguably a basic human right.
- It is a human right to be born and to develop in an environment that is not contaminated by manmade pollutants that are harmful to health (even from the foetal stage). The basis for a healthy life is especially important for children; no mother wants to pass on pollutants to her baby, but this is the reality of today.

Professor Dr. Nic van Larebeke, Ghent University: Environmental Burden of Disease (with some key input from David Gee, EEA)

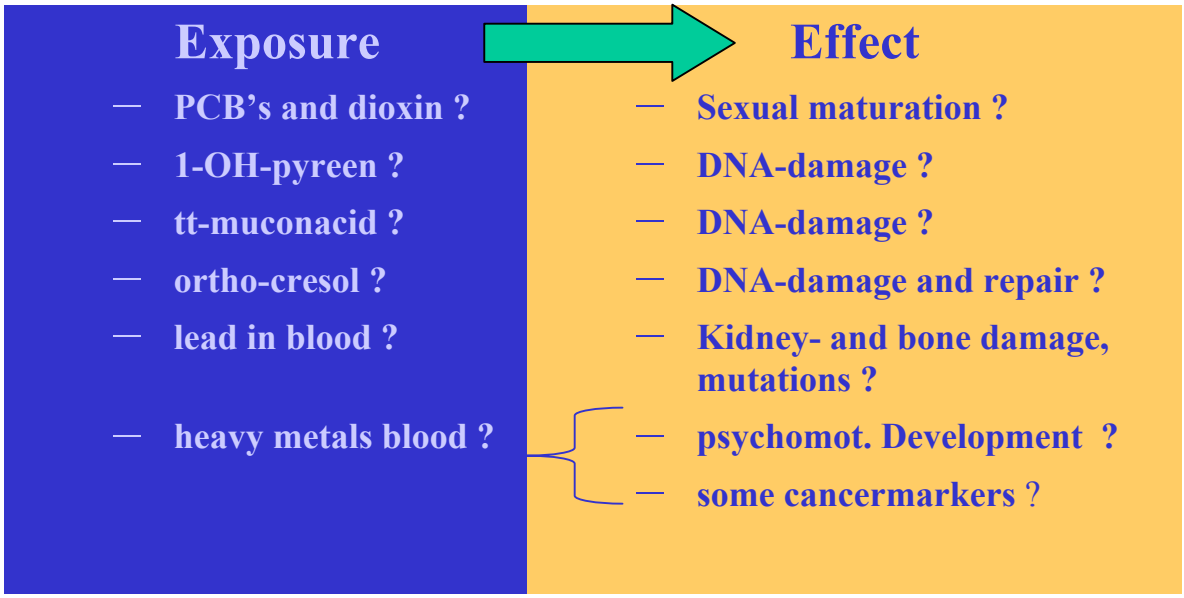
Life expectancy is increasing, but not the chances for a good health at older age. The incidence of chronic diseases as well as cancer is increasing. I am a cancer specialist, but perhaps my findings are also true for other diseases. Some problems of epidemiological studies lead to underestimation of cancer risks:

1. Epidemiological studies don't have a low sensitivity; relative risks lower than 1.5-2 cannot be detected.
2. Negative "confounding": Swedish teachers show a relative risk of 0,48 for lung cancer after correction for smoking.
3. Follow up time is too short compared to latency time of cancer for human beings.
4. Dose-response relation: inaccuracies in assessing exposure lead to underestimation of risk increase.
5. Exposure to many air pollutants happens for a large part through food – for example PACs (polycyclic aromatic compounds).

A Nature publication showed a high correlation between lung cancer mortality and lichen diversity in a part of Italy.

Swedish male farmers showed lower cancer incidence than the general population, despite a high exposure to carcinogenic agents; the incidence amongst male farmers was 82% instead of 100% for all cancers (Wiklund & Steineck, 1988).

The Flemish Environment and Health study indicated the following exposure effect relations:



The next text on multi-causality was chosen by David Gee:

"x % of cancer is caused by smoking, y % by diet, z % by alcohol, and so on; when all of these percentages are added up, only a small percentage, much less than 40 %, is left for occupational or environmental causes. But this is fallacious because it is based on the naive view that every case of disease has a single cause and that two causes cannot contribute to the same case of cancer. Since diet, smoking, asbestos, along with other factors interact with one another and with genetic factors to cause cancer, each case of cancer could be attributed repeatedly to many separate causes. The sum of disease attributable to various component causes in reality has no upper limit".

Source: K. Rothman, "Epidemiology: an introduction", p. 13 (2002)

Adding up and being cautious not to go over 100% is suggesting that every cancer has one cause; but there are a multitude of factors.

The next slide from David Gee demonstrates this approach. Gene expression can be influenced by lifestyle. Both the genes and environmental exposure can be necessary to cause the cancer.

This means that adding up leads to a much higher percentage than 100%.

APPROACHES TO CANCER CAUSATION: "CO-CAUSALITY"

Genes + gene expression	+	Environmental exposures	=	Cancer
100% necessary	+	100% necessary	=	"200%", i.e. no upper limit

and, together

= **S U F F I C I E N T**

Source: (EEA – after Rothman)

The implications of multi-causality are:

1. Timing of the dose can make the poison; early exposure is far more important than late in life, and exposure in the womb is extremely important. Exposure at the age of 70 is not so important. Swedish research shows that exposure below the age of 20 is important, and especially the prenatal phase.
2. "Confounders" (elements from outside that are normally taken out of the research, but that can actually influence the results) are sometimes co-causal factors
3. Simple genetic determinism becomes complex systems dynamics

4. “Consistency” of scientific results can be unusual: different outcomes do not necessarily mean that studies point in different directions.
5. ”Small” environmental causes can be very important:
    a. As links in an interdependent causal chain
    b. As ”Triggers” of all diseases e.g. asthma. It is not correct to say that asthma is not ’caused’ but only ’triggered’ by pollution. Inflammation is a very important element in the carcinogenesis process.
    c. For large ”secondary” benefits e.g. Noise improvement from traffic reduction
6. Effectiveness evaluation of policy measures will be difficult
7. Relevance of the precautionary principle and differential levels of proof.

A working definition of the precautionary principle is:

“[it] 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”. EEA, 2002

It’s the **Timing of the Dose** that Makes the Poison for Developmental and Reproductive Harm:

”The time of life when exposures take place may be critical in defining dose-response relationships of endocrine disrupting substances (EDS)s for breast cancer as well as for other health effects” WHO/IPCS ”State of the Science of EDS’s”, 2002)

We need to pay more attention to very early effects. The early stage is so important because in early life already an accumulation of mutations take place. 25% of all cell divisions and mutations have occurred at birth, mainly from stem cells. Human cells are generally resistant to carcinogenesis. Many proteins interact to determine gene expressions and thus it takes a long time before malign transformations are there. If you have more mutations from early life, you will be more vulnerable.

Professor Dominique Belpomme, University of Paris, Chairman of ARTAC, European Georges Pompidou Hospital: the Paris Appeal

Prof. Dominique Belpomme

There are two important messages:

1. Cooperation between NGO’s and science is very important
2. There is no doubt about the relation between health and environment: 2 out of 3, or even 3 out of 4 cancers are caused by the environment.

For fatal cancers, the first step lies in pregnancy. But there is societal refusal to accept the scientific proof. Now we have to convince other scientists. For decision makers we have to create a shock. We

do this with the Paris Appeal. The Paris Appeal is an International Declaration on diseases due to chemical pollution, from May 7, 2004. (www.artac.info). It will take a long time, but it's a first step..

First the definition of health: Health is "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (*Constitution of the World Health Organization* (WHO) of 7 April 1948).

If the environment is not okay, well-being will not be okay. So it is not only pollution, but also other environmental and eco-system problems that can influence well-being. But the Paris Appeal focuses on chemical pollution. An overview:

Cancer (1):

- A leading cause of death before 65 years.
- 25% of cancers due to smoking / 75% due to mutations induced by environmental factors, mainly chemical.

Infertility (2,3):

- 15% of couples are infertile in Europe.
- Drastic increase of male infertility over the last 50 years: 1% yearly decrease in spermatic count in areas polluted by chemicals (pesticides).

Decrease of birth rate:

- 2.1 children/woman; drastic demographic consequences for Europe (WHO report) Portugal has only 1.1 child/woman.

Allergy (4):

- Doubling number of cases over the last 15-20 years.
- 20% of French citizens have allergies – possible role of chemical pollution. Asthma figures are increasing.

1- Nicolopoulou-Stamati P., Hens L., Howard V.C., Van Larebeke N. Cancer as an environmental disease, Geb.Ed Springer, 2004, 236 p.
2-Carlsen E. et al. Br. Med.J.,1992, 305 : 609-613.
3-Van Waeleghem K., De Clercq N., Vermeulen L., Comhaire F. Human Reproduction, 1996, 112 : 325-329.
4-www.allergique.org

The lives of children are in danger:

- In Europe, environmental factors cause 1/3 of diseases among children and adolescents (1)
- Foetus contamination: chemical pollutants pass through the placental barrier.
- Contamination of breast milk (2)
- Cancer (3): 1% yearly increase of incidence of children cancers in Europe. A second cause of mortality.
- Leukaemia (4): X2 increase in number over the last 20 years
- Congenital malformations of the reproductive tract (5): X3 increase in number in agricultural area polluted by pesticides
- Asthma and allergies (6): Drastic increase over the last 15-20 years of asthma

1- Valent F et al, The Lancet, 2004, 363, (9426), 2-Noreen K, Mieronyte D, Contaminants in Swedish human milk, Organohalogen Compounds, 35/1-4, 1998 3- IARC,6E.Steliarova-Foucher et al, The Lancet , 2004, 364 ; 4- Pr.Alan Preece, University of Bristol, 2004*; 5- INSERM; 6- WHO Regional Office for Europe. Copenhagen, European Environment Agency. Tamburlini G et al., 2002:44–47 (Environmental issue report, No. 29).

Similar figures on cancer in children are found in the USA. In male children there are 15 times more congenital malformations proven by scientific literature.

But there is a complete societal refusal of these scientific data. We have to face a new scientific medical paradigm. The group of researchers needs to convince the overall scientific community. We do not need more research, there are enough data.

The Paris Appeal has three articles:

Article 1 The development of numerous current diseases is a result of the deterioration of the environment

Article 2 Chemical pollution represents a serious threat to children and thus Man's survival.

Article 3 As our own health and that of our children and future generations is under threat, the Human race itself is in serious danger.

Signatories include:

- The Standing Committee of European Doctors, representing around 2 million European doctors;
- More than 1000 scientists from Europe: France, U.K, Belgium, Germany, Italy, The Netherlands, Spain, Sweden, USA, Canada, Switzerland, Japan, India.
- Several medicine Nobel Prize winners such as François Jacob and Jean Dausset, Right livelihood award winners, and members of the different National Academies of Medicine and Science.

The Paris Appeal lobbied for a strong REACH and convinced some members of the European Parliament. Our next step will be on the 9th of November 2006: with a EUROPEAN COLLOQUIUM AT UNESCO “Health, environment and sustainable development: an international assessment”. We need concrete measures that are independently defined.

Participant comments to the first two presentations

- Part of decreased child rate is due to social factors. 15% of the couples do not want children, but another 15% faces unwanted infertility. Why do women not want children? Is the problem also education?
- After high pollution disasters, a shift in male/female ratio can be observed, leading to a decrease in number of boys born.
- It is not possible to tie trends explicitly to certain environmental causes.
- Allergies in Europe are increasing, but in the last 3-5 years asthma in Northern Europe has slightly decreased: a result of less air pollution?

Ludwine Casteleyn, Human Bio-monitoring Group, adviser to the Flemish Government: a response

Ludwine Casteleyn

Casteleyn is working on the interface of science and policy on the issues of bio-monitoring and survey of environmental exposure and health effects.

Human bio-monitoring can be confronting, it makes information more personal and brings the issue closer to politicians and the public. But at this moment we have to convince the Member States to take a consistent approach. The question is: should it be a European or an international approach? Member States have their own specific situations. Another problem is that politicians have little time, so they need easy, clear messages. But in the scientific community there are different views and debates.

Mentioning absolute numbers of people who are affected is more convincing than giving percentages.

Human bio-monitoring can deliver quick results, but interpretation of results and formulating policy responses takes a lot of time. But people should not be bothered with bio-monitoring unless policy responses are made.

Some people say that a clean environment does not exist and scientists say we have no control population that is not in some way contaminated, so we must be careful with conclusions. We have a right to health care, but do we also have a right to a clean environment? Is such a demand feasible or will politicians show us the door?

Discussion on the three presentations

The discussion was around 4 themes

Paris Appeal

- There is some discussion on the 3 articles of the Paris Appeal. Especially the concept of the threat to Man' s survival meets some resistance, even with some signatories. It only applies when fertility is wiped out completely. There will always be scientists who give different opinions. The articles speak about problems, whereas politicians want to hear solutions. ARTAC will present solutions at the November meeting.
- Put yourself in the shoes of your opponents, and stick to facts. Often we use emotions too much. Science is far more convincing for our opponents but also for the ground troops in hospitals and elsewhere. Many colleagues will find the Paris Appeal message too green. But facts on dioxin levels that cause specific problems in newborn babies will convince them.
- One size does not fit all: use different lobby strategies depending on your audience.
- There is a difference in language use between groups: for doctors the article 3 is a logical conclusion, it is a medical problem, but for politicians it's not their language.

Prof. Cramer concludes:

1. Look at who you are addressing
2. Use facts and science
3. Focus not on problems, but on solutions

Message to politicians and the public

- Science will never give the full proof, therefore scientists need to support the precautionary principle.
- Industry provides the objects of material wealth that people want, but people also want a healthy life and healthy babies: industry can also develop less harmful products. Some industries find this interesting, for example applying new car technology. In Flanders the incineration industry managed to reduce pollutants by a factor 100-1000 in 5 years, after politicians spoke out in public. But industry is not one bulk, and not all industries want to be frontrunners. Industry lobbyists in Brussels are most concerned with liability, and not with win-win.

Prof. Cramer concludes: stress quality of life, of children of elderly to appeal to people.

Multi-causality approach and better environmental health analysis

- The European Commission is now focusing on multi-causality, large-scale cohort studies and recognises human bio-monitoring. Also health impact assessment, monitoring and application are all in the framework setting on environment and health. But there are some problems with the practical logistics, for example in Holland lack of experience with selected research groups. However this is not the Commission's job, the Commission is just inviting the scientific community. But the competitive process for obtaining research funds, as set up by the Commission, is not necessarily effective – it works out badly in some fields.
- The thematic strategy on pesticides, which is now on the political agenda, is addressing the health aspects only in a cosmetic way. We need the precautionary principle here.
- In the REACH debate NGO's proposed that uncertainties need to be communicated to policymakers. Impact assessments are not including health impacts, per se. In REACH the implementation of the substitution principle is very complicated. There is now a proposal that third parties can propose substitution plans. Companies need to enter the arena with safe alternatives and push out competitors.

Prof. Cramer: It seems that the research issue is now covered, but policy making itself is lacking?

- The Commission should ensure that leading scientists are involved. The working group in January with Brunekreef and others on air pollution is a good example.

Prof. Jacqueline Cramer

Sufficient evidence for paradigm shift?

- Are the cases in the Paris Appeal the right ones to use? Nobel prize winners checked and signed. But negative studies are also published. Negative epidemiological studies cannot prove anything. There will be scientists who say studies are controversial. Many scientists will genuinely not agree with the paradigm shift. Not even all participants in this workshop are already convinced by what they know now. Meta analysis studies need to be promoted, instead of additional, repeating studies.

Prof. Jacqueline Cramer concludes from discussion:

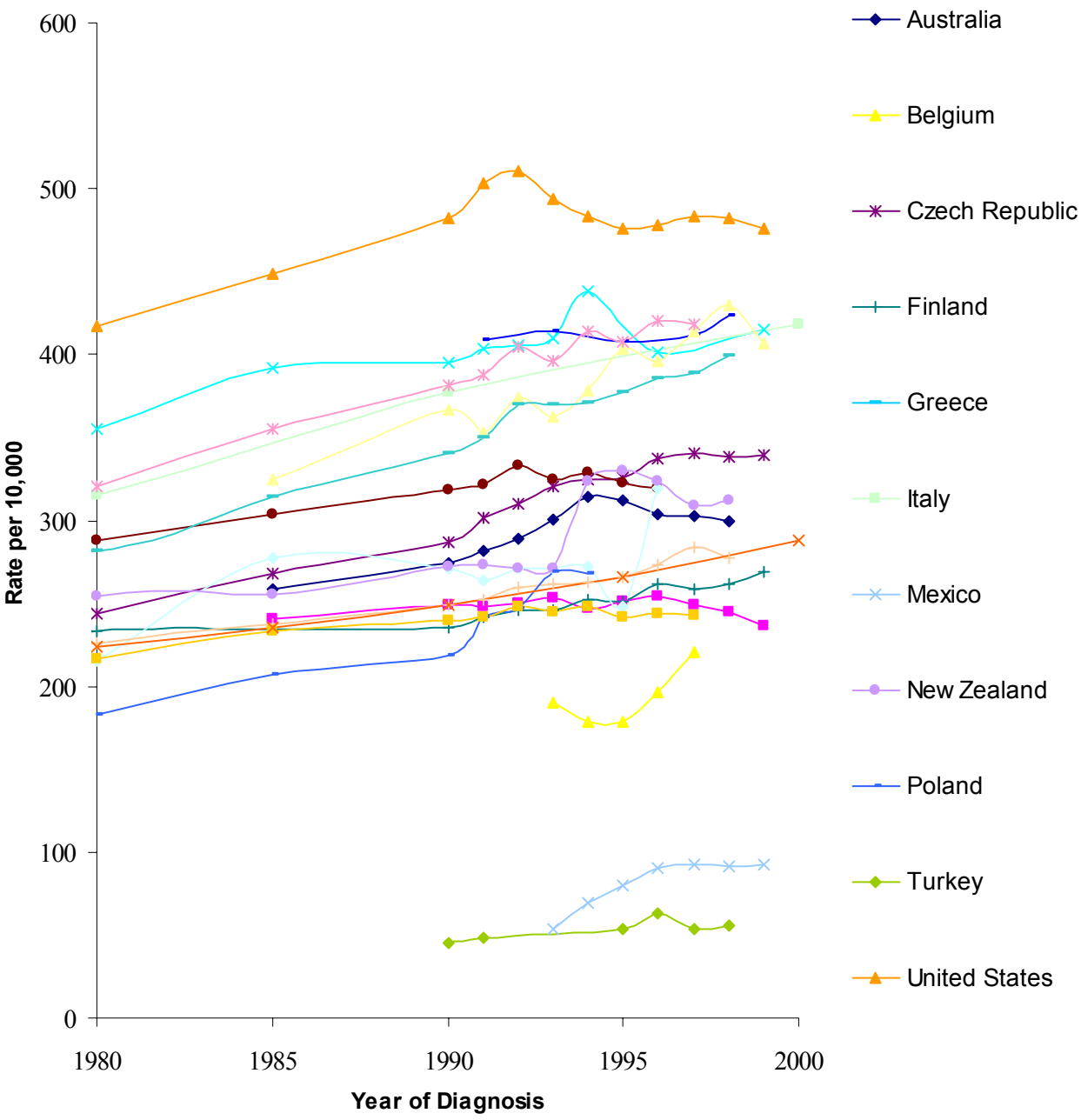
1. The issue of multi-causality and better environmental health analysis is now acknowledged by the Commission. The remaining concern is implementation in policies and regulation.
2. The way air pollution has been handled is an example of a good approach.
3. There will always be other opinions. Should we try to convince everyone or simply appeal to the precautionary principle?
4. Promote meta-analysis instead of repeating studies.

Afternoon session

Case 1: Cancer and environmental links

Professor Dominique Belpomme, University of Paris, Chairman of ARTAC, European Georges Pompidou Hospital

Since 1980, cancer incidence in many countries has increased. Figure: Cancer incidence in the world.



In France, the cure rate is 45%, but there is no increase in five year survival for advanced cancers in the last 20 years. One out of four cancers is caused by tobacco. Smoking is decreasing, but cancer is increasing, and there is a big difference between men and women. See figure next page.

Incidence and mortality of tobacco smoking-related cancers. 2000. France

	Men (M)		Women (W)		Total (M+W)	
	Total	Linked to tobacco	Total	Linked to tobacco	Total	Linked to tobacco
Mortality	92 311	33 231	57 734	2 309	150 045	35 540 **(23,6%)**
Incidence	169 025	57 969	117 228	4 689	278 253	62 658 **(22,5%)**

➢ 1 cancer out of 4 is tobacco smoking-related

www.artac.info

There is a growing incidence of cancers partially or totally caused by physio-chemical factors, in the period 1980-2000 in France:

Partially linked to tobacco	Bronchus (M: +10%: W: x2) Kidney (x2) Bladder (+22%) Pancreas
Non linked to tobacco	Breast (x2) Prostate(x3)
Non linked to tobacco / alcohol / obesity	Leukaemia (+30%) Nervous System (x2) Lymphoma (x2) Children (+30%)
Asbestos	Mesothelioma (x2-5)
Pesticides	Testis (+40%)
UV	Melanoma (x3)
Radioactivity	Thyroid (x2-3)

In Denmark the increase in testicle cancer was even larger than in France. These results can only be partially explained by better screening, as has also been shown in Norway. For several cancers there are no screening tests in use, and other cancers already increased before screening tests were generally applied. And early detection normally leads to lower mortality rather than to higher incidence.

Ageing plays a role: the general opinion is that we see more cancers because people get older. But exposure is also longer. And we see higher cancer incidence at all age categories. In the USA, as well as in Europe, the growth rate for childhood cancers incidence is on average at 1% yearly over the past 30 years.

Carcinogenesis needs a critical number of mutations (3 to 6). A mutation is always induced by environmental factors. A sequence of mutations is alternated with promotion factors. Except for smoking, all classical lifestyle-related factors are not mutagenic. Most of them act as promoters or co-carcinogens. Lifestyle, apart from smoking, is a necessary but insufficient factor:

- Alcohol (co-carcinogenic)
- Ingestion of animal fats (mono-unsatured fatty acids): lack of proven epidemiologic link (IARC)*
- Obesity: proven epidemiologic link
- Hormones (contraception, post menopausal treatment)
- Stress
- Sedentary

*International Agency for Research on Cancer

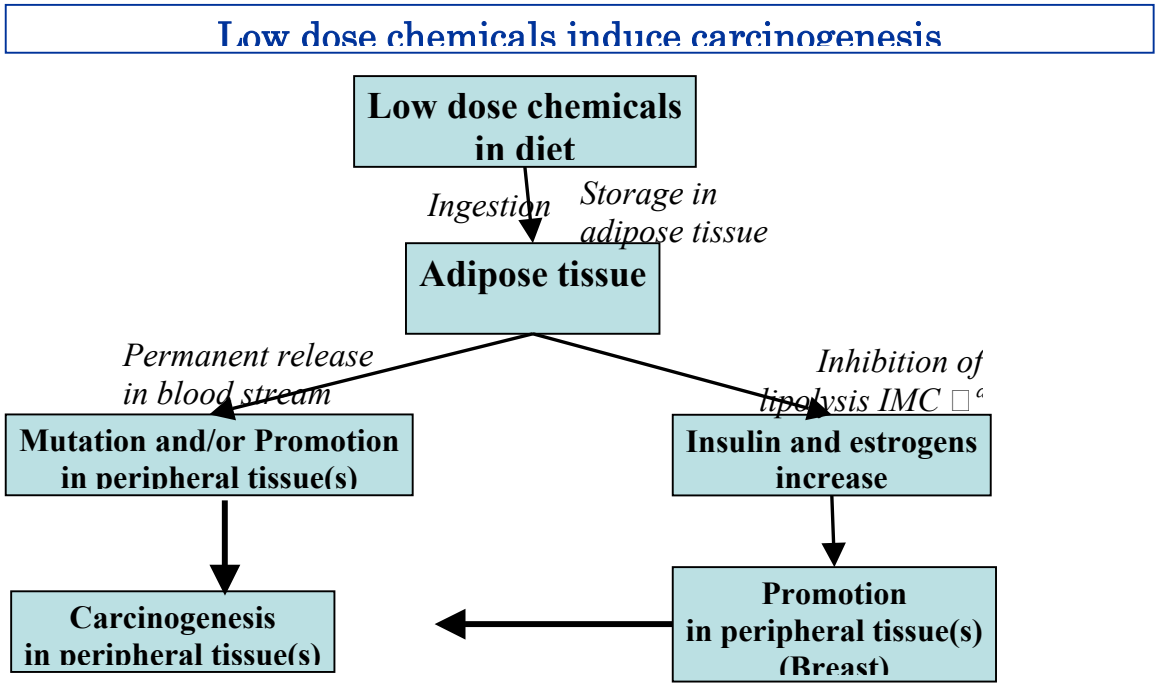
Philippe Irigaray, PhD, Biochemist, CNRS-ARTAC

Irigaray continues: a certain dose intensity is not required, but multiple repetition of doses, i.e. duration of exposure is important to induce carcinogenesis. Xenomolecules incorporated in organism are primarily hydrophobic and bio-accumulative. Due to their lipophilic properties, they are mainly concentrated in lipids.

An example: a common food pollutant, benzo[a]pyrene, inhibits adipose tissue lipolysis and causes weight gain in mice. Chronic administration of B[a]P in mice on normal diets leads to significant weight gain despite no change in food intake.

(Irigaray P, Ogier V, Jacquenet S, Notet V, Sibille P, Mejean L, Bihain BE, Yen FT. Benzo[*a*]pyrene impairs *b*-adrenergic stimulation of adipose tissue lipolysis and causes weight gain in mice: A novel molecular mechanism of toxicity for a common food pollutant. *Febs J.,* 273: 1362–1372, 2006.[a])

The same mechanism of lipolysis inhibition leads to an increased cancer risk, as shown in the following diagram.



- Lassiter RR, Hallam TG. Survival of the fattest: implication for acute effects of lipophilic chemicals on aquatic populations. Environ. Toxicol. Chem., 1990, 9: 585–595.
- Geyer HJ, Scheunert I, Karl R. Correlation between acute toxicity of 2,3,7,8 tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) and total body fat content in mammals. Toxicology, 1990, 65: 97–107.
- Geyer HJ, Schramm KW, Scheunert I. Considerations on genetic and environmental factors that contribute to resistance or sensitivity of mammals including humans to toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) and related compounds. Ecotoxicol. Environ. Saf., 1997, 36: 213–230.
- Hutcheon DE, Kantrowitz J, Van Gelder RN, Flynn E. Factors affecting plasma benzo[a]pyrene levels in environmental studies. *Environ Res*., 32: 104-110, 1983.

In an article to be published by Belpomme D., Irigaray P. et al. “Increased cancer incidence: the environmental impact on carcinogenesis.” The conclusion is that complementary action of lifestyle and environmental factors are together accountable for co-carcinogenesis promotion probably in a 50-50 ratio. Smoking and environmental factors are accountable for mutations in a 25-75 ratio respectively.

This leads to the hypothesis that one out of two cancers is caused by environmental factors.

This research was done in cooperation with Boston University.

Prof. Dr. Nic van Larebeke, Ghent University

The probability that mutations occur in 6 genes is 1 in 10^{-30}; when the probability for each gene mutation doubles, the total probability for 6 gene mutations is 64 in 10^{-30}: so we see a 64-fold increase. Complicated organisms need a low mutation rate; with a ten times higher gene mutation rate evolution would have only led to the level of the banana fly!

Low doses of radiation are relatively more efficient when mutation frequency is compared to exposure intensity. This is due to an increase in repair capacity at higher doses. After another increase the repair mechanisms become exhausted and damage increases again, until after a very high dose the cells simply die and nothing happens. See figure 3.1.

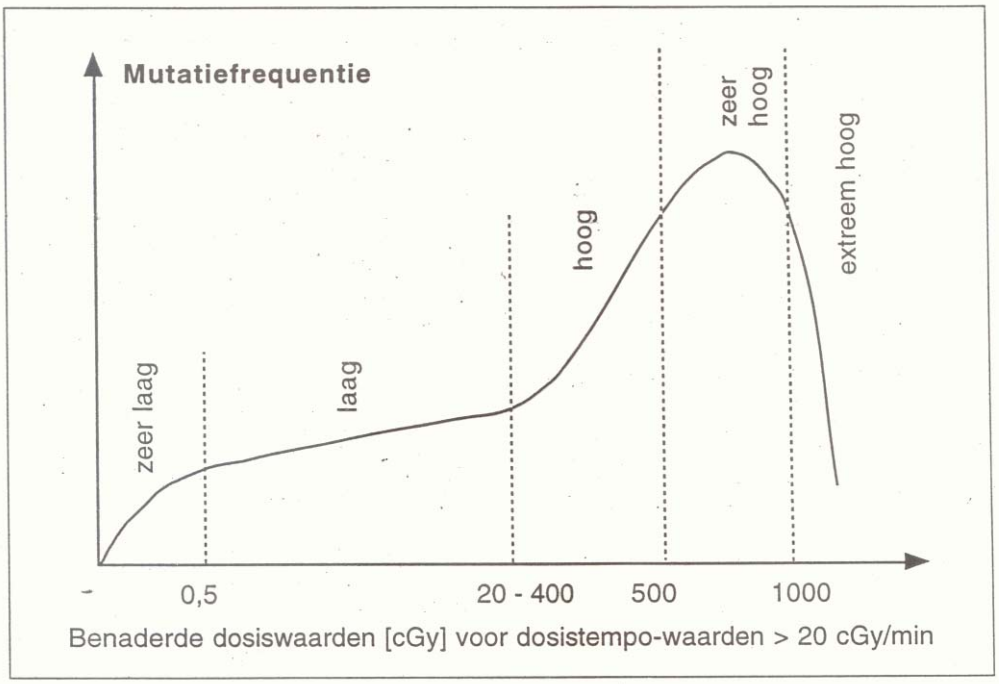


Fig. 3.I. : Mutatiefrequentie in functie van dosis van ioniserende straling voor low-LET straling, (X- en gammastralen).

Columbia University found, unexpectedly, that irradiation of 10 % or 100% of cell nuclei has the same result. This is explained by communication between cells.

Another experiment by the University of Washington showed that dicentrism in cells – destabilising the chromosomes – is induced by only a small dose which triggers the effect.

Some chemical compounds are binding on the same receptors as natural hormones, where they can activate the cell at lower natural hormone levels than without the binding of these chemicals. The cumulative effect of several different chemicals has been demonstrated: while each of 11 compounds did not yield any effect, the combination itself showed a rather high effect.

An experiment done by Professor Guillette with sex reversal in crocodiles showed that very low concentrations of compounds led to a shift of more females. This effect was not dose dependent.

BPA hormone (Bisphenol A, a xenoestrogen) increases cell proliferation in prostate cancer only in low doses. The possible explanation is that in higher doses the effect of binding to specific receptors might disappear.

John Newby, University of Liverpool

Presentation: “Environmental Influences in Cancer Aetiology”, a study done by John A Newby[*] and Dr. C Vyvyan Howard[**]

*** Department of Human Anatomy and Cell Biology, Faculty of Medicine, The University of Liverpool, UK. jackan@liverpool.ac.uk**

**** Centre for Molecular Biosciences, University of Ulster, UK. v.howard@ulster.ac.uk**

Cancer incidence and prevalence

- The highest cancer burden is in the developed world (Stewart and Kleihues, 2003, Shibuya et al 2002)
- The incidence of cancer in Europe represents over 25% of the world cancer burden (Bray *et al* 2002). Cancer Research UK estimates that around 2% of the UK population (1.2 million) are alive with a diagnosis of cancer
- WHO suggest that worldwide cancer rates are set to increase by as much as 50% by the year 2020 unless further preventative measures are put into practice (Frankish 2003)

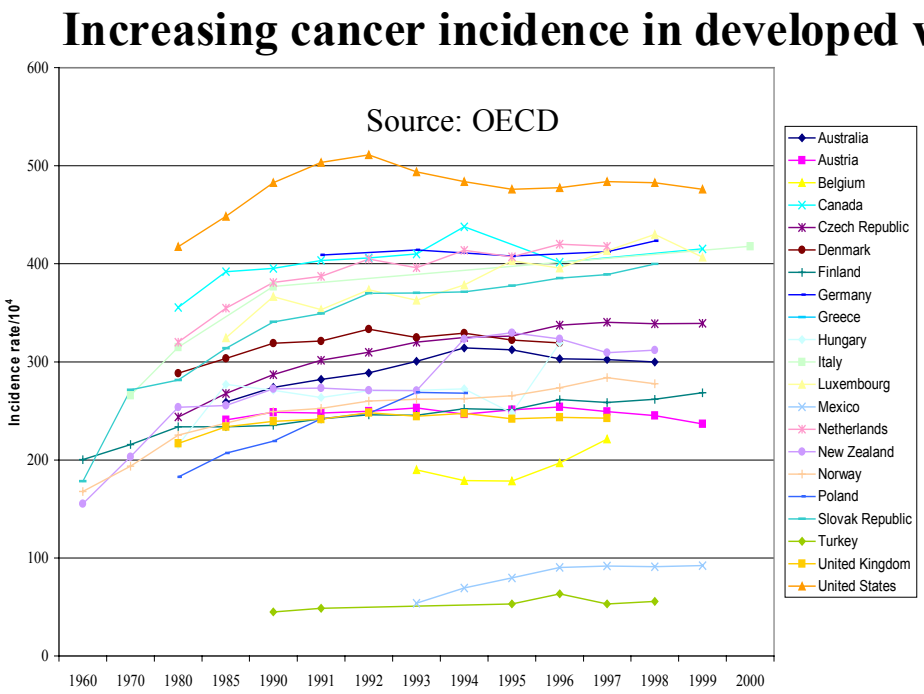
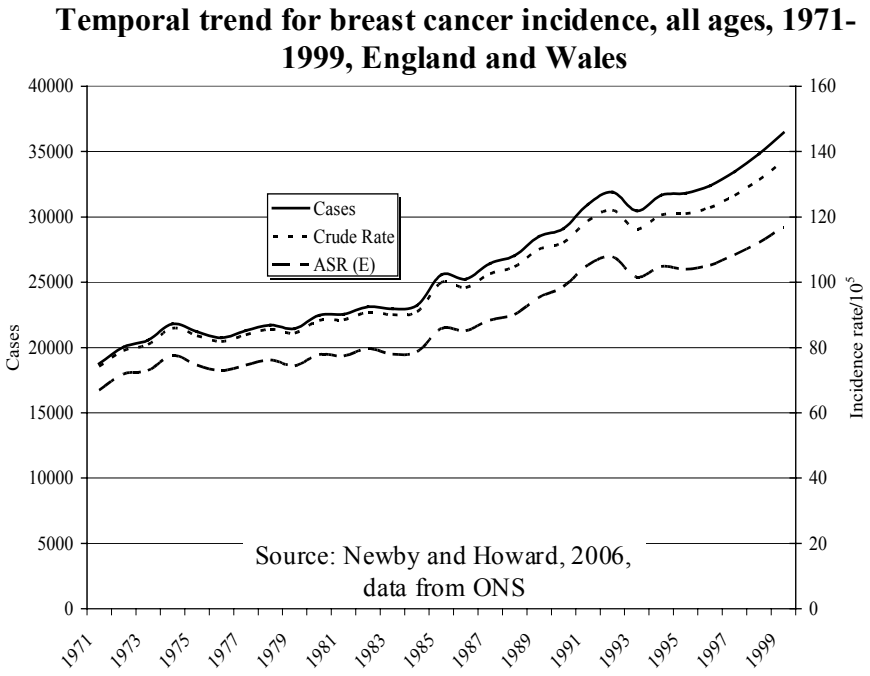


Figure Cancer incidence in developed world



Cancer: what role does the environment play?

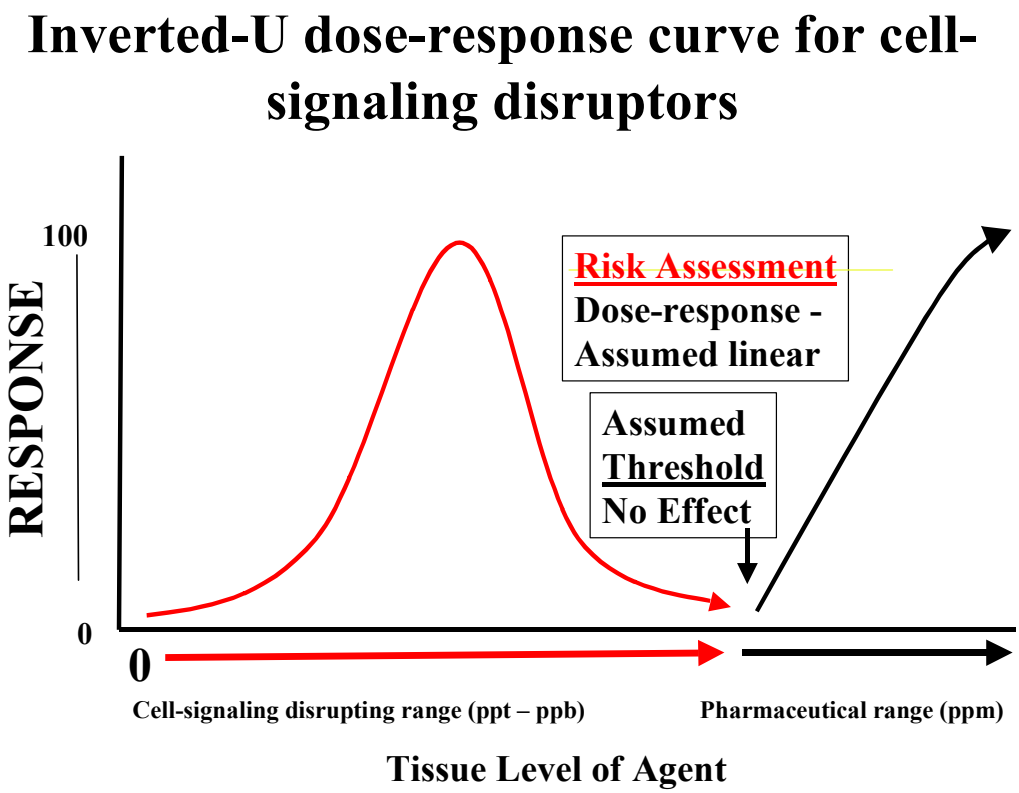
- The environment is implicated in the majority of cancers
- Two recent studies have demonstrated that environmental influences prevail in cancer aetiology
- (Lichtenstein *et al* 2000, Czene *et al* 2002)
- The results from a study observing concurrent cancer incidence in a cohort of identical twins indicated the environment rather than genetics predominates in the aetiology of cancer (Lichtenstein *et al* 2000)
- A structural equation model to get statistically significant estimates of the proportion of genetic and environmental influences for specific tumour sites showed the only tumour site where genetic influence predominated more than environmental influences was for the thyroid (Czene *et al* 2002)

Xenochemical exposure

- Chemical production in the last half of the last century produced halogenated molecules such as organochlorines and organofluorines for use in the plastic and pesticide industries as well as others
- Evolution has avoided the incorporation of such molecules in the mainstream of biochemistry and as a consequence they have a general tendency to be toxic to most forms of life
- Dioxins, pesticides, PCBs and phthalates may have the potential to be endocrine disrupting and interfere with developmental processes that are regulated by oestrogenic hormones and their derivatives such as testosterone

Endocrine Disruption by Xenoestrogens

- Are environmental contaminates at levels too low to be major factors in cancer aetiology?
- Many environmental xenoestrogens when tested show low oestrogenic potency and many xenochemicals have weak carcinogenic potential, BUT
- Low oestrogenic potency should not be used as a marker of the capability of a chemical to cause oestrogenic responses and endocrine disruption. Why?



Input from John Peterson Myers, Ph.D.: Conceptual shifts in toxicology

Conceptual shifts in toxicology: John Peterson

OLD	*NEW*
High level contamination overwhelms detoxification and other defence mechanisms	Low level contamination hijacks control of development
"The dose makes the poison"	"Non-monotonic" dose response curves are common, in which low level exposures cause effects that disappear at higher levels
Only high levels of exposure matter	Impacts caused at what had been assumed to be "background" levels
Focus on adults	Periods of rapid growth and development (prenatal through puberty) are most sensitive to exposure
A small number of "bad actors"	Many chemicals thought safe are biological active and capable of interfering with signaling systems

OLD	*NEW*
Immediate cause and effect	Long latencies are common; fetal programming can lead to disease and disabilities decades later
Examine chemicals one compound at a time	In real life, mixtures are the rule. They can lead to effects at much lower levels than indicated by simple experiments with single chemicals.
Focus on traditional toxicological endpoints like mutagenesis carcinogenesis, cell death	Wide range of health endpoints, including immune system dysfunction (both hyper and hypo-active); neurological, cognitive and behavioural effects; reproductive dysfunctions; chronic diseases
One-to-one mapping of contaminant to disease or disability	Same contaminant can cause many different effects, depending upon when exposure occurs during development and what signals it disrupts. Multiple contaminants can cause same endpoint, if they disrupt the same developmental process.

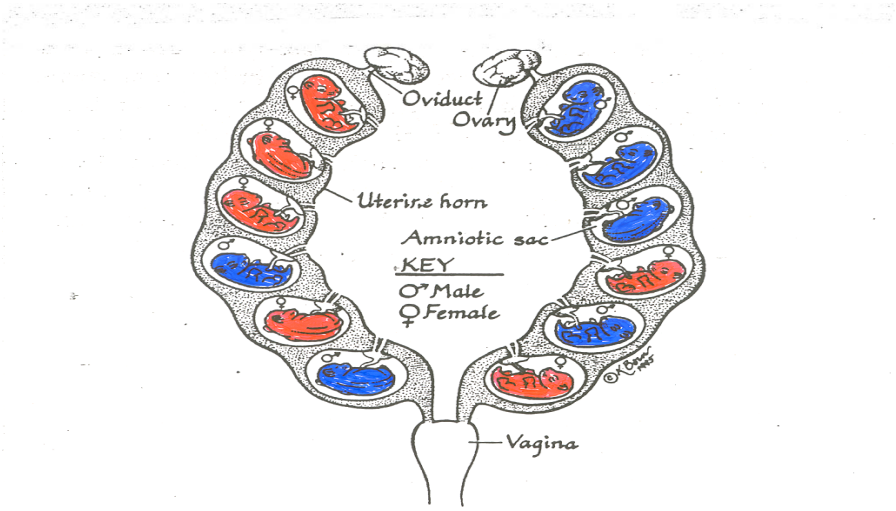
Low-level exposure to xenochemicals

- The intrauterine environment has been shown to be exquisitely sensitive to ambient hormone fluctuations at a few parts per trillion (vom-Saal and Dhal, 1992)
- This is approximately the same concentration that dioxins and other organochlorines are found in serum (Howard and Newby, 2004).
- The high rates of cell proliferation and differentiation render a developing child's cells susceptible to mutagenic and epigenetic alteration (Anderson *et al.,* 2000)

The uterine environment is exquisitely sensitive

- There are critically sensitive periods during organogenesis and environmental exposure to chemicals may have differing or no adverse effects on a developing foetus, depending on precise time of exposure.
- A specific developmental process occurs during a specific period of time.
- Thus, a chemical may have an adverse effect at one point in time but before or after that point in time the chemical may have no effect at all (Dolk and Vrijheid, 2003, Pryor et al., 2000, Hajek et al., 1997)

The developmental process is both sensitive and vulnerable



Behavioral and reproductive differences in mice can be predicted to a remarkable degree by their position, which is related to hormone exposure, in the womb. (Adapted from vom Saal and Dhar, 1992)

Prenatal exposure to endocrine disrupting chemicals (xenoestrogen BPA)

- Oestrogen receptor has been described as promiscuous
- BPA can affect oestrogen homeostasis
- Endogenous oestrogen binds to albumin or SHBG (Sex hormone-binding globulin) in plasma, bound and free oestrogens in plasma are in dynamic equilibrium
- During pregnancy endogenous oestrogens go up but SHBG and albumin also go up

Prenatal exposure to endocrine disrupting chemicals (xenoestrogen BPA)

- Free oestrogen levels in plasma remain fairly constant so oestrogen is not readily bioavailable to foetus (Rang *et al.,* 1995)
- Bisphenol A, PCBs and other organochlorines have been shown to pass directly across the human, primate and F344/DuCrj (Fischer) rat placenta (Hill *et al.,* 1980, Slikker *et al.,1982)*
- Diethylstilboestrol (DES) crosses the primate placenta in an unconjugated form (Soliman *et al.,* 2003, Covaci *et al.,*2002,Sala *et al.,* 2002, Takahashi *et al.,*2000)

Fetal origin of adult disease hypothesis: testicular cancer ***(from*** *Hoei-Hansen et al., 2003, Sharpe 2003, Skakkebaek, 2001, Sharpe and Skakkebaek, 1993)*

- Compounds exhibiting oestrogenic activity may be a factor in testicular dysgenesis syndrome (TDS).
- A collection of male reproductive tract disorders, such as testicular cancer, cryptorchidism, low sperm count and hypospadias, may have common aetiology during foetal life. Each of these disorders is a factor for any of one of the other disorders.
- A factor implicated in aetiology of one of these can also be a factor in aetiology of one of the other disorders

Xenoestrogens and testicular cancer

- The average age of testicular cancer incidence is 25–30 years, suggesting that the exposure to carcinogens was in early life or even *in utero* (Sharpe, 2003)
- The worldwide rate of testicular cancer has doubled in the last 40 years (Huyghe et al., 2003)
- Raised levels of HCB, PCBs, DDE and chlordane found in mothers of those with testicular cancer cases compared to controls (Hardell and Eriksson 2003)
    - The cohorts were born during the time of highest concentrations of POPs in population (1970s).
- The major endocrine disrupter, Vinclozolin (fungicide), has been shown to have an *in utero* effect resulting in maldescent of the testes in neonatal rats (Shono *et al.,* 2004)

Left John Newby

Conclusions

- Increasing cancer incidence affects the whole age spectrum
- The environment is implicated in the majority of cancers
- There is a conceptual shift in toxicology from high dose to low dose effects
- Low oestrogenic potency should not be used as a marker of the capability of a chemical to cause oestrogenic responses and endocrine disruption
- The mixture of xenochemicals in environment consisting of tens of thousands of congeners, enantiomers and metabolites, is beyond the current ability of toxicologists to analyse
- Elucidating cause/effect relationship by epidemiology to specific environmental contaminants is improbable
- Therefore, we should not wait for an unobtainable certainty before action is taken

Discussion

Acceptation and use of the information

- Scientists who are not familiar with this area of science feel they cannot judge the information. Distinguished institutes still use other figures, for example the Queen Wilhelmina Cancer Fund in Holland puts 1% to environmental causes of cancer. This has to be addressed before formulating policies. Genes as well as environmental factors are individually different, except in twins, so how can we distinguish individual susceptibility?
- Prof. Van Larebeke: There are twin studies as well as tissue studies. Scandinavian research showed that less than 20% was inherited, and for example with breast cancer, about 5 to 10% is explained by genes.
- Prof. Belpomme: Our main discovery is that inherited polymorphic genes favour susceptibility to environmental factors, so there is no contradiction. Our findings will be published in a peer reviewed paper.
- Links between smoking and lung cancer should lead to implementation of EU anti-smoking regulation, but for example in Germany this is not the case. Similar for radiation- regulation is

needed where an accident would cause a long-term effect on future generations, while tobacco effect stops immediately. However, the EU is at the moment very reluctant with new regulation.

- All EU countries should stimulate research into the causes of increased childhood cancer.

Prof. Jacqueline Cramer concludes from discussion:

1. Publish peer reviewed articles.
2. Contacts between new paradigm scientists and established bodies are needed.
3. Translate the information into a language that journalists and the broader public can understand.
4. Regulate, implement and stimulate.

We can learn from the experiences with air pollution, in the next session.

Case 2: Health effects of air pollution

Prof. Klea Katsouyanni, Department of Hygiene and Epidemiology, University of Athens Medical School

The effects of air pollution on health became an important issue for public health after the severe air pollution episodes that occurred in Northern Europe and North America in the first 6 decades of the 20th century, to which thousands of deaths have been attributed. The awareness of the consequences led to measures that contributed to a substantial decrease of PM (particulate matter) and other characteristic gaseous pollutants concentrations.

From about 1970 to 1990, the prevailing opinion among scientists and decision makers was that current air pollution levels did not have important adverse health effects. Since roughly 1990, it became evident that the current, relatively lower air pollution levels (mainly ambient particles) had adverse, short-term and long-term health effects including an increase in mortality. The findings came mainly from epidemiological studies. Recently, experimental findings support the epidemiology.

These results had an impact on setting guidelines and standards in the U.S. (Environmental Protection Agency (EPA), the European Union and the World Health Organisation (WHO).

How do we measure PM?

- Black smoke (black particles with mean aerodynamic diameter <4μm)
- TSP (Total Suspended Particles)
- PM_{10} (Particles with mean aerodynamic diameter <10μm)
- $PM_{2.5}$ (Particles with mean aerodynamic diameter < 2.5μm, "fine" particles)
- Coarse fraction (Particles with mean aerodynamic diameter <10 and >2.5μm)
- (Ultrafines <0.1 μm)

Large particles stick in the upper part of the respiratory track, and are therefore less harmful, but counted relatively higher due to their weight. This is why smaller particle standards were proposed.

	% (95% CI) increase in outcome per 10μg/m³ increase in pollutant	
Mortality	**PM10 or TSP**	**Black smoke**
All natural causes (APHEA2, 21 cities, lags 0 and 1; Epidemiology 2001; 12: 521-31)	**0.6 (0.4-0.8)**	**0.6 (0.3-0.8)**
All natural causes (APHEA2, distributed lag models, 10 cities; Epidemiology 2002; 13:87-93)	**1.6 (0.4, 4.1)**	
Cardiovascular causes (APHEA2 , 21 cities, lags 0 and 1; Epidemiology 2005, in press)	**0.8 (0.5, 1.1)**	**0.6 (0.4, 0.9)**
Respiratory causes (APHEA2 , 21 cities, lags 0 and 1; Epidemiology 2005, in press)	**0.6 (0.2, 1.0)**	**0.8 (0.1, 1.6)**

Table: Short-term effects of PM on health. Results from the multi-centre European project "Air Pollution and Health: a European Approach" (APHEA2)

The effects of air pollution on health are often conveniently classified in short-term (days-weeks) and long-term effects, although there is probably a continuum of effects in the time scale, which are not yet fully understood. APHAEA 2 is a network existing since 1992. Peer reviewed results where published and made an impact.

Effect modifier	Low*	High*
Average long-term NO_2	0.19	0.80
Average annual temperature	0.29	0.82
Proportion of population >65 years	0.54	0.76

* "Low" effect modifier level is defined as the 25th percentile and "high" as the 75th percentile of the corresponding effect modifier distribution across cities. The actual levels are for NO_2 40 and 70µg/m^3, for temperature 9 and 14^{0}C, for the proportion of persons >65 years 13% and 16% respectively.

Table: Percent increase in the daily number of deaths associated with an increase of 10µg/m^3 in PM_{10} concentrations, by levels of important effect modifiers (APHEA2, Epidemiology, 2001; 12: 521-

Short-term effects

A 24 hour increase in 21 European cities showed clearly an effect; more days gave an accumulative effect. In the US similar figures were found. Hospital admissions for asthma, COPD (Chronical obstructive pulmonary disease) and other respiratory problems were related to PM 10 and black smoke concentrations in a statistically significant manner (Atkinson et al 2002). The same was found for cardiovascular admissions except stroke (Le Tertre et al 2002).

Long-term effects

There are 5 key studies, of which two US studies were the most influential. The American Cancer Society (ACS) study with 151 cities and 500,000 citizens is one of these. It showed effects at rather low levels (Pope et al 2002):

Adjusted mortality relative risks (RR) associated with 10µg/m^3 change in $PM_{2.5}$:

All cause	1.06 (1.02 – 1.11)
Lung cancer	1.14 (1.04 – 1.23)
Cardiopulmonary	1.09 (1.03 – 1.16)
All other cause	1.01 (0.95 – 1.06)

For example, mortality risk for lung cancer is 14% higher due to a 10µg/m^3 change in $PM_{2.5.}$ A Netherlands cohort study which used NO2 as equivalent for PM 2.5 found similar results. In Hong Kong and Dublin beneficial effects on mortality were seen when air pollution decreased.

37 European scientists wrote a letter to the European Parliament Committee for the Environment on the new draft directive on PM, raising these points:

(The letter sent from scientists with recognized work in the field of air pollution and health, can be found at www.iras.uu.nl)

- Allowance of subtraction of PM of "natural" origin. As these have always been included in the research, this is scientifically unwarranted.
- Although there is adequate recognition of the health effects of fine PM, these are accompanied by recommendations to lower the levels by 20% down to 7ug/m^3 and not by legally binding procedures.
- The "cap" of 25 µg/m^3 is too high, considering the evidence for health effects from the US and Europe and the current levels in Europe. Thus most countries are already below this limit and will have no motivation to take measures.

Fintan Hurley, Institute of Occupational Medicine (IOM), Edinburgh, UK

Prof. Klea Katsouyanni presented two paradigm shifts in our understanding of air pollution and health:

1. From peak level to 'normal level' damage; i.e. health effects are not restricted to air pollution episodes, but occur at 'normal' levels of air pollution also ('daily variations' in air pollution).
2. Long-term effects are more serious than accumulated short-term effects.

I was involved in the methodology for CAFE (Clean Air For Europe). This was a useful and necessary program. Health Impact Assessment (HIA) in CAFE was part of a Cost-Benefit Analysis (CBA) of policy options and scenarios. IOM led on HIA methods within the CAFE CBA team. HIA methods were consistent with best current understanding, and in particular, were based on recommendations from WHO reviews and working groups.

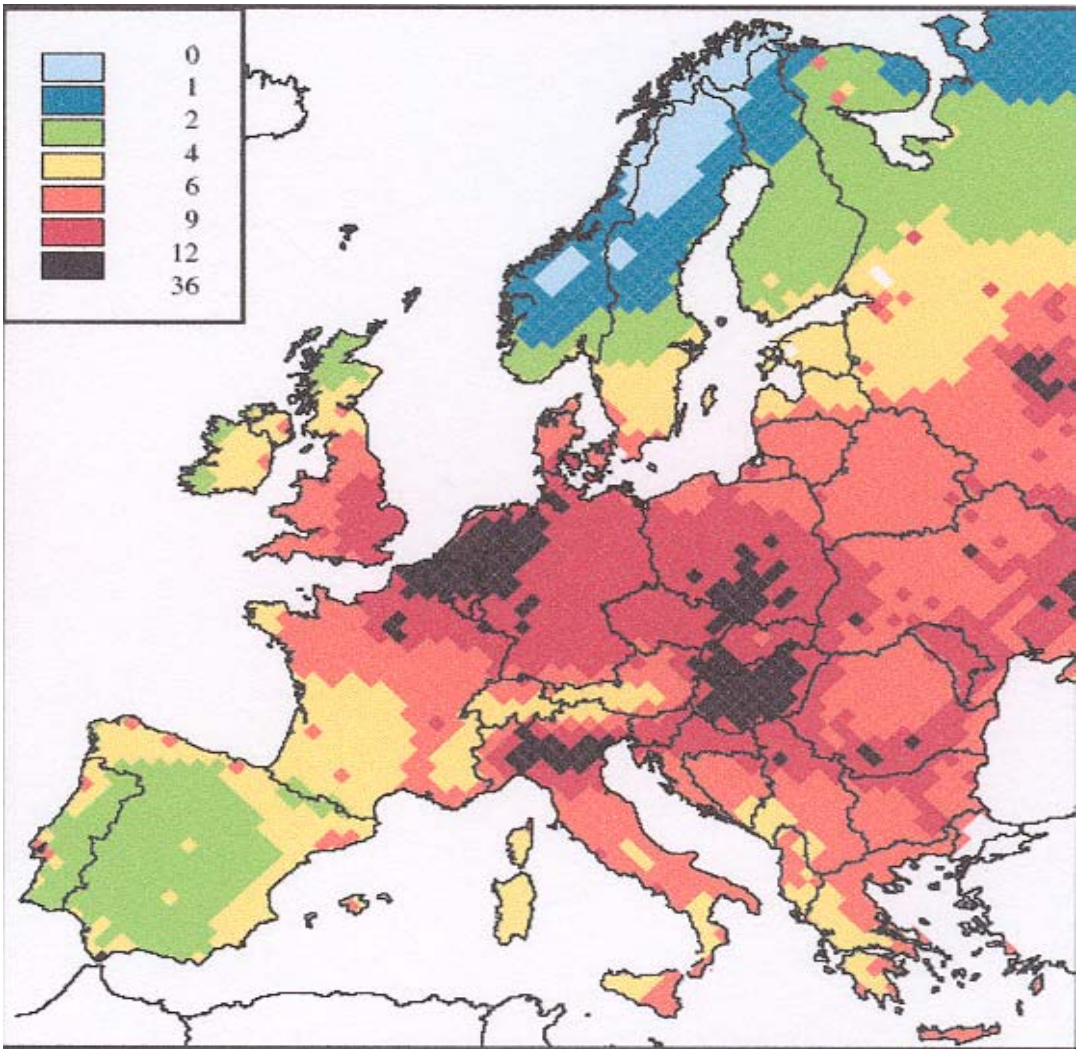
The process was led well by DG Environment, who arranged widespread consultation on the methodology for HIA and CBA. This included a high-level peer review by a group of US scientists. The final recommendations on regulating particulate matter (PM) are not adequate, but it seems that proposals from DG Environment were diluted seriously by the Commission as a whole.

HIA results showed, as expected, that by far the most important health effect was the impact on mortality (or on life expectancy) of long term exposure to ambient particles.

See the figure next page: Estimated effect of anthropogenic PM2.5 on life expectancy in months. From calculations carried out by IIASA in Vienna.

We tried to put a money value on mortality and morbidity risks, recognising there is no safe level. The results are summarised clearly in the Section 7.4.of the Commission's own Staff Paper:

http://europa.eu.int/comm/environment/air/cafe/pdf/ia_report_en050921_final.pdf



The Cost Benefit Analysis showed that benefits of a 20% reduction in $PM_{2.5}$ across the EU-25 outweigh the cost by a factor 6 - 23. An analysis of estimated marginal costs and benefits of further reduction, i.e. CBA of going from 20% to 25% reduction in $PM_{2.5}$, again showed benefits of further reductions being much higher than costs.

Input from Prof. Brunekreef (not present)

Now I show you some slides from Bert Brunekreef from the Institute for Risk Assessment Sciences from the University of Utrecht about 'Manufactured uncertainty'. We need to know the *nature* and the *direction* of uncertainties. Apart from uncertainties directly connected to the scientific work, in the PM case there were uncertainties created by industry lobbyists, by the European bureaucracy and in the popular press. In the case of particulate matter (PM) we faced strong attacks on the integrity of scientists by the popular press, with slogans such as 'the PM panic machine'. In this way the issue of uncertainty was used to obscure the fact that we know a lot about air pollution and health. For example there are uncertainties in the HIA/CBA analysis above, but the size of the difference between estimated benefits and costs is very big, and that gives great confidence in the economic case for reducing particulate air pollution.

Prof. Cramer concludes: scientists agreed to a certain point, but then the lobby machine started.

Dr. Med. Stephan Böse O'Reilly (German Network – Children's Health and Environment; Paediatrician, Specialist in Environmental Medicine, Master of Public Health post grad.):

"Financial burden to the German health care system caused by environmental hazards for children in Germany."

This is a first presentation of ongoing work with the University of Cologne, mainly Dr. Andreas Gerber (Institute of Health Oeconomics). Environmental Tobacco Smoke (ETS) is the main indoor pollutant in Germany. As cancer in children is relatively rare, it does not contribute so much to health costs as other diseases.

Hazards studied were:

- ETS: 25% pregnant women smoke and 50% of children are exposed to ETS at home
- Accidents: Traffic related accidents

Connected diseases are:

- Asthma bronchiale: main chronic disease of children, 6,5% prevalence
- Otitis media (ear infection): frequent disease, 30% in the first two years of life
- Lower respiratory tract infections
- Preterm and low birth weight

Number of victims of traffic accidents in 2004 under 15 years:

13.241 children as cyclists

12.359 children as car passengers

9.684 children as pedestrians

The costs were calculated as **Direct costs:** Medication, Outpatient health services, Hospital services and Rehabilitation services. Calculated **Indirect costs:** Loss of productivity of the parents. The costs might be underestimated. For example future costs for preterm children were not included.

For accidents, costs included were: hospital, outpatient care, emergency transport, rehabilitation, police, lawyers, court cases, insurances, reproductive costs.

Estimated annual costs in million Euro

Asthma	490
Otitis	90
Lower respir. tract infections	389
Low birth weight	84
Preterms	1,157
Accidents	1,022

Burden of disease

Disease	Risk factor	Incidence of the risk factor	Relative risk [1] /Odds ratio of the risk factor	Incidence of the disease	Population 2003	
					All (in 1.000)	Children (in 1.000)
Asthma bronchiale	ETS	50% (<6 Y.)	1,21	7-13%	82.532	16011 (<18 Y.)
Otitis media	ETS	50% (<6 Y.)	1,62	30% (<3 Y.)	82.532	2.260 (<3 Y.)
Lower respiratory tract infections	ETS	50% (<6 Y.)	1,57	*	82.532	3.766 (<5 Y.)
Low birth weight infants	ETS	25%	2,7	5,5%	82.532	Births: 706
Accidents	Road traffic			23% (<18 Y.)	82.532	16.011 (< 18Y.)

Die Kinderärzte

For asthma, nearly 500 million euro is needed. This amount is not yet related to environmental factors. We recently calculated that the costs of environment related asthma and PM10 could be 100 million euro.

To calculate environment attributable costs, the environmentally attributable fraction (EAF) is calculated:

EAF = (proportion of non-exposed * 1 + proportion of exposed * relative risk – 1) / (proportion of non-exposed * 1 + proportion of exposed * relative risk)

From EAF to Environmentally Attributable Costs

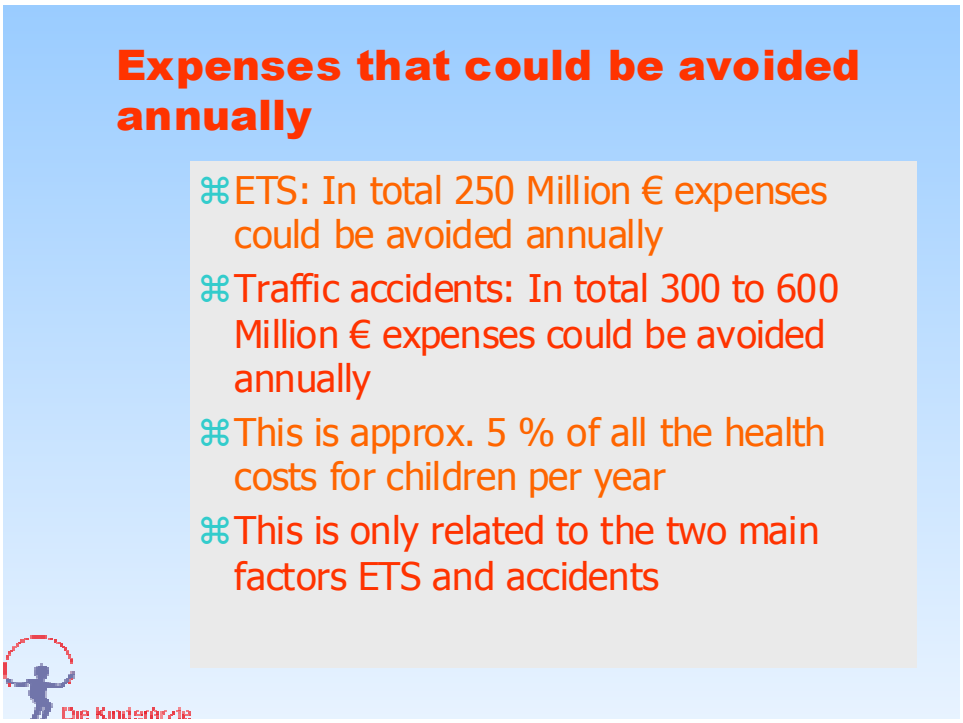
Cost of disease = incidence rate of the disease * EAF * population (children) * cost per case

	Population (children)	Cost per case	Environmentally attributable costs
Asthma bronchiale	10000000	501,44	47.636.483,94 €
Otitis media	2259650	139,44	16.069.896,68 €
Lower respiratory tract infections	3766080	416,12	70.333.581,64 €
Low birth weight infants	706721	2157,43	21.086.691,50 €
Preterm's	706721	20480	86.841.876,48 €
Total			241.968.530,23 €

Die Kinderärzte

For accidents, experts estimate that 60% could be avoided. If Germany would be as good as Sweden, 30% could be avoided. This lead to an estimate of 300 to 600 million of costs that could be avoided.

The total picture:



These are only the two main causes of morbidity and mortality due to environmental hazards. Other risk factors such as noise, outdoor air pollution, chemicals hazards indoors, and others are not calculated. Other diseases such as Sudden Infant Death Syndrome (SIDS), cancer, developmental disorders were not taken into account. Therefore this study is a very conservative estimation. Could it be that up to 10 % of all the health costs for children per year are related to the environment?

Discussion

Learning from the 2 cases

- Work systematically and be patient: the first publication on health effects of low air pollution levels based on research in Athens was in 1996; it was received with laughter. In 1999 the Bilthoven conference, with Bert Brunekreef, still concluded that there were no acute effects of lower levels. Now this has all changed, but we came a long way. It was a matter of luck, of the right persons and of Commission support.
- The industry has promoted diesels for 20 years without debate-- this is difficult. Industry made a big point of uncertainty. We could have been better prepared for these attacks.
- The evidence was based on traditional science and epidemiology and even then it was already very difficult to convince others. In the chemicals case there is the additional problem of new evidence which does not rely on traditional epidemiology and toxicology.
- We need to: 1. examine the uncertainties; 2. stimulate the European debate between the two scientific camps such as Wilhelmina Foundation and Prof. Belpomme.
- Prof. Belpomme: this is too early, we first need our peer-reviewed publications. Science is limited and will not prove everything, and negative epidemiology studies will not prove absence of risks. Traditional institutions will stick to their 1% environmental causes. Industry will say that the science is not good enough. Thus, the main force is now the European societies and citizens. We have to communicate that children are in danger and that loss of fertility will lead to demographic problems. Losing 100 million people will be bad for the economy.

- But it is not just governments and industry we have to convince of the problems of environmental exposure, it is also many scientists that dismiss the idea of low-dose exposure to environmental contaminants as a problem in diseases such as cancer.

Discussion on WECF Draft Recommendations

The draft recommendations are being discussed and participants are requested to give their comments.

Remarks on the draft recommendations are related to reducing pesticide dependency as well as use reduction; eliminate CMRs[1] independent of exposure; reduction of exposure should be related to reducing duration of exposure; and note that low doses and multiple causes have been underestimated in the past. It is also advised to mention using the precautionary principle where uncertainty is visible. Prevention (principle) is not as strong as the precautionary principle, as prevention becomes relevant when harmful effects are proven. Adopt precautionary principle with the aim of preventing disease. NGO's will use "precautionary manner." A paradigm shift in REACH would be to base policy on hazardous nature of chemicals rather than exposure, which is individually different. Noting vulnerability of certain groups is important (noting inequalities—exposure depends on age and place where one lives) and is so far ignored by NGO's. Mention that we do not want to wait for definitive evidence, but are working on it.

Banning all CMR products is asked by some but for others this is too much. 10% of the non-polymers belongs to this group. In most cases exposure reduction is still very important; only for some receptor binding substances this is not working. Introduce the term physical chemical hygiene: on a level of the individual and society we have to reduce the levels of chemical and radiation pollution, as with germs.

The discussion on the draft recommendations could not be concluded due to time constraints.

[1] CMRs refers tosubstances carcinogenic, mutagenic, or toxic to reproduction

Concluding remarks

A new paradigm - or conceptual shift - is evolving in science in the field of environmental effects on health. The old paradigm, using the single-causality principle and traditional methods of epidemiology and toxicology, find that a very small portion of diseases can be linked to environmental factors (in many cases less than 5%). Policy makers base their actions on these assumptions.

However, the new paradigm, based on a multi-causality approach and research that looks at complex interactions from multiple exposures and long-term effects of low dose contaminations, taking into account vulnerable periods, shows a much stronger relation between environmental factors and health effects. For cancer, some research results show that in more than half of all cases environmental factors play a crucial role in disease development. WECF takes this information very seriously and concludes that scientists and politicians should take a closer look at the new information and concepts.

A clear conclusion is that other scientists and politicians who still work from the perspective of the old approach, need to be convinced by this new conceptual framework of the significant relation between environment and health.

It is important to acknowledge there will always be controversies in research results and uncertainties, but it is important to understand the extent and direction of these uncertainties. And to what extent are uncertainties manufactured or enlarged by interest groups to halt policy measures?

We should maintain the precautionary principle, as science has its limitations and full proof can never be guaranteed. Where there is already proof of adverse health effects of environmental factors, urgent measures need to be taken without waiting for additional findings. If it were discovered that environmental factors have no adverse effects when tested under multi-causality and multiple exposure conditions policy measures could be lifted. In the interim, EU policy makers should regulate and implement according to the precautionary principle and at the same time stimulate further research, taking long-term health effects and uncertainties into account, not just short-term economic effects, being cognizant of potentially manufactured uncertainties from interest groups like industry.

Other important recommendations from the workshop to help convince the scientific community and policy makers include:

- Focus on scientific data based on published, peer reviewed sources, and communicate to policy makers and the general public
- Formulate clear, consistent, and convincing messages
- Avoid using the same message for all parties, but adapt them to the particular audience
- Emphasise effects on children, other vulnerable groups, and socio-economic and demographic consequences
- Don’t just focus on the problems, but propose solutions
- Use absolute numbers rather than percents, both of environment related increase of diseases and other health effects, which can speak more loudly than impersonal percentages
- Show (or recommend studies on) costs and benefits, also in absolute numbers, of proposed measures to reduce environmental stressors in light of the new scientific paradigm
- Focus on convincing industry, as they are crucial actors (and forerunners can be allies) and are concerned about their liability and responsibility to the public

Follow up

These draft conclusions and recommendations will be finalised under the responsibility of WECF. WECF will use them as input for the scheduled High-Level Roundtable with European politicians and policymakers, DGs, NGOs, etc. in October 2006, with special concern for gender aspects and children’s health. The information that resulted from this workshop will also be used in other fora, such as at the EU, Pan European, UN, and national levels. WECF plans to continue the work on environment and health in the next year.

WECF thanks Jacqueline Cramer, all speakers and participants for their input and cooperation and will inform them of the outcome of this workshop and the High-Level Roundtable.

WECF, June 2006