

US EPA ARCHIVE DOCUMENT

Biomonitoring in Europe



- Ethics

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ESBIO-Pilotproject

NEWGENERIS-Newborn/mothers

REPROTECT-Alternatives to animal testing



What is Human Biomonitoring?

“Monitoring activities, using biomarkers, that focus on environmental exposures, diseases and/or disorders and genetic susceptibility, and their potential relationships”.

In HBM, the concentration of a pollutant - or its metabolite(s) - is determined in a biological sample, generally blood or urine. In a similar way, other types of biomarkers can help assess the reaction of the human body to environmental pollutants

What is added value of biomonitoring?

Emission

Ambient level

Exposure

Biomarkers of exposure

Internal dose
Biological effective dose

Biomarker of effect

Early response
Altered structure and function

Disorder
Disease

Biomarker of susceptibility

- Within the chain it is **much closer to health effects than environmental monitoring**
- HBM results **integrate the contribution of the different sources and routes of exposure**

air

food

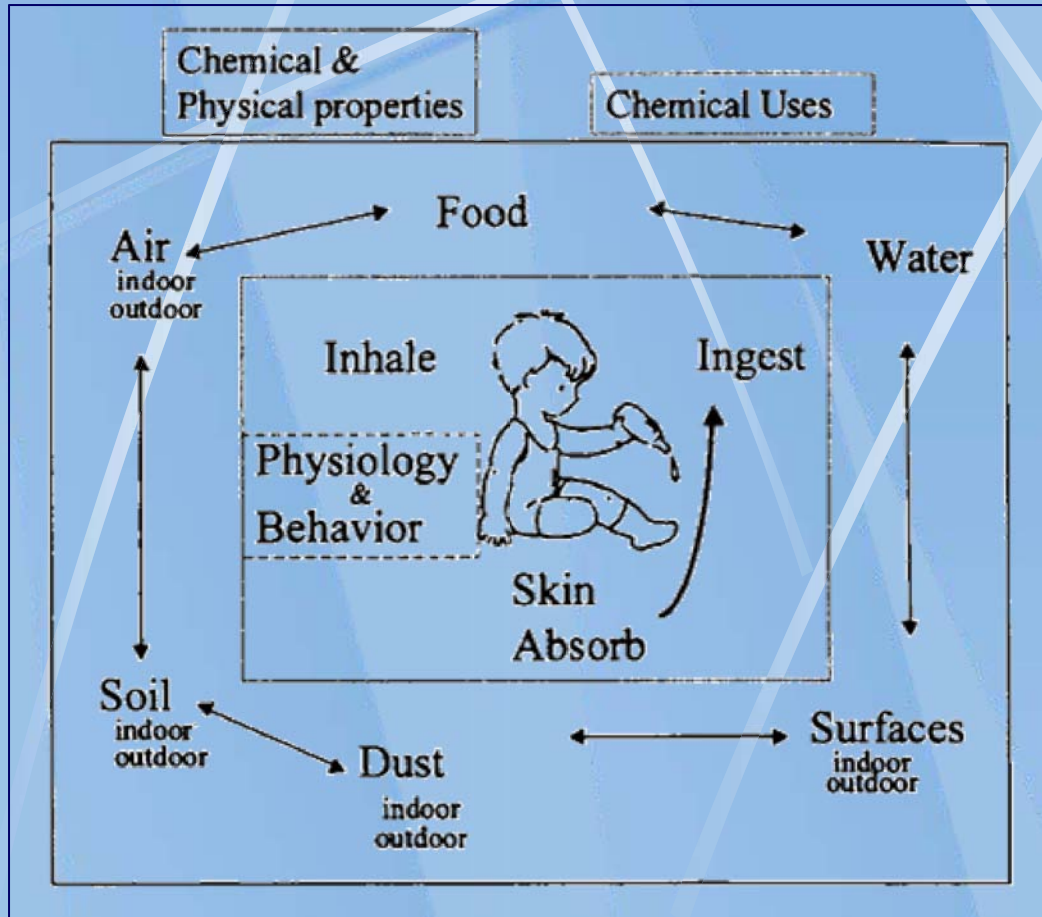
consumables

water

soil



Children as a vulnerable group



From Armstrong et al., 2002

- Large surface in comparison to bodyweight
- Absorption through skin, high metabolism
- Greater penetration across the intestines.
- Consuming various things (dirt)
- Incomplete structures in the brain
- Liver and kidneys are unripe by birth
- Bonestructure under development

Objectives of biomonitoring

- Activities that aim at periodical measurements in order to produce **information on the prevalence of exposure to environmental agents and the related public health impact** with a view to developing and evaluating **policies** that protect health (**SURVEY projects**)
- Activities that aim at improvement of knowledge on causal links between environmental factors and health by **hypothesis generation and testing (RESEARCH projects)**.

Generations

13 families from 12 EU countries – Oct 2005



WWF **DETOX** CAMPAIGN

GENERATIONS 

Results of WWF's
European Family Biomonitoring Survey

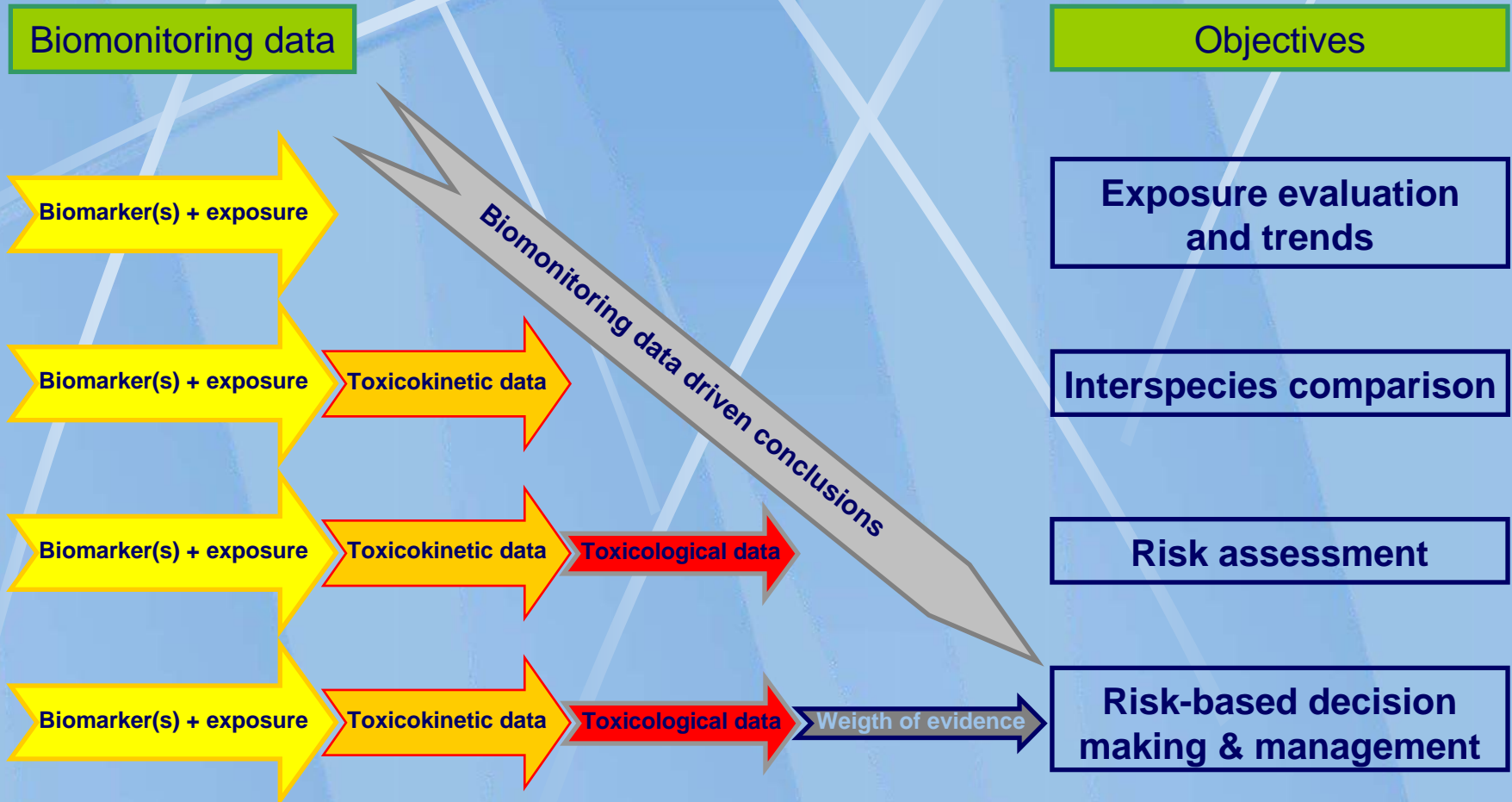
WWF, 2005



Belgium, Denmark,
Finland, France,
Germany, Greece,
Hungary, Italy,
Latvia,
Luxembourg,
Poland, Sweden

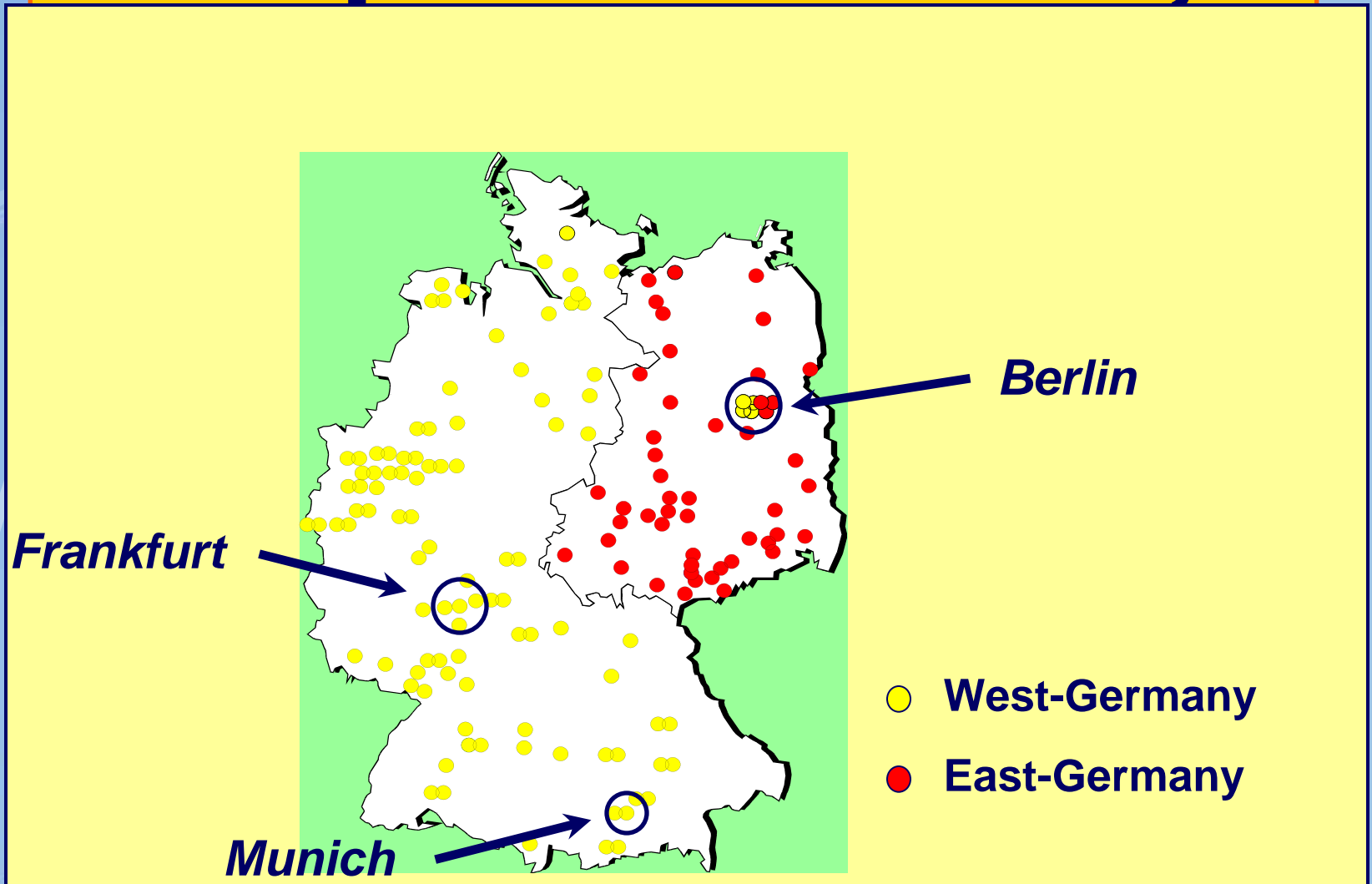


A brief introduction to HBM



(ECETOC 2005)

Sample Points GerES II,

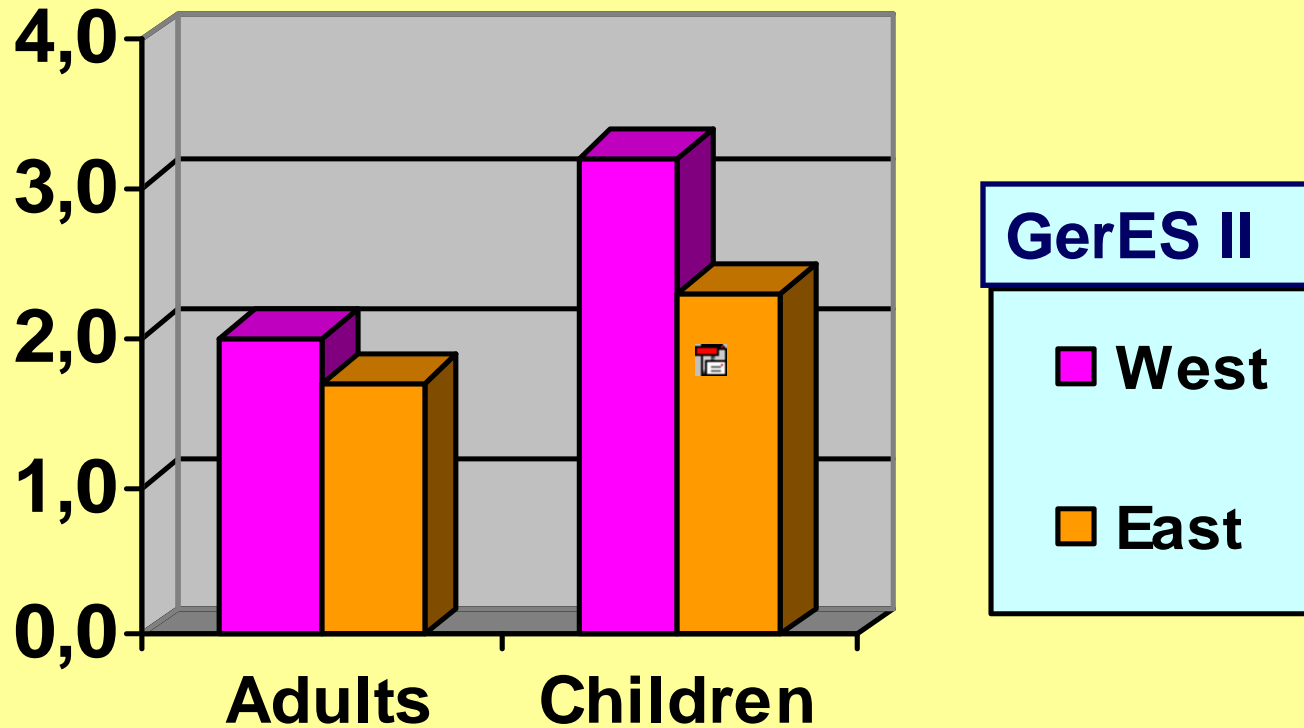


B. Seifert, K. Becker, C. Schulz, C. Krause, Federal Environmental Agency, Berlin, Germany

Ethics Biomonitoring 2007 LEK

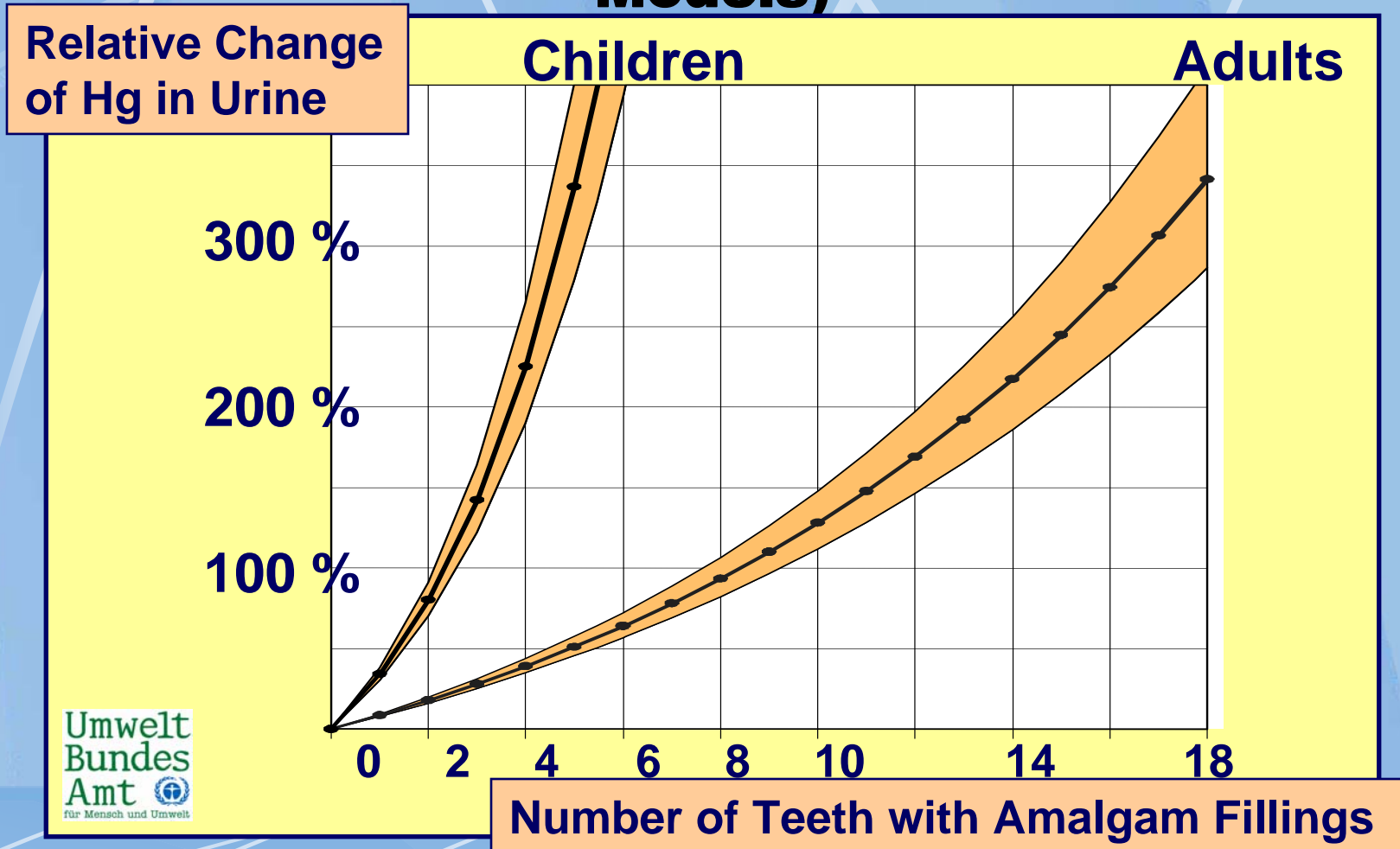
PCP in Urine: Adults and Children

$\mu\text{g/g Crea}$

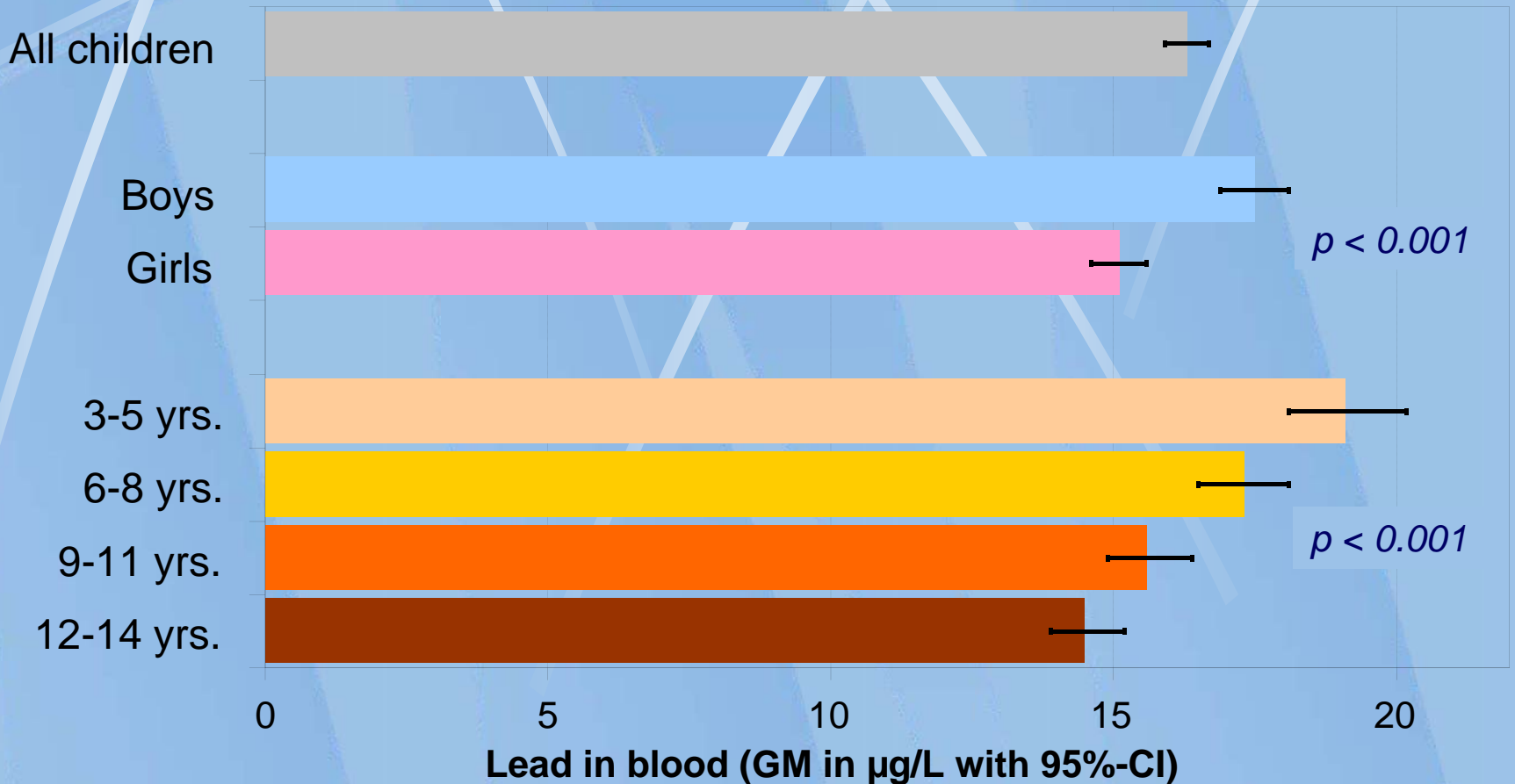


Change of Mercury in Urine as a Function of Teeth with Amalgam Fillings

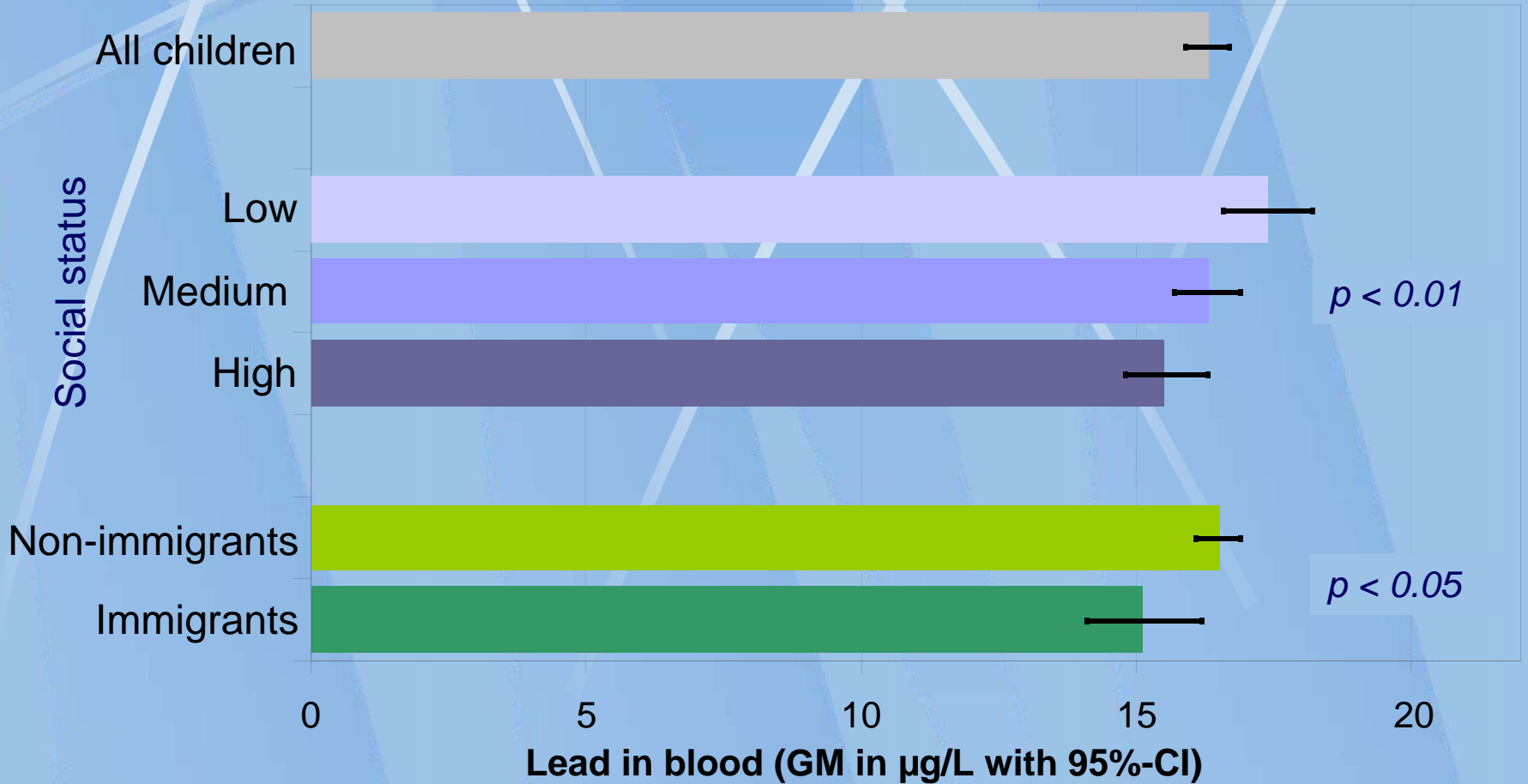
(GerES II 1990/92, Multiple Regression Models)



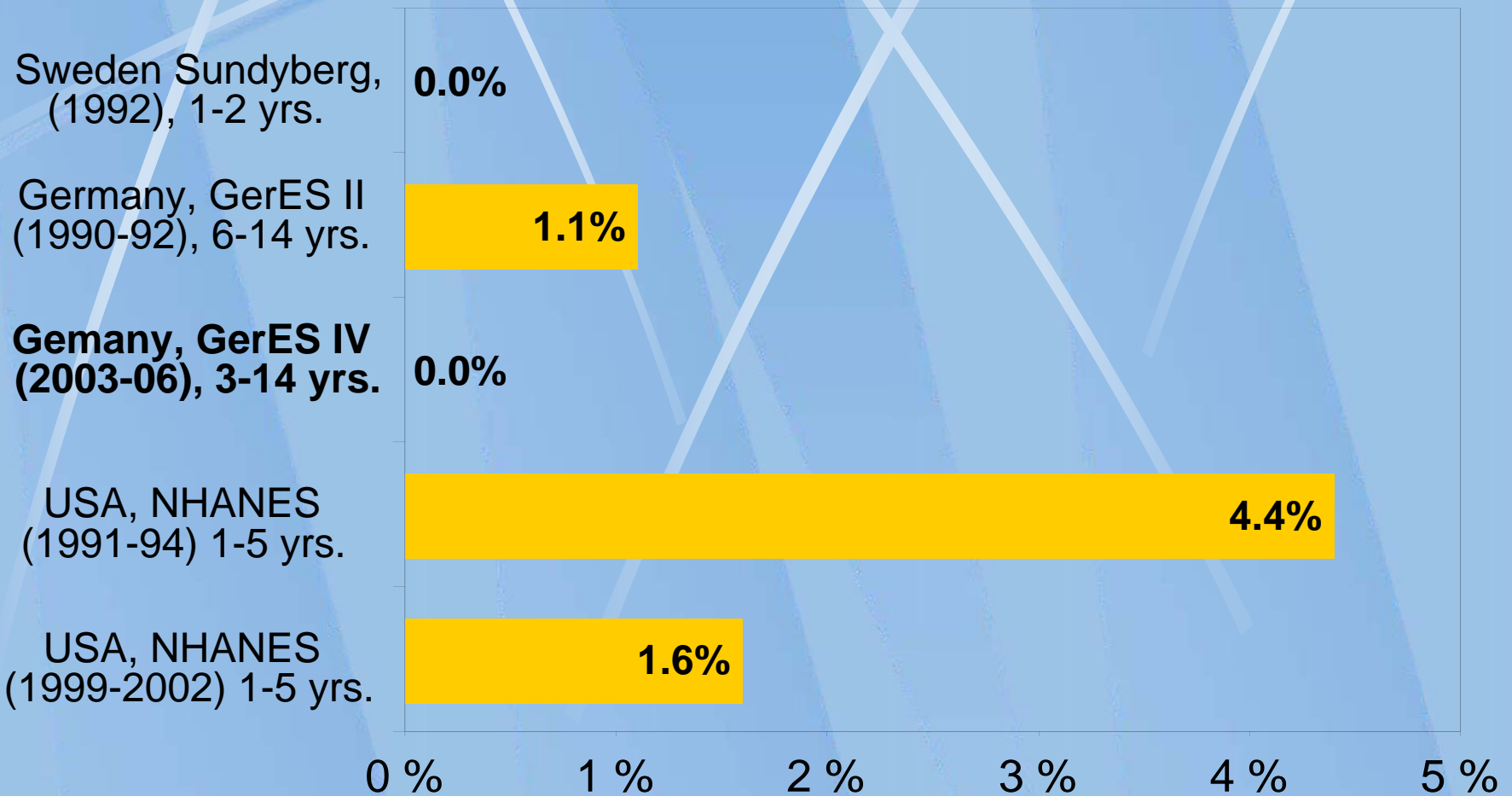
Lead in Blood: Higher Exposed Groups (1)



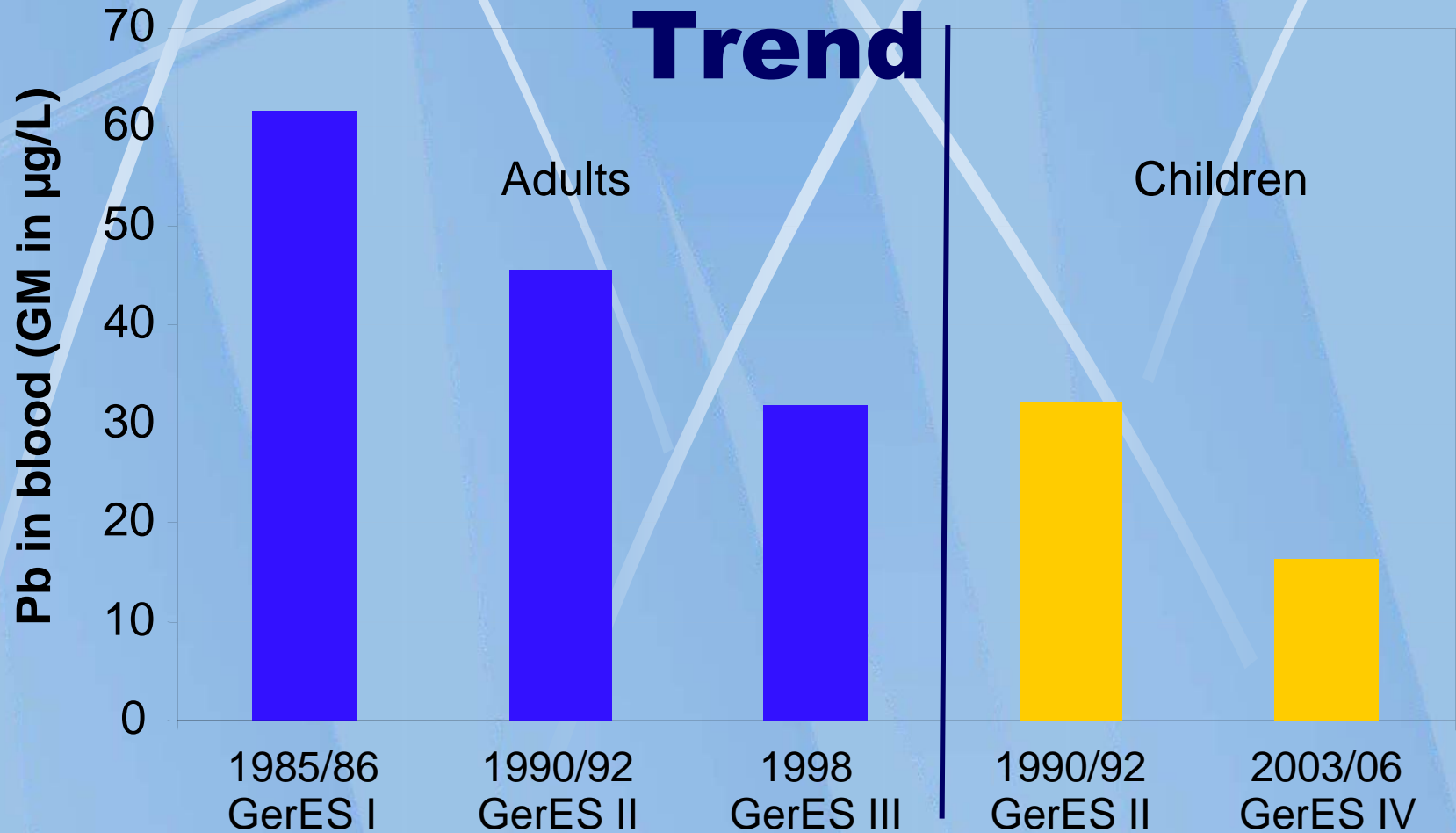
Lead in Blood: Higher Exposed Groups (2)



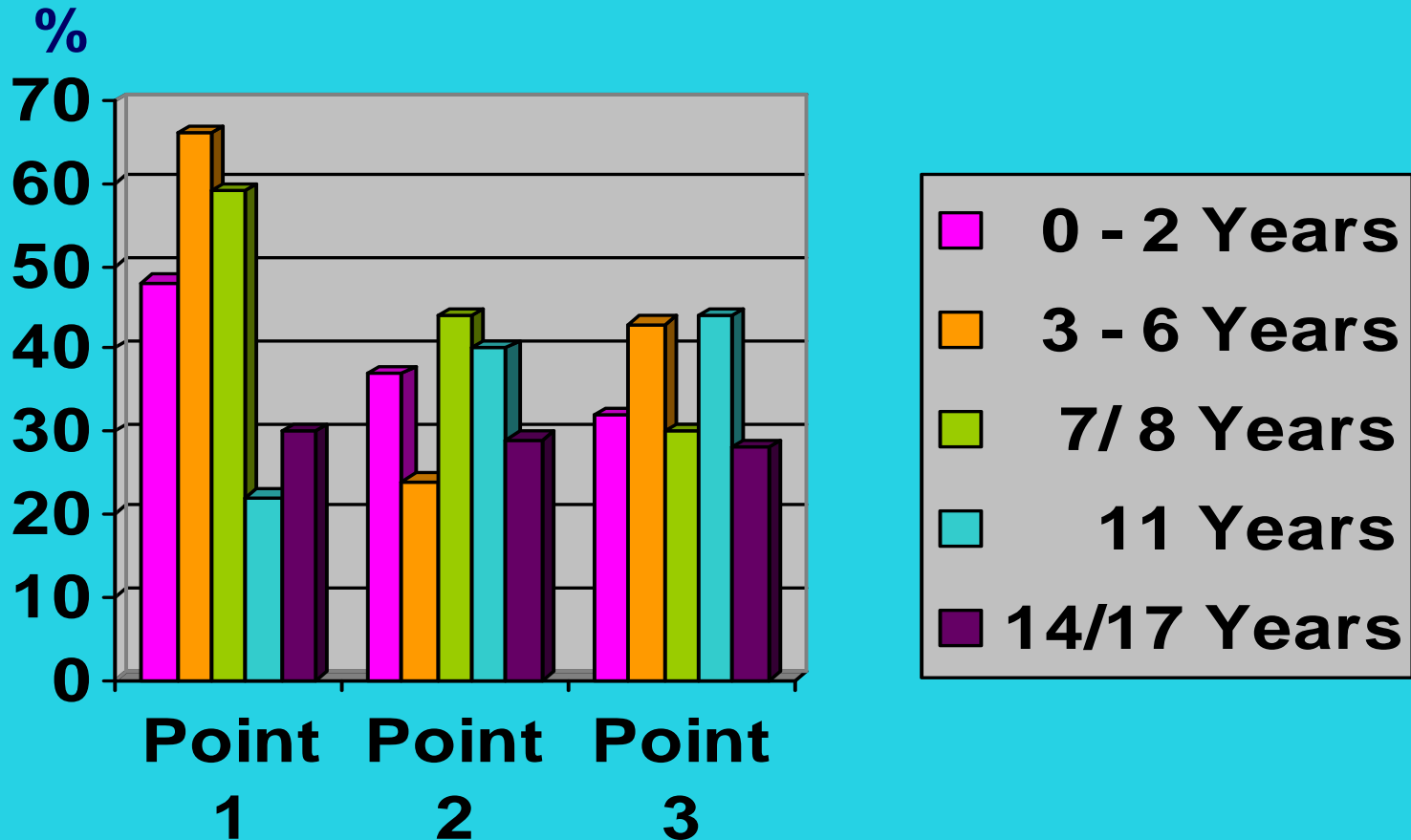
Lead in Blood: Percentage of Values > 100 µg/L



Lead in Blood: Time Trend



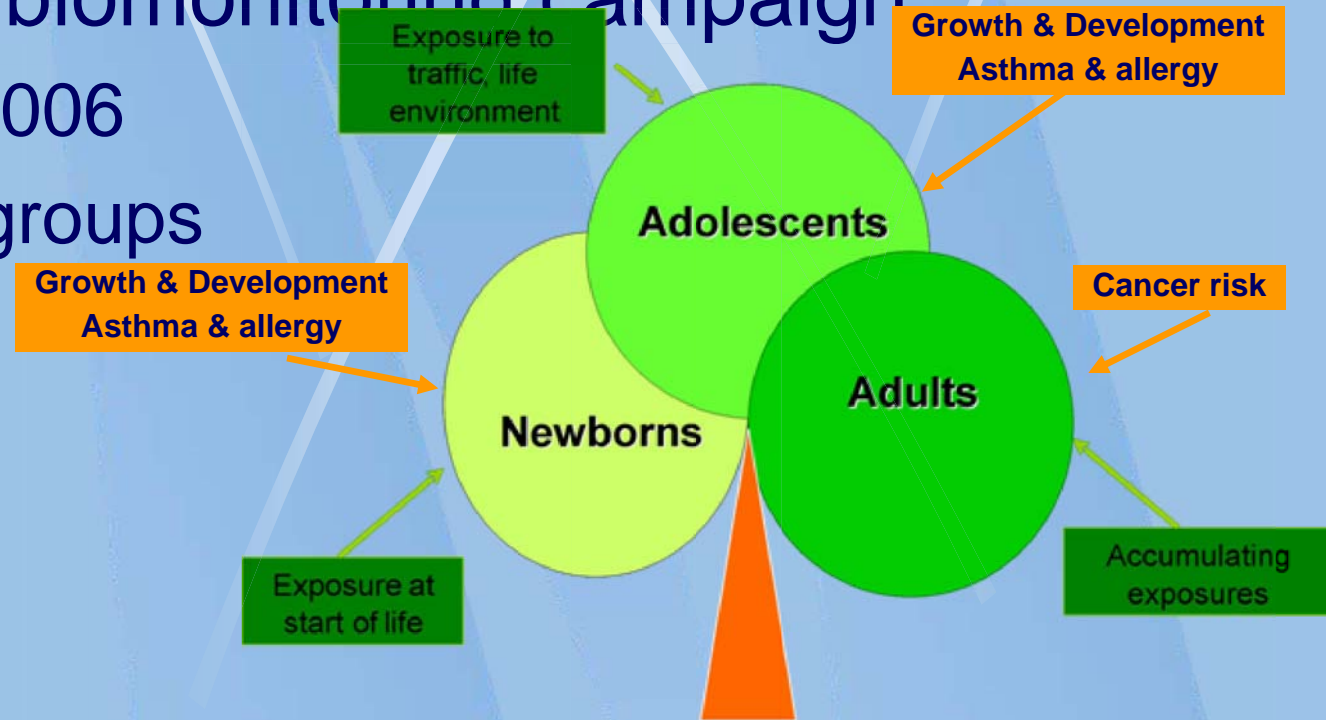
Response Rates in GerES IV Pilot Study (3 out of 4 Sampling Points, Summer 2001)



HBM in Flanders

- Flemish biomonitoring campaign

- 2002-2006
- 3 age groups



Action 3: develop a coherent approach to HBM in Europe

STEP-BY-STEP APPROACH

- Develop comparable protocols addressing initiation, performance and follow-up of biomonitoring activities (2004-2006)
- Develop tools to translate results into a response system : integration scenarios & communication strategies (2004-2006)
- Start an EU Pilot Project by 2007

[http://www.brussels-conference.org/Download/baseline_report/BR Biomonitoring final.pdf](http://www.brussels-conference.org/Download/baseline_report/BR_Biomonitoring_final.pdf)

<http://europa.eu.int/comm/environment/health/pdf/040330biomonitoring.pdf>

EU WIDE PILOT PROJECT

- “Learning by doing” tool
- Test and validate common harmonised approaches for all steps
- Facilitate the establishment of collaboration networks and the sharing of methodologies
- Promote the idea of harmonisation in biomonitoring.
- Identify possible problems linked with such harmonisation

Exposures

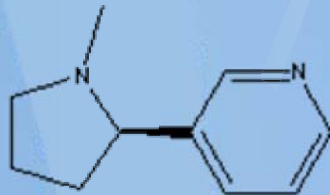
- Heavy metals – lead, cadmium, mercury
- Pesticides – diet, indoor-environment
- Softeners – toys, cosmetics, indoor-environment, diet (wrapping)
- Organic solvents
- Carcinogenic substances

Heavy Metals in urine & blood

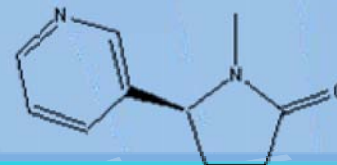
- Lead [blood]
- Cadmium & Mercury [urine & blood]
 - Cd in urine reflects entire body burden, while blood reflects current exposure
 - Hg in urine reflect exposure to inorganic Hg, blood carries also organic Hg (Methyl-Hg)

Nicotine & Cotinine in urine

- Determination of nicotine and cotinine in urine enables a differentiation among smokers and non-smokers (with and without ETS exposure).
- Active and passive exposure to tobacco smoke has an influence on Heavy Metals and PAH-metabolites in urine and marks an important confounder in regard to assess adverse health effects



Nicotine



Cotinine

Tobacco

Reduced birthweight

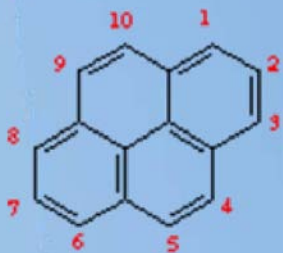
Reduced intelligence

Reduced functions

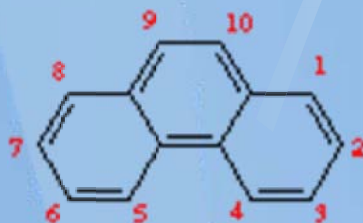


Metabolites of PAHs in urine

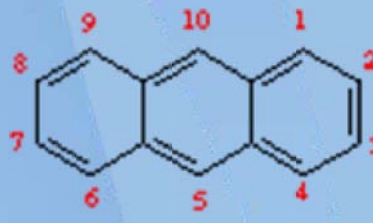
- PAHs represent a large group of compounds, formed during incomplete combustion and are taken-up via inhalation or ingestion.
- Clues to children's elevated susceptibility to PAHs and age-dependent carcinogenesis.
- Validated marker metabolites are 1-OH-Pyrene and isomers of OH-Phenanthrene
- Recently: Phenanthrene-1,2,3,4-tetrol



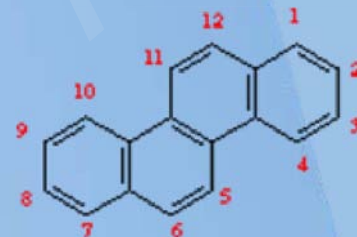
Pyrene



Phenanthrene



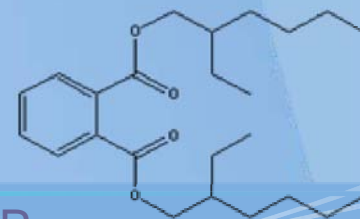
Anthracene



Chrysene

Phthalate Metabolites in urine

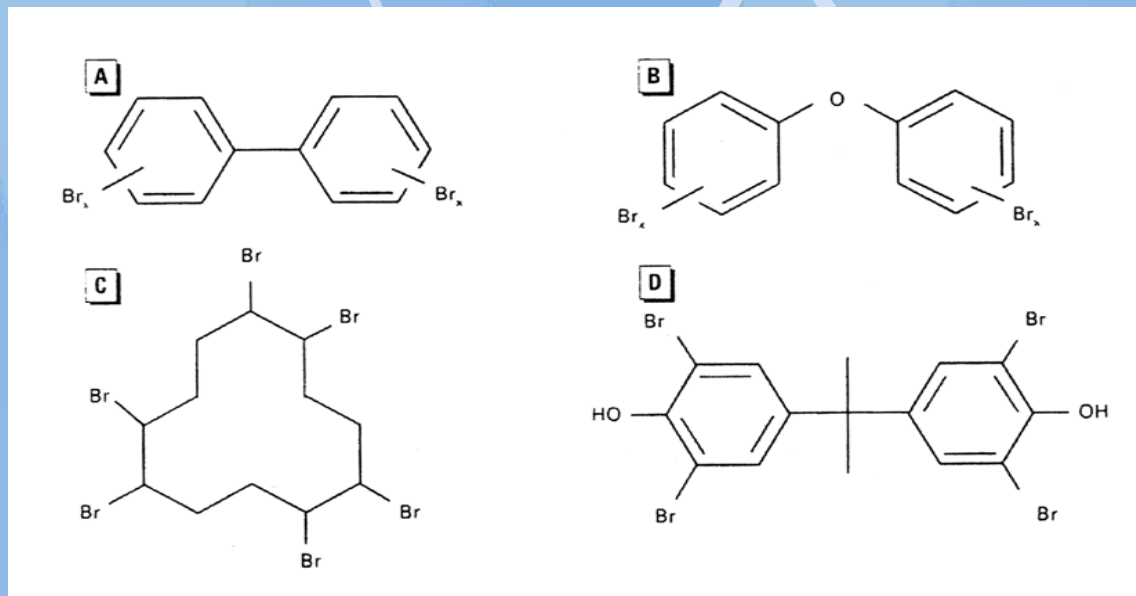
- Di(2-ethylhexyl)phthalate (DEHP) is widely used as a plasticizer for PVC.
 - Other widespread Phthalates are Di-butyl-phthalat (DBP), Butyl-benzyl-phthalate (BBP) & Di-isononyl-phthalate (DINP).
- In animal studies, several phthalates show anti-androgenic activity and exposure to high doses of DEHP, DBP and BBP during the foetal period have produced lowered testosterone levels, testicular atrophy, and Sertoli cell abnormalities in male animals and, at higher doses, ovarian abnormalities in female animals (NHANES, 2005).



DEHP

Brominated flame retardants(BFR)

Chemical structure



A = BBP (polybromerere diphenyls)

B = PBDE (polybromerere diphenyl ethers)

C = HBCD (hexabromocyclodecan)

D = TBBPA (tetrabromobisphenol)

Step by step strategy

- A first step could be to **bring together existing expertise and experiences in the member states with a view of harmonising their way of proceeding through the use of comparable protocols and harmonised data treatment.**
- Before deciding on how to carry out a full scale Europe-wide biomonitoring project relevant to child health, the feasibility of such project should be studied in a **pilot project** that should test out the common harmonised approaches as developed in the working group.
- In order to allow information from biomonitoring programmes to be useful in reducing the disease burden and to identify and prevent new health threats caused by environmental factors, **appropriate tools should be developed for translation of results into intervention strategies and for effective communication with policymakers and the public.**

“The European Environment and Health Action Plan 2004 to 2010”

ESBIO

- Expert team to Support **BIO**monitoring
- 22 experts fra 17 EU memberstates + Croatia
- National governments, research and universities, industry, NGO



- ES BIO = Expert team to Support BIOmonitoring
- Participants of ES BIO

no.	Participant organisation name	short name	country
1	BIPRO GmbH	BiPRO	Germany
2	Flemish Centre of Environmental Technology	VITO	Belgium
3	Federal Environmental Agency	UBA	Germany
4	Institute for Occupational Medicine, WHO Collaborating Centre	NIOM	Poland
5	Instituto de Medicina Preventiva, Faculdade de Medicina de Lisboa	IMP	Portugal
6	University of Copenhagen	UCPH	Denmark
7	University of Leuven	KUL	Belgium
8	National Institute of Public Health Surveillance	InVS	France
9	ENVIRON	ENV	Netherlands
10	State General Laboratory, Ministry of Health	SGL	Cyprus
11	Initiativ Liewensufank asbl International Baby Food Action Network	IL-IBFAN	Luxembourg
12	Oil companies' European organisation for environment, health and safety	SHELL	Belgium
13	Institute for Medical Research and Occupational Health	IMI	Croatia
14	ARPA Lombardia	ARPA	Italy

Why a EU coordinated approach?

● Comparability would contribute to the EU Strategy for E & H by:

- Providing data on **distribution of exposure and related health impact** across Europe
 - definition of **reference values**
 - detection of **spatial differences** in exposure (populations/regions at risk)
 - detection of **temporal differences** in exposure
- Providing policy makers with better information on **control measures** to be taken
 - identification of **priorities** in exposure reduction strategies
 - allowing **follow up** of the efficiency of reduction strategies,
 - allowing a **geographically differentiated E&H policy**

Why a coordinated EU approach?

- Enable a **more effective use of resources** by shared development of tools and strategies
- Enable **more meaningful results** of national surveys as the number of study subjects involved becomes larger
 - *Surveys do not aim at testing hypotheses. To study the cause-effect framework and to document the level of scientific evidence of a cause-effect link properly defined **research studies** are needed. Therefore research projects should be 'grafted' on the surveillance framework where possible.*
- Contribute to detect areas or population groups subject to elevated exposure and - by envisaging appropriate control measures - to better **environmental equity**.

Relevant Ethical Principles in Medicine

Respect for the autonomy of persons: respecting the self-determination of individuals and protecting those with diminished autonomy;

Beneficence: giving highest priority to the welfare of persons and maximizing benefits to their health;

Non-maleficence: avoiding and preventing harm to persons or, at least, minimizing harm;

Justice: treating persons with fairness and equity, and distributing the benefits and burdens of health care as fairly as possible in society.

WP 4

A protocol to be developed at an early stage describing rationale, justification of study, calculation of minimum number of study persons needed for sufficient power of study, recruitment of study persons

Informed consent and information of ethics committees ao before initiation of studies

Biobanking issues to be solved

Incentives for participation, special concerns regarding children

Information about study results, including right not to know

Follow up

Harmonised approaches to steps of recruitment, information, consent, data protection, biobanking, dissemination and data/sample transfer between countries and institutions should be considered eg in future directives/guidelines for human environmental biomonitoring in Europe (and worldwide).

Type of REC:

- Most countries have RECs at a national level (Sweden, Lithuania, the Netherlands, Germany, the UK, Portugal, Ireland, Denmark, France, Estonia and the Slovak Republic. Most of these countries also have regional, local and institutional (universities etc.) RECs.

Legal Provisions:

- Very different sets of national rules have been made in the European member states. Some countries have adopted specific laws as to the review performed by a REC (Denmark, Sweden, Lithuania, and France). These sets of rules differ very much and some are more specific than others. In other countries, for example Estonia, the relevant rules consist of a chapter of the Medical Act.
- In other countries the legal provisions are laid down in several separate laws (for example Spain and Slovakia).

Official opinion of Biomonitoring:

- Germany's national REC (the NEC) has stated an official favourable opinion (Biomonitoring is a vital part in future research). All the other countries have not stated an opinion, except indirectly the UK and Estonia at a regional REC level.
- In UK, the Medical Research Council is part of the funding of UK's major Biobank Project 2005. Also, in Estonia, the Estonian Genome Project, which is a non-profit organization founded by the Estonian Government in 2001, involves the creation of a Gene Bank that will contain health and genetic data for the Estonian population.

Independence:

- Independence in this regard means independent from governmental or state control. In Denmark, Estonia, France, Ireland, Portugal and the UK at local level the RECs are independent. These countries comply with Article 13 of the Helsinki Declaration stating that RECs must be independent from “any kind of undue influence”. However in the UK at national REC level (COREC), Germany, the Netherlands, Lithuania and the Slovak Republic the national RECs respond directly to the state. In Sweden and Spain the RECs are formally independent yet the state retains some control.

Approval/Advisory:

- This topic relates to whether the RECs have to approve of a research project prior to initiation or if they simply offer advice.
- In the Slovak Republic (national and local levels), the UK (national level) and Germany (national level) the RECs only have advisory powers and are not concerned with approving research projects.
- In the Netherlands and Ireland the RECs hold both approval and advisory powers.
- In the remaining countries the RECs have approval powers.

Mission/Task:

- All the RECs have been appointed with similar tasks. These are 1) approval of research projects 2) producing suggestions for legislation 3) monitor RECs at lower levels 4) working as a body of appeal 5) educating the public and taking part in public debates etc.

REC approval of data from third parties:

- Only in Sweden it is required that RECs approve of data from third parties. When Swedish researchers use tissue samples from foreign biobanks/donors, and if the project is initiated in Sweden or is financed with funds from Swedish grants, the project must also be considered by a Swedish research committee.^[1] Yet, the Swedish law is not apparent in cases when samples are received in Sweden from another country – it is for the researchers to estimate whether a permit is needed or not. However the Data Protection legislation of the countries often ensure that data from third parties are being checked and approved of thus these countries have similar rules as Sweden. They are just not encompassed by the RECs.

- [1] Research ethics guidelines for using biobanks. Adopted by the Swedish Medical Council (MFR) in June 1999

The right NOT to know:

- Various ethical/legal instruments recognise this right, for instance the European Convention on Human Rights and Biomedicine and the UNESCO Universal Declaration on the Human Genome and Human Rights.
- Furthermore, in relation to genetic issues and unexpected findings, the Council of Europe has made a **Recommendation**[1], in which it is suggested that unexpected findings only shall be communicated to the person tested if they are of direct clinical importance to the person or the relatives. Moreover, it is stated that Communication of unexpected findings to family members shall only be authorised by national law if the person tested refuses expressly to inform them even though their lives are in danger.
- The foundation and conditions for the exercise of the right NOT to know is uncertain in national laws. Some countries (fore example Denmark), recognise the right *not* to know as a legal right. Moreover, the Estonian Human Genes Research Act, which regulates the establishment of a gene bank (the Estonian Genome Project), expressly states that a gene donor has the right NOT to know his or her genetic data.

● [1] No. R (92)3 Genetic Testing and Screening for Health Care Purposes

Incentives:

- Spain, the Netherlands, Germany, the UK, Denmark and Ireland all have a stated opinion in regard to incentives. Generally incentives are allowed as long as they do not function as actual payment for taking part in a research project and provided that the compensation is not capable of influencing the choice of the research subjects to participate or not. The remaining countries have no official opinion regarding incentives.

Directive 95/46/EC

Article 1: *“In accordance with this Directive, Member States shall protect the fundamental rights and freedoms of natural persons, and in particular their right to privacy with respect to the processing of personal data.”*

- The Directive was initially drawn up as a consequence of modern information technology. In the mid 90s it became apparent that especially computer technology and the diffusion of the Internet would enable transfer and processing of data in a much larger and faster scale than seen before. As a result of this development it became furthermore apparent that the privacy of natural persons could be compromised unwanted.

Sanctions:

- The Directive states that the Member States are entitled to lay down suitable sanctions in their national legislation. This construction makes extended interpretation possible. Most countries make a distinction between administrative and criminal offences (Ireland, Germany, Poland, Sweden, Holland, Portugal and Denmark). Administrative offences are most commonly defined as offences committed during the collection, use and processing of personal data (not deliberately). In case of liability the data controller is being fined. The size of the fine varies from around 3.000 € (Holland, Ireland) to X € depending on the seriousness of the breach (Germany, Poland Sweden, Denmark). Criminal offences involve deliberate breaches of the national data protection legislation or breaches of the national penal code concerning data protection and may result in imprisonment (Ireland, Germany, Poland, Sweden, Holland, Portugal and Denmark all have legislations concerning possible imprisonment for criminal offences).
- The UK, Slovakia, Spain and Lithuania do not have provisions regarding criminal offences and there is no basis for imprisonment for breaches. Spain, the UK and Slovakia have provisions for administrative offences which may result in levy of a fine.

Personal Identification Number (Article 8(7)) of the Directive:

- Most of the concerned countries do have provisions implemented regarding a personal identification number (hereinafter referred to as PIN) and the processing/use of such a number. The only country without a personal identification number is Germany. In Germany there only exists personal numbers used for tax payment and other related issues, but not a general identification number. Thus Article 8(7) of the Directive has not been implemented in Germany.
- Spain, Portugal and Ireland do not have provisions regarding PIN in their legislation regarding data protection. In Portugal the Constitution explicitly states that an “all-purpose” number shall not be used. However, other identifiers, which are not of general application, are established by law in Portugal.
- The general condition for using a personal identification number is the requirement of obtaining consent from the data subject. Moreover, processing of PIN is, generally allowed without the consent of the data subject when prescribed by law or other legal acts (e.g. Estonia and Lithuania).

Processing of data entails various aspects of data protection.

“any operation or set of operations which is performed upon personal data, whether or not by automatic means, such as collection, recording, organization, storage, adaption or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combinatin, blocking, erasure or destruction”

Study planning



Funding



Study approval



Recruitments



Informed assent/consent



Sampling of biological material



Analyses of biological samples



Verification of results



Communications of results



Follow up

Researchers, Statistician, Communities, Participants representatives

Regulators, Politicians, Industry

Research ethics committees (regional and/or institutional)

Study persons, Parents or other relatives, School teachers, Patients organisations, Nurses, Technicians, Paediatricians, Researchers

Researchers, Technicians, Statistician

Researchers, Paediatricians, Nurses, Technicians, Media

Regulators, Communities, Industry, Participants representatives

Researchers, Paediatricians, Nurses, Technicians, Media

Results

An overview on available practices regarding data protection and ethics committees in the form of information sheets on regulation regarding data protection and on regional ethics committees are published at the ESBIO webpage

Most countries comply with Good Clinical Practice Directive and Data Protection Directive by national legislation

Only Germany and Belgium have specified how to handle biomonitoring information from surveys

Rules of biobanking have to be followed unless samples are collected and handled within a single institution

The level of anonymisation is different in selection and communication

Justified concept for dissemination and communication of results within participants of the pilot project

- **Transparency in all steps**
- **Stakeholder involvement**
- **Comply with ethics and data protection**
 - Informed consent with sufficient information about current and future use of samples and data
 - Biobanking, including data and sample sharing
 - Incentives
 - Children
- **Governmental interests/roles**

Acknowledgement

Marike Kolossa and Nils Kirsch, German
Federal Environmental Agency

Kirstine Hvidtved Ekholm, Thomas
Ostermann, University of Copenhagen

PRIVIREAL

ESBIO