Sustainable and Precautionary Risk Assessment and Risk Management of Chemicals

Part I: New Strategies for the Ecological Risk Assessment and Risk Management of Substances

New Strategies for the Ecological Risk Assessment and Risk Management of Substances

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1. Principles

At the 1992 UN Conference on the Environment and Development in Rio de Janeiro, over 170 nations agreed upon the environmental policy ideal of sustainable – and therefore environmentally sound – development. Borrowing from the 1987 Brundtland Commission, the Enquete Commission of the 12th Bundestag, “Protecting Humans and the Environment”, described the ideal as the aim of producing development which meets the needs of the living people, without endangering the well-being of future generations.

Sustainability is intimately related to the precautionary principle. As early as 1986, six years before the Rio Conference, the German government’s “Guidelines of Precautionary Environmental Care” clearly stated the link between precaution and a sustainable future.

Herein, the precautionary principle involves three components:

- eliminating concrete environmental hazards ("danger prevention"),
- avoiding or reducing risks to the environment in advance ("risk prevention"),
- acting to shape our environment in the future, in particular to protect and improve the fundamental basis for life ("care for the future").

Risk prevention entails considering even those possibilities for harm “which cannot be ruled out, but where current information neither confirms nor denies certain causal relationships, and there is therefore no hazard, but only a suspicion or cause for concern." *Care for the future* is best described as “developing environmentally sound production processes and products, preventing – or at least avoiding as far as possible – emissions of pollutants at their source”.

The importance of the precautionary principle is also emphasised in EU treaties, for example in Article 174 par. 2 of the Amsterdam Treaty: "Community policy on the environment shall aim at a high level of protection taking into account the diversity of situations in the various regions of the Community. It shall be based on the precautionary principle and on the principles that preventive action should be taken,

that environmental damage should as a priority be rectified at source and that the polluter should pay."

The European Commission published a communication on 2nd February 2000 on the precautionary principle (COM 2000 (1)), explaining how the principle, which applies not only to the environment but also to human, animal and plant health, is to be put into practice in risk assessment and risk management, and how it should not be used arbitrarily as a pretext for protectionist measures. However, the communication has significant deficits. In particular, the principle is only held applicable to risk assessments where scientific information on identified risks is inconclusive. The aspect of precautionary, proactive prevention of pollution (care for the future) is more or less ignored. Measures taken on the basis of the precautionary principle are generally intended to be temporary in order to be adapted according to new knowledge, and they should be subject to a cost-benefit analysis, including socio-economic considerations. During its meeting in Nice on 7. – 9. December 2000, the European Council explicitly confirmed the position of the Commission in its conclusions.

A look at legal risk assessment for chemicals confirms that it has remained almost exclusively at the level of averting concrete hazards ("danger prevention"). Van der Kolk, responsible for assessing existing substances in the Netherlands, highlighted this deficit at an EU workshop on “Industrial Chemicals: Burden of the Past, Challenge for the Future" on 24th/25th February 1999 in Brussels with the following:

"- Rio Declaration: Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.

- EU practice: Where there is lack of scientific certainty of serious or irreversible damage, even cost-effective measures will be postponed."

This dilemma becomes especially clear in the case of existing substances. Since 1994, only 41 substances have been technically evaluated in the European Existing Substances Programme, while the EU directive on existing substances 793/93 lists c. 2600 chemicals with high production volumes, and the EINECS list, which contains

all substances produced and used before 1981, contains over 100,000 entries. The reasons that even high-priority substances require so long are twofold: firstly, the procedures themselves are complicated; secondly, a high level of scientific certainty is required to justify risk reduction measures. For this reason, a debate on reorienting chemicals policy is underway in Europe, with environmental groups and many Member States demanding greater efficiency and more weight to be given to the precautionary principle. The conclusions on chemicals policy reached by the EU Council of Ministers on 24th June 1999 point in this direction (see chapter 3).

However, regulations for specific media, e.g. the German Water Management Act or the Federal Immission Control Act, provide a predominantly emission-based framework for action on substances, more or less restricted to the medium in question. The shifting of pollutants from one medium into another is prevented, in principle and frequently also in practice. However, executive regulations do not generally achieve this consistently. For example, § 3 (2) of the Waste Water Ordinance provides that no processes be used which simply shift pollution to other media, such as to air or to soil, where there is a better technology available. However, the sector specific appendices in the ordinance do not provide quantitative requirements for air emissions caused by waste water treatment. In addition, the regulatory approach is restricted to point sources, and generally fails to consider discharges from diffuse sources. Substance specific regulations in media-based legislation are limited to a few substances especially dangerous for the media, for example heavy metals, PCB and PAH in the Federal Soil Protection Ordinance.

The principles of precautionary environmental policy and the instruments available to the state have remained more or less the same in the last 10 to 15 years. However, economic change and increasingly more detailed scientific information make it necessary to examine whether the way precautionary environmental policy is applied to chemicals is still up to date, where state action can be made more efficient or must be toned down, and which indirect instruments for modifying behaviour should be given more weight. There have been important changes in the use of chemicals which can impact on the environment, and these must be taken into account:

- State regulation has proven successful in chemicals policy. Germany has banned the manufacture or use of a number of environmentally hazardous substances, or has introduced stringent emissions limits. These substances include persistent chemicals like DDT, PCB, pentachlorophenol, lindane and dioxins, and the bans were exceptionally successful, most now having been implemented across Europe. Concentrations measured in the environmental media in Germany today

are below those measured in the 1980s, although they now remain stable at a level which is still too high.

- Direct emissions by manufacturing and processing industry have fallen, thanks in great part to regulations for waste water, waste and exhaust gas. However, attention should now shift to diffuse pollution from products, for example plasticizers, flame retardants and residues of pharmaceuticals. Frequently, too much is asked of users and consumers, or they are given no assistance in replacing hazardous pollutants with less harmful products and processes. There are virtually no recognised procedures or guidelines for proactive environmentally sound behaviour with respect to chemicals. It is significantly harder to find the original polluter in the case of pollution from products than with direct emissions.

- Problems with substances have become more global. It cannot be expected that environmental concentrations of certain persistent or bioaccumulating substances will become negligible, although they are banned in Germany, because they are highly mobile, and therefore present a threat far from the regions where they are used. Despite a fall in concentrations of these pollutants, and after fully exploiting the possibilities for domestic action, risks to public health and the environment in Germany can often not be ruled out. For example, despite a downward trend, infants' intake of dioxins is still above the tolerable level. It can be assumed that still many substances are in use which are persistent and bioaccumulating and can be transported over great distances.

- The task of assessing substances and designing subsequent regulations has become far greater, due to the large number of substances to be covered under various rules, and also far more complex, due to standardised procedures. With the additional need to harmonise regulations across several national and EU levels, this has produced delays and inefficiency, especially in respect to existing substances (see chapter 3).

- The global dimensions of environmental problems make voluntary solutions more difficult. It is frequently impossible to gain commitments from all those involved in production and processing around the world, or to monitor compliance. Legally binding international agreements for substance regulations are therefore increasingly important.

- It has proved impracticable to examine every potential negative property of substances. The extremely limited possibilities for comprehensively examining

every relevant substance have been made abundantly clear in the recent debate on endocrinally active chemicals in the environment, which can cause irreversible damage in organisms exposed to low concentrations at critical stages of development. It is therefore important to minimise the discharge of substances into the environment as a precaution, even where their harmful properties are not yet proven (see part II).

Moreover, environmental problems today are not primarily caused by specific pollutants or processes. A major problem rather lies in the quantities of material and energy resources consumed, and the form of this consumption. The substances a product contains are generally only a small fraction of the substances transported and consumed during its manufacture and processing. Integrated, cradle-to-grave substance flow analysis is therefore required, especially for mass products.

The 12th Enquete Commission of the German Bundestag "Protecting of man and the environment" formulated four basic rules for a sustainable precautionary management of chemicals and substances, and the corresponding Commission of the 13th Bundestag added a fifth rule, relating to public health.

To build a management of chemicals and substances oriented around the principles of sustainability and precaution, environmental quality and action targets must be set to provide actors with guidance and security. Environmental quality targets which describe the desired state of the environment can only partially be described in a general form, e.g. with respect to “hazardous” substances. For example, the Swedish parliament passed an act on “Environmental Quality Objectives” in April 1999, including a target for chemicals. “The environment must be free of anthropogenic substances and metals which represent a threat to health and biodiversity. This means that environmental concentrations of naturally occurring substances must be close to their background levels, while concentrations of substances produced by humans should be near zero." (Swedish environment ministry, June 1999).

This target reflects similar formulations in marine protection agreements (HELCOM and OSPAR), although the Swedish formulation does not specify which properties render substances dangerous to health and the environment. In its report on "Action Areas and Criteria for a Precautionary, Sustainable Substance Policy, Using the example of PVC" (in English: March 2001), the German Federal Environmental Agency (UBA) described five substance related environmental action targets as steps towards relieving the environment. These targets are presented below in a slightly changed version:

- *The irreversible discharge of persistent and bioaccumulating, or persistent and highly mobile, xenobiotics into the environment is to be avoided completely, irrespective of their toxicity. This also applies to substances whose metabolites exhibit these properties.*

  Where xenobiotics remain in the environment for a long period, harmful effects can never be ruled out, even if they are as yet unknown or not fully researched. Where the substances accumulate in organisms or are highly mobile, this presents an especially high risk.
- *The irreversible discharge of xenobiotics with carcinogenic, mutagenic or reproduction toxic effects (CMR substances) into the environment is to be avoided completely. This also applies to substances whose metabolites exhibit these properties.*

  These properties affect key functions in organisms and ecosystems, which thereby could be affected irreversibly.
- *The anthropogenic release of persistent and bioaccumulating, persistent and highly mobile, carcinogenic, mutagenic or reproduction toxic natural substances into the environment must not lead to an increase in geogenic or biogenic background concentration.*

  This requirement corresponds to the first two, but it is impossible to reach zero pollution for naturally occurring substances.
- *The anthopogenic release of other (eco-)toxic substances (including naturally occurring substances) which do not fall into the above categories into the environment is to be reduced to the technically unavoidable level. This also applies to substances whose metabolites exhibit these properties.*

  This requirement means precautionary prevention of pollution and health risks from toxic substances.
- *An increase of chemical discharges into environmental media is to be avoided, regardless of the effects known so far and other intrinsic properties, where high distribution and/or low exchangeability makes recovery practically impossible.*

  This final target is a “requirement to minimise” substances not covered by the first four, and aims to reduce pollution in general, especially of the atmosphere, seas and ground water, where lower emissions do not at all or only in the long run lead to lower substance concentrations.

Persistence and bioaccumulation is a combination of properties which is increasingly being recognised as problematic in the European debate on chemicals. Regardless of the results of quantitative risk analysis (comparison of exposure and effect), such substances pose a risk, as their discharge into the environment is irreversible, they remain there for long periods and they can additionally accumulate to potentially harmful concentrations in organisms. Knowledge on harmful effects in principle can never be complete, and a biological effect frequently emerges only from long-term multigeneration studies, which are complex, and therefore seldomly conducted. When new discoveries are made, the persistence of such substances means that harmful effects cannot be eliminated for long periods. This is especially true for environmental sinks, such as the seas.

Persistence and mobility in combination also represent a particular hazard. Highly mobile substances which are persistent can spread over long distances through the atmosphere, and either affect atmospheric chemistry (e.g. CFC) or be precipitated in areas far from the source of emission (e.g. POP). High mobility in the soil or ground water is also particularly critical: if persistent substances enter aquifers, they will remain in the ground water for long periods. Contaminated ground water cannot be completely cleaned up, and this is a special problem if the source is used for drinking water, as contaminated drinking water does not meet hygienic standards irrespective of toxicologically based limit values. Two examples are methyl-t-butylether (MTBE, fuel additive) or n-phenylsulphonylsarcosin (metabolite of an anti-corrosion agent).

However, the combination of the properties high mobility and persistence, unlike persistence and bioaccumulation, has received very little attention in the European debate as yet. Apart from licensing for crop protection agents, ground water has also received little attention at all in legally based assessment of chemicals. However, in the frame of the EU risk assessment of existing substances, recently risk reduction measures for MTBE are recommended solely based on its relevance for ground and drinking water.

It should be noted that, in its most recent special report “Environment and Health – assessing the risks correctly”, the German Council of Environmental Advisors (SRU) does not agree that persistence is especially important: “The council cannot accept risk assessments based solely on the nature of exposure or substance properties” (Tz. 137). This is a relatively traditional understanding of risk. More recent approaches to risk assessment, such as those of the German Scientific Council for Global Environmental Change (WBGU, annual report for 1998), which covers

properties like ubiquity, persistence and reversibility as well as the extent and likelihood of harm, are referred to, but not accepted. The SRU favours assessments which take account of the precautionary principle where little secure information is available. It obliges the state to systematically extend the knowledge on the risks and to justify precautionary measures transparently in the political process.

As in the aforementioned report of the Federal Environmental Agency (UBA) on "Action Areas and Criteria for a Precautionary Sustainable Substance Policy Using the Example of PVC", these environmental quality and action targets and the need to conserve resources mean that the following areas require action:

- *Reducing the material used for products and services:* functions in demand should be fulfilled with as little material intensity as possible.

- *Reducing consumption of natural material resources:* this should be understood as an incentive for technical progress towards conserving resources.

- *Reducing energy utilisation during product life-cycles*, in particular to minimise releases of mass pollutants such as climate gases (e.g. CO_2) and acidifiers.

- *Increasing products' long-term fitness for use:* this is also a measure to minimise material flows. It concerns a product’s durability and suitability for repair.

- *Improving environmentally compatible recovery options:* this concerns both a product’s recyclability and the environmental compatibility of recycling methods.

- *Minimising emissions to the technically unavoidable level:* the levels and harmfulness of emissions should be minimised, and anthropogenic material flows should be separated from natural substance cycles.

- *Reducing the complexity of material flows*: this applies to the number of levels and the interdependence of technical processes, as well as risks for accidents, for example due to risk potential of intermediate products.

- *Reducing risks to prevent an overburdening of the environment with ecotoxic and toxic substances:* this applies to (eco-) toxic substances where a comparison of exposure and effect, including effects in combination, reveals a risk.

- *Developing and implementing substances with environmentally and health compatible properties:* the concept of sustainability requires the prevention of the discharge of persistent and bioaccumulating/highly mobile substances. Developing substances which are “green by design” should help in future to replace substances with a hazardous profile which are currently indispensable.

The relative importance of the abovementioned action areas will vary for different substances and substance flows, and may compete with one another. For example, for substances applied to the environment directly, such as crop protection agents, their properties and application techniques (to reduce consumption) are most important. In contrast, for substances used in closed systems, such as phosgene, the controllability of substance flows is most important.

In principle, a vertical approach which considers only single substance flows is not sufficient. What is needed is a horizontal comparison of the alternatives (including avoiding the use of the substance). Hereby the considerable gaps in our knowledge about the environmental and health effects of most chemicals in commercial use pose a serious problem. Alternatives must be sufficiently tested before their introduction, and comparative product assessments lack the necessary transparency. Our knowledge about the chemical composition of products is generally inadequate, as is the information about their areas of application.

2. Substance-based targets for certain environmental media: the necessity and options for their implementation

The discharge of substances can affect different media within very different time frames. Unless they accumulate in sediment, organic substances in flowing water generally decrease relatively quickly or are transferred to other media. By halting or reducing the discharge, negative effects can be relatively rapidly and completely eliminated. In other media, particularly the marine environment and ground water, negative changes are more difficult to correct and often completely irreversible for long periods. Once a substance reaches these compartments, their poor potential for degradation means that a substance may be predictably persistent, even if tests have shown it to be principally degradable. There are also (almost) no technological methods for recovering substances from these media, once they have spread.

There are therefore especially strict precautionary requirements for these compartments in regulations and international agreements. For example, § 34

Wasserhaushaltsgesetz (Water Management Act) requires categorically that there must be "no need for concern about harmful pollution of the groundwater or any other negative change of its properties" caused by substances. This ambitious target is also expressed in the lines of the Convention for the Protection of the Marine Environment of the Northeast Atlantic (OSPAR) which call for reducing concentrations of anthropogenic substances to almost zero within one generation.

However, legislators did not directly define instruments to attain these targets. The following illustrates this "instrument gap" with the aid of the example of the implementation of the marine protection agreements.

The Commissions for the Helsinki Convention on the Protection of the Marine Environment of the Baltic Sea (HELCOM) and the Oslo and Paris Convention for the Protection of the Marine Environment of the Northeast Atlantic (OSPAR), at their meetings on 23rd–27th March 1998 in Helsinki and 20th–24th July 1998 in Sintra, decided on strategies to eliminate by the year 2020 (i.e. within one generation) discharges of substances which are hazardous, i.e. whose persistence, bioaccumulation, toxicity or ecotoxicity makes them especially problematic, or which give cause for concern for other reasons. This was also the target set by the ministerial declaration of the 4th North Sea Conference in 1995. In order to achieve these targets, substances are to be identified according to their inherent chemical properties and their incidence and discharge levels into marine waters. A still unspecified programme of action is then to reduce marine discharges, eventually eliminating them altogether, and thereby to finally reduce concentrations of naturally occurring substances to their background levels and the concentrations of industrially synthesised substances to almost zero.

A decision taken at Barcelona in 1976 calls for reducing discharges of (eco-)toxic and persistent or bioaccumulating substances which could reach the marine environment of the Mediterranean to a level which is neither harmful to humans nor the environment by 2005, with the eventual goal of eliminating them altogether.

National regulations are inadequate for implementing the marine protection agreements; EU-wide approaches are significantly more effective. However, a problem often arises in that the EU is a signatory to various marine protection agreements, including OSPAR, but is still not prepared to implement its decisions fully. An example is the foreseen regulation by the EU Commission for short-chained chlorinated paraffins within the existing substances programme. While PARCOM decision 95/1 considers it necessary to cease using this substance group in four

areas, the draft EU guideline continues to permit numerous environmentally open applications mentioned in the decision – paints, lamination, sealants, rubber, plastics and textiles. The regulation restricts itself more or less to fields of application (including some which were not mentioned by PARCOM, such as leather) where a PEC/PNEC ratio > 1 has been found. The proposed measures affect the sources of more than 95 % of current total pollution. However, future shifts in the pattern of application or new applications have not been ruled out. The Environmental Committee of the European parliament on 8th January 2001 heavily criticized that the PARCOM decisions were implemented only incompletely.

The debate on reorganising EU chemicals policy brought a recognition by the Council of Ministers in Luxembourg (24th June 1998, No. 5-7) that community chemicals policy should make a major contribution to enabling the community and its Member States to comply with such international commitments, although no concrete proposals were made as to instruments or procedures for implementation.

Existing EU regulations for chemical risk assessment in the Technical Guidance Documents (TGD) currently do not contain final assessment methods for the seas. There is now a broad consensus that the PEC/PNEC model, which generally produces meaningful results for local and regional assessments in limnic and terrestrial areas, does not apply to the particular hazard situation in the seas. Above all the potential hazard from bioaccumulating and persistent substances, which accumulate in the food chain, is thereby underestimated. Therefore, the following additional aspects should be taken into consideration:

- Accumulation of hazardous substances in certain areas (sinks) of the marine environment can have unpredictable long-term effects, and would be practically irreversible.
- Remote stretches of ocean should remain untouched by anthropogenic hazardous substances, as their intrinsic value must be protected from the effects of human activity.
- The open seas cannot meaningfully be divided into separate areas within which PEC values can be calculated.

The current marine EU assessment strategy must therefore be extended, in terms of both time frame and scope. This applies especially to PBT substances (**p**ersistent, **b**ioaccumulating, **t**oxic), which remain in the environment for long periods and can accumulate in living organisms, because they can cause harmful effects long after and far away from the actual emissions. This hazard actually exists for any

environmental compartment, but is especially significant for the seas for the following reasons:

- Once such a substance has reached the open seas, emission reductions do not necessarily lead to a fall in concentrations.
- Owing to the slow reproductive cycles of many important marine species, the possible effects of chronic exposure will not be recognised until it is too late.

OSPAR and the EU Commission are currently working on a joint assessment model to take these aspects into account (Draft Summary Record DYNAMEC (2), 99/10/1, Annex 6). The proposed strategy contains three levels:

- local assessment
- regional assessment
- assessment of the open seas

At first, discharges by point sources are assessed locally, as the highest concentrations, and therefore an increased risk, is to be expected in the immediate vicinity of the source or in the nearest sink. The methodology described in the TGDs is essentially appropriate for local assessments, and may be used with few modifications: a quantitative approach (PEC/PNEC ratio) is generally practicable.

A regional assessment may become necessary where the discharges from several point sources are combined, or significant discharges are transported (atmosphere, dredged material), for example. The key step in this case is to circumscribe the marine area to be assessed. The protected region may be an especially sensitive stretch of sea, such as the tidal shallows or other coastal regions. The PNEC should then be determined on the basis of long-term test results on organisms relevant for this subcompartment. It is planned to generally apply higher safety factors when calculating PNEC values in order to account for the higher diversity of the marine fauna.

A third assessment phase will be required for PBT substances because, as explained above, a quantitative approach using the PEC/PNEC ratio would underestimate the risks. The substances' intrinsic properties create an immediate need for action where there are significant emissions into the seas: any emission sources identified (even diffuse sources) must be closed.

If this strategy can be embodied in the Technical Guidance Documents, Europe-wide implementation of the substance based goals in the marine protection agreements in the frame of the existing substance programme would become easier in the future.

The OSPAR DYNAMEC process is currently ranking substances which are potentially hazardous to marine environments according to their inherent properties and their possible discharge into the seas, in order to identify the most hazardous. Substances characterised as high-priority indicate a need for speedy action to halt further discharges into the marine environment.

Experience to date with regulating toxic and persistent substances shows that no time is to be lost, if we are to come close to the marine protection agreements' targets for 2020. It already seems too late for those especially persistent chemicals which are also highly mobile. For example, data from the German Environmental Specimen Bank show that concentrations of PCB, DDT and its metabolites in wild organisms in Germany have remained constant for many years, despite an earlier downward trend, although these substances have been banned in Europe for ten or twenty years (however, the still widespread incidence of PCB in products with a long useful life, e.g. sealants and small condensers, must be taken into account here).

To speed up measures aimed at meeting the targets in marine protection agreements, there are generally two options:

- A Council initiative could ask the EU Commission to propose a feasible EU-wide regulation (political activity).
- National legal regulations, taking into account the legislation relating to the internal market, could put the Commission under pressure to implement the decisions completely and throughout the EU (legal activity).

Since there is currently no adequate legal framework for protecting the marine environment in the EU, Member States have some room for manoeuvre in making domestic regulations, but the final and preferable goal is an Europe-wide implementation.

Discharges of hazardous substances can be reduced by bans and restrictions on their manufacture or use, as well as reducing emissions from industrial plants. The following EU legislation could function as possible instruments here:

- the EU Integrated Pollution Prevention and Control (IPPC) Directive, 96/61/EEC (sector specific recommendations for reducing emissions from plants with best available techniques, BREFs, as in the Seville process),
- EU directives on substances and products (67/548/EEC, 76/769/EEC) and the EU Existing Substances Regulation 793/93.

These instruments are not mutually exclusive, but complement one another. It should be emphasised that the IPPC Directive regulates only emissions from point sources, and not from diffuse sources like products. However, blacklists of substances whose application is not BAT within a certain sector can produce significant emission reductions, e.g. the ban on substances like mercury, chromium or organic tin compounds in cooling waters.

A complete strategy therefore contains the following options:

- Rapidly completing a marine environment assessment module to be integrated into the EU's technical guidance (the TGD), without using PEC/PNEC for the open seas, but rather basing assessment on inherent substance properties.
- Producing an assessment module for ground water, which should also aim for complete prevention of anthropogenic discharges ("near-zero concentrations"). The key substance properties are persistence and mobility.
- Making EU chemicals policy – especially on existing substances – more efficient, to implement the substance based goals in marine protection agreements quickly (see chapter 3).
- Examining the feasibility of passing national legislation to further restrict short-chained chlorinated paraffins, as proposed EU restrictions under the Existing Substance Regulation do not fully implement the PARCOM decision 95/1.
- Improved co-ordination between the departments involved in marine protection and chemicals policy implementation within the EU and within Member States.
- International monitoring programmes within the marine protection agreements can identify sources and causes of pollution, and help to justify measures and monitor their efficiency, although the difficulty in gaining representative data means the instrument must be restricted to substances with at least a potential need for regulation. Monitoring of effects (i.e. observing biological effects in sensitive marine areas, e.g. tidal shallows) may indicate further need for action.

3. Options for more efficient risk assessment and risk reduction of chemicals

3.1 Description and criticisms of current procedures

The need for clear principles in chemicals assessment for existing regulations has been met at EU level by Technical Guidance Documents (TGD), which provide binding principles for assessments of *existing* and *new substances* in Member States. The basic principle for determining environmental risk for single substances is a comparison of the measured or calculated concentration of a substance in each environmental compartment (PEC) with the concentration at which no negative effects on the ecosystem are expected (PNEC). There is nonetheless a fundamental problem in that our knowledge about harmful effects will always be incomplete. Available studies, mostly acute to subchronic, do not indicate all possible effects, e.g. effects on the endocrine system (see part II). At present, the precautionary principle is only satisfied in that gaps in the data on effects are filled by high assessment factors, while missing information about exposure is compensated by assuming "realistic worst case" scenarios.

The procedure has generally proven adequate. The question remains, however, whether this procedure produces appropriate results for substances with certain problematic properties (persistence/bioaccumulation, persistence/mobility and CMR). Also, the procedure is not applicable to certain compartments, in particular the open seas or ground water (see chapter 2). In these cases, the goal should be to design regulations without a quantitative comparison of exposure and effect.

An additional problem is that the European Existing Substances Programme has, despite great efforts, succeeded in technically completing the risk assessment for only 41 substances. The key reasons for this unsatisfactory result up to now are:

- complex, contradictory, and above all incomplete data,
- the considerable efforts associated with a *comprehensive* risk assessment,
- before the assessment is concluded, the options for refining the results with additional, more precise data are fully exploited,
- the structure and complexity of the administrative procedure.

The greater difficulty in assessing existing compared to new substances is to some extent unavoidable for a number of reasons:

- Data for new substances are collected before they are marketed, depending on the production volumes. Exposure can be modelled on the basis of the substances' properties and intended use, which can generally be described unambiguously. In contrast, existing substances are produced or marketed in quantities of well over 1000 t/a. They have been in use for many years and have

numerous, frequently unknown applications. It is therefore very difficult to determine the exposure in all the relevant environmental compartments and subcompartments. Any available data from monitoring must also be included.
It is also time-consuming and irritating that industry fails to provide sufficient data, especially on exposure, and that too little is generally known about emissions during down-stream use of chemicals. Detailed knowledge about such data is required in most cases, in order to identify the most significant sources of emissions and take appropriate measures to reduce them.

- In contrast to new substances, for which well-defined data on their effects are presented according to internationally agreed guidelines, the data for existing substances, from which an overall view of the threats to each environmental area has to be deducted, are generally copious, heterogeneous, frequently non-standardised and contradictory. Crucial basic data are often missing.

- While the main goal of examining new substances is to determine whether there are objections to their marketing, existing substances must be examined to determine existing risks and, where necessary, minimise them. Such reduction measures mean intervening in markets, and must therefore be well-founded.

These framework conditions require more flexible and efficient examinations for existing substances, in order to accelerate the process and introduce measures to minimise risks at an early stage.

Another serious delay is in the administrative procedure, both on national and at EU level. Within the EU Commission, the Directorate-General Environment (formerly DG XI) is responsible for the Existing Substances Regulation, but the DG Enterprise (formerly DG III) is charged with implementing risk reduction measures relevant for the internal market. In future, the DG for Consumer Policy and Protection (formerly DG XXIV) will also be involved. Collaboration is anything but smooth: in Germany, three agencies are concerned with assessments – the UBA (environment), BgVV (consumer protection and veterinary medicine) and the BAuA (occupational health and safety) – not counting the additional unit for registration at the BAuA. Furthermore, the German Administrative Ordinance on Existing Substances provides for participation by the Advisory Committee on Existing Substances (BUA). At EU level, the risk assessments are frequently discussed at Technical Meetings at the European Chemicals Bureau (ECB), and the OECD is also involved. At all levels, industry has opportunities to exert an influence or provide additional data. Any

change in the data stock necessitates a comprehensive redraft of the assessment report in most cases.

These problems have caused Germany and other EU Member States to consider urgently how the assessment process can be speeded up. The following points on EU's chemicals policy were taken up by the Council of Environmental Ministers in their conclusions on 24th June 1999, but need some refinement and concrete specification.

3.2 Options for precautionary and efficient management of existing substances

The conclusions of the Council of Ministers are aimed at making assessment of existing substances more efficient. Point 18 of the conclusions affirms that the precautionary principle, the goals of sustainable development and a smooth functioning of the internal market should provide the basis for a new chemicals policy. The Environmental Ministers asked the Commission to develop a White Paper where the strategy for a future chemicals policy of the EU should be presented basing on the Council conclusions [Remark: The Commission published this White Paper at 13th February 2001].

The following points in the Ministerial Declaration are especially relevant to this discussion:

<u>Shifting the burden of proof: more responsibility for industry (point 20)</u>

The demand that industry assume more responsibility for collecting and evaluating data should be welcomed. This responsibility can be met by laying all the relevant data on the table from the outset, and not waiting until a need for regulation appears likely under the TGD. On the other hand, assessment by industry itself is counterproductive. In the experience of the UBA, it takes considerable time to uncover and eliminate the causes of implausible assessment results – namely faulty, sometimes even biased, initial parameters. The full responsibility of state authorities should nonetheless, as the Council describes, focus on the substances which a suitable priority-setting has identified as potentially seriously problematic (see point 23).

A voluntary commitment by the ICCA (the International Association of the Chemicals Industry) declares its willingness to provide basic ecotoxicological and toxicological data, including a preliminary hazard assessment, for c. 1000 high-volume

substances until 2004. German chemicals industry is participating on c. 160 substances. This OECD-co-ordinated initiative is a welcome step towards identifying substances which have an especially high potential need for regulation. However, up to now industry has not selected a single environmentally relevant substance.

In the draft German book of environmental law (UGB) drafted by an independent expert commission, § 600 UGB-KomE renews the current division of roles between authorities and producers, but it takes up the problem on p. 1450, calling for a change in the burden of proof at EU level: "It would better reflect both the precautionary principle and the polluter-pays principle if the burden of doubts as to a substance's impact on the environment or public health should fall on the creator of a potential source of hazard, rather than – even if only for a short time – on the general public."

Assessing and managing risks (point 21)

The goal of comprehensive scientific risk assessment is to determine whether action is required to reduce risks from substances. The EU Existing Substances Regulation 793/93, Articles 10.3 and 11, requires the rapporteurs of risk assessments for high-priority existing substances to present a risk reduction strategy. If this strategy proposes restrictions on the marketing or use of a substance, an analysis of its advantages and drawbacks and the availability of substitutes is also required.

The strategy is developed according to the EU '*Technical Guidance Document on Development of Risk Reduction Strategies*' of October 1997. The rapporteur presents the risk assessment and risk reduction reports to the EU Commission, where they form a basis for the necessary political decisions and legislative or other measures. The goal is also to structure the decision-making process better and more transparently.

Important aspects of a goal oriented linking of risk assessment and management regarding the contents as well as the organization were discussed at a conference in Bielefeld 1999: "Reforming the European Regulation of Dangerous Chemicals". (Proceedings "Risk Assessment and Risk Management of Toxic Chemicals in the European Community" (Nomos Verlagsgesellschaft Baden-Baden 1999)).

The following points are particularly important for rapidly and efficiently developing and implementing risk reduction strategies:

- Effective risk reduction strategies can only be elaborated with a thorough knowledge of the risk assessments behind them. The exposure analysis within the risk assessment must always have reduction strategies in mind, just as the development of a reduction strategy must continually refer back to the risk assessment. Both the content and authors of risk assessment and risk reduction strategy must therefore be closely interconnected.

- A comprehensive cost-benefit analysis should not generally be required. Instead, a cost-efficiency estimate should find the cheapest way to eliminate the risks determined by the risk assessment. Owing to the lack of certainty in estimating long-term environmental harm, which hardly is to monetarize, quantitative cost-benefit analyses frequently dominate the short-term economic advantages of continued use of the substance.

- In order to implement the risk reduction strategies smoothly in actual regulations, this task should fall within the competence of the Environment DG of the EU-Commission.

- If the assessment cannot be concluded within a specific timeframe, due to lack of data, a secondary assessment conclusion should come into play, to prevent the process from freezing up. It could be formulated like this: ‘There is cause for concern, although the information is insufficient to determine this with certainty; preliminary risk reduction measures will be introduced; producers and importers importers have the opportunity to remove this cause for concern.

- Applications of especially problematic substances (PBT and/or CMR) should be banned completely or only permitted if it can be demonstrated that the application is safe (e.g. substances handled in closed systems). Where certain applications cannot be substituted at short notice, these should be authorized explicitly and transition periods should be laid down. After the transition periods expire, the total ban will come into force. This has been put into practice in the EU directive 86/94/EEC on the degradability of detergents: certain non-ionic detergents (EO/PO detergents in the beverage industry and in metal processing) were initially excluded from the ban of use, despite being insufficiently biodegradable, until the transition period had expired. A similar procedure was used in the ordinance banning CFC and halons (FCKW-Halon-VV), which requires regular reports on substitution options.

- In cases where no complete ban is proposed, it must be assured that new areas of application or an expansion of permitted uses do not counteract the benefits of the original strategy. This could be achieved by requiring explicit permission for any such changes – a *de facto* permission or notification procedure.

- Involving industry more in the responsibility for risk reduction and substituting hazardous chemicals is worth considering. One practice has become established in the UK, linking voluntary commitments or binding contracts with civil law. After identifying an unacceptable risk, and therefore a need for action, a dialogue with the affected industry requires it to develop a proposal for technical solutions or substitution within a certain time. The proposed solutions are agreed between the affected manufacturers and users or their associations for a given trial period. With the support of participating industry, a regulation then comes into force, to ensure full implementation in the entire sector. This prevents free-riding by companies who counteract the voluntary agreement and seek short term financial benefits, and rewards those volunteers who develop marketable alternatives at an early stage.

Removing existing deficits in collecting exposure data (point 22)

Experience to date in assessing substances under the EU Existing Substances Regulation shows that deficits in determining exposure data are one of the key reasons for the EU's slowness in assessing the risk of existing substances.

The EU regulation only requires producers and importers to provide the data listed in Appendix III of 67/548/EEC, which contains little information on exposure. Only when a substance appears on a priority list the data must meet the requirements in Appendix VII A (basic requirements for new substances). However, the data provided by industry often fail even to satisfy these requirements. To identify and assess high-priority substances in future, Appendix III must be revised to require exposure data to be provided together with the IUCLID data.

A questionnaire covering the necessary exposure data for existing substances has been developed by the OECD and further developed by the EU; it is a specification and extension of Appendix VII A. Unfortunately, it is not used by all Member States. Legally requiring industry to provide complete exposure data according to the questionnaire would considerably speed up risk assessment of existing substances (see also point 23). At present, numerous time-consuming interviews with

representatives from each production location are needed to clarify which data are required, and the data must then actually be submitted.

Exposure data is particularly poor for down stream uses. The data needed for an assessment are not available to manufacturers or importers and are often extremely difficult to trace, if this is at all possible. The EU legislation must include the down stream users in future.

A product register might be a suitable aid in gathering more precise information on human exposure, the release of chemicals into the environment and substance flows than it is available today. A research project commissioned by the UBA is currently examining whether and under what circumstances to develop an European product register can be developed. In several European states, especially Scandinavian states and Switzerland, such registers already provide valuable information.

The aforementioned ICCA initiative should also provide sufficient exposure information to help speed up and improve selection of high-priority existing substances.

Making risk assessment flexible - targeted risk assessment (point 23)

Making risk assessment flexible must be considered together with the issues of point 22 (deficits in collecting exposure data), point 24 (measures based on inherent substance properties) and point 25 (substance grouping). A minimum of data, including meaningful exposure data, is generally needed, at least for production volumes > 1000 t/a. Only then can priorities be set reasonably and systematically. During this priority-setting, more attention should be paid to the results of other prioritising procedures, such as the OSPAR DYNAMEC list and the COMMPS list under the EU water framework directive. A series of steps, involving a basic assessment beyond priority-setting, such as generic exposure calculations or estimates based on structure-activity relationships, can reveal whether a substance requires a comprehensive risk assessment or merely a targeted risk assessment or an assessment based primarily on its inherent properties (point 24). The priority-setting could also identify the substances which pose a potential environmental threat, but where the single-substance approach of the EU existing substances regulations does not provide appropriate instruments, for example substances which consist mainly of mixtures (petroleum-derived hydrocarbons), or are discharged into the environment as unintentional by-products (polychlorinated dibenzodioxins and dibenzofuranes, or octachlorostyrene). Such chemical pollution is better controlled

with other legal instruments, such as the IPPC or the solvents directives, or with instruments still to be developed. The final selection should then contain mainly the substances for which risk reduction measures according to the Existing Chemicals Regulation are very likely to be required. It must be emphasized that at least simple regulations (e.g. labelling, workplace safety) can be introduced on the basis of basic data, without waiting for the entire assessment.

A targeted, or “tailor-made”, risk assessment is a reasonable substitute for a comprehensive risk assessment in cases where the risk is only suspected in certain areas (e.g. the workplace) or environmental media (e.g. water or soil), or where there are already sufficient risk reduction measures in place for some areas. A limited assessment could also be adequate for substances that are only intermediates, or where exposure is only expected in specific applications or sectors. Current law under § 9 par. 3 of the EU regulation does not permit to ignore aspects of an assessment simply because they are considered unimportant in a specific case. Until the regulation is suitably amended, such aspects should be mentioned briefly in reports, for formal completeness’ sake.

As shown in point 21, risk assessment and risk management interact closely with one another. An extended priority-setting and an initial assessment must first identify the key information requirements and determine where emission reduction measures will probably be necessary. The detailed assessment will then only be required for these aspects, in order to sufficiently justify the necessary measures.

Where feasible and meaningful, the extended priority-setting should also group substances with similar structures into substance groups, or those with similar applications to use clusters, and later assess them jointly (see point 25).

Effective risk management measures for substances with certain inherent properties (point 24)

As shown in chapter 1, substances which are both persistent and bioaccumulating/*or* persistent and highly mobile *or* which exhibit CMR properties, must be considered particularly hazardous. The action target is to avoid irreversible discharges into the environment as completely as possible. Therefore an authorization procedure for unavoidable applications would be the preferable measure to prevent exposure of humans or the environment (see point 21 and chapter 3.3). These substances should in future be subject to a simplified assessment procedure, not involving the PEC/PNEC ratio. Nevertheless, qualitative exposure data on the type of application

and quantities used, and on the emissions arising, are also required in order to take the appropriate risk reduction measures (see chapter 2). If the assessment shows that the substances meet the criteria of the UNEP POP convention, efforts should be made to have them included in this global prohibition and restriction instrument. The criteria for classifying substances as persistent, bioaccumulating and highly mobile still are to be specified in detail. If a substance is found in human or environmental samples, especially from remote areas far from the sources, there is already reason for concern. In these cases, emission reduction measures should be aimed for without requiring further tests on adverse effects.

Substance grouping (point 25)

Grouping of substances instead of assessing single substances separately can mean a considerable efficiency gain, during the extended priority-setting or risk assessment, or when carrying out risk reduction measures (see point 23).

Approaches can be distinguished as follows:

- Grouping substances based on structural similarity (e.g. homologous substances), QSAR techniques may be used for the extension of the data. If substances being assessed together exhibit the same type of effect, the PEC should usually relate to the total concentration of all members of the substance group.
- Use clusters of substances used for the same applications make comparative assessments possible. Much of the necessary examination of substitution issues has then already been completed when introducing risk reduction measures.

Substituting hazardous with less hazardous substances (point 26)

The substitution principle should be included in the discussion on risk reduction measures, and the use cluster approach also makes such a procedure possible. A strong incentive for substitution would be created if the substitution requirements under § 16 par. 2 of the Hazardous Substances Ordinance were extended to cover not only substances which are harmful for human health but also environmentally hazardous substances.

Stricter time frames for risk assessment and appropriate responses to failure to meet deadlines (point 27)

The chemicals industry's response to public pressure, in stating its willingness to provide basic data by 2004 for c. 1,000 high-volume substances to enable a preliminary assessment of potential hazard, is to be welcomed. If this deadline is not met or the data are so incomplete that the target cannot be achieved, the EU should set strictly binding deadlines, after which any substance will automatically be considered a new substance. A second stage should extend the procedure to cover existing substances with a production or sales volume > 10 t/a. If existing substances exceed the given tonnage limits in future, this is to be communicated, and the necessary data provided speedily.

More information from manufacturers for substance users (point 30)

The polluter-pays principle and especially the responsibility of the producer for its products requires that manufacturers and importers provide their clients with the necessary information. Therefore, manufacturers and importers should be required to provide the users with all the information about substances' inherent properties needed (improved safety data sheets). A note (e.g. "incompletely tested substance") should explicitly indicate whether essential basic data are unknown. Classification or labelling, in particular, must make clear whether a substance cannot be classified on the basis of performed tests or due to lack of data. This would give the user or consumer the option of selecting the least hazardous of a number of substances, when a choice exists.

Under the new Administrative Ordinance on the Classification of Water-Hazardous Substances (VwVwS), this precautionary kind of system is already in use. If basic data are not available, the official classification automatically results in the worst case possible according to whatever data is available.

Information for users and consumers about risks could be improved by lists of substances for which insufficient data has been made available or which have dangerous properties ("undesirable substances"). These lists could be regularly published, either by or in co-operation with the authorities, as has been done in Denmark and Sweden. When managing substance flows (see chapter 4), substance lists based on industrial sectors would be useful, creating a considerable incentive to use less hazardous substances (see point 26, and chapter 3.3 for "whitelists").

Scrutinising existing structures and instruments (point 33)

As described in chapter 3.1, existing structures are too complicated, time consuming and bureaucratic, involving EU committees, the OECD and a Scientific Committee. Even if assessment standards are uniform across Europe, their application differs from state to state. The role of the central European Chemicals Bureau (ECB) in Ispra therefore needs significant enhancement. As commissioner M. Wallström explained at a CEFIC Workshop in Brussels on 6th December 1999, the EU Commission considers a central authority for risk assessment and chemicals management, possibly by expanding the ECB. Transferring competence to European institutions should be welcomed in principle. Such an agency should nevertheless genuinely save resources and improve efficiency. It should be ensured that the expertise of national authorities is exploited, as is the case when new pharmaceuticals are licensed by the central EMEA in London, for example, making use of rapporteurs from Member States and their expertise. Maintaining expertise in Member States is also necessary in order to formulate and implement ambitious national environmental targets. Up to now, it has not been clarified how the Commission wants to implement these plans.

Further measures not addressed in the Council of Ministers' conclusions

- The Technical Guidance Document (TGD) for assessing existing and new substances is currently under revision. New scientific results need to be considered, knowledge gaps (e.g. on risks to the marine environment, see chapter 2) must be filled, and biocides included. The revision should also further develop procedures for assessing risks to ground water and the atmosphere, possibly based on the approaches already developed for crop protection agents. This would represent a significant step towards harmonising assessments, and in the medium term, procedures for industrial chemicals should be fully harmonised with assessments of crop protection agents. Moreover, integrating pharmaceuticals (and cosmetics) is especially important, as they have not as yet been subject to (adequate) environmental risk assessments.

- Classification and labelling rules should be developed further. In particular, rules for classifying terrestrial environmental hazard must be determined. The initiative to develop criteria for substances which accumulate in the food chain is to be welcomed. Harmonising classification systems and labelling, especially with the rules on transporting hazardous goods, should also be pursued further.

- It would be illusory and is not intented to wish a comprehensive risk assessment for all existing substances. This is not even realistic for the c. 3,000 high-volume chemicals. As explained above, a valid priority-setting procedure is therefore needed to identify potentially hazardous existing substances. In the long term, however, the majority of the c. 100,000 entries in the EINECS list cannot continue to enjoy a permanent production and distribution license, and it is an open secret that the majority of the substances in the list are not, or no longer on sale. The Danish environment ministry has made an interesting proposal for giving the list a "spring clean" ("A strategy for intensified efforts in the field of chemicals", January 1999): levying a charge for every substance which is still in regular use.

  Since there is no legal framework for levying such a charge, levying a special charge for a further sales license in every member state would probably be the most suitable instrument. If the charge, possibly calculated according to market volume, is not paid, the substance would eventually be removed from the list and would need to be registered as a new substance in order to receive a new license.

3.3 Options for an efficient precautionary policy on new substances

In contrast to existing substances, the notification procedure for new substances, with its legally required tests certainly is a "filter" for marketing new substances. The graded obligation to provide data for assessment is a relatively well-functioning system which is uniform across the EU.

The recent discussion in the EU on streamlining the procedure for new substances, by some Member States frequently justified as a way of freeing resources for assessment of existing substances, should not be allowed to lead to the provision of less information, as this could prevent possible environmental risks to be recognised in time. The resources expended on assessing new substances are so small in comparison with activities on existing substances that even a reduction would hardly lead to a significant increase in the assessment of existing substances.

The discussion on streamlining the new substances procedure was initiated primarily by SLIM, an activity under the EU Commission's Directorate-General for the Internal Market (formerly DG XV), which examined directive 67/548/EEC, on which the procedure is based, for ways of increasing efficiency. The SLIM group eventually concluded that the directive essentially fulfills its purpose in its present form. The group's proposed improvements address various areas of the directive. Some welcome proposals were, for example, to structure the directive more clearly and

reorganise Appendix 1 more effectively, and to improve data sharing. This means that, when two manufacturers from different EU Member States notify the same substance, data on the substance should be mutually transferable (as provided at a national level in Germany by the Chemicals Act), also avoiding the need for unnecessary animal experiments. However, the proposal to shift responsibility for producing risk assessments from authorities to industry itself is critical. It is not helpful, as past experience has shown that risk assessments produced by industry must be scrutinised carefully, which generally occupies authorities for just as long as a risk assessment itself. The proposal to soften data requirements for intermediate products must also be criticised, as the past has also shown how, especially in case of accidents involving intermediate products, a lack of necessary data causes problems.

As for chemicals with particularly hazardous properties (persistent/ bioaccumulating, persistent/mobile or CMR, see chapter 1), introducing a separate procedure instead of the currently used notification procedure should be considered. If a registered substance which could, if used improperly, enter the environment, exceeds certain yet to be determined thresholds, it would be necessary to immediately determine by extensive testing whether the substance has a combination of harzardous properties. A licence would then have to be granted within a predetermined period. The independent commission of experts working on the German book of environmental book of law (UGB) also suggested to "consider the community-wide introduction of an authorization procedure for certain hazardous substance groups" (UGB-KomE, p. 1450). It should be emphasised that research by the BAuA (Anmeldestelle) and by the UBA has shown that the existing data for several new substances are inadequate for a safe judgement as to whether they are persistent organic pollutants (POPs). The existing system for presenting substance tests should therefore be revised to make it possible to identify new POPs with confidence in cases where a suspicion exists. The UNEP POP convention passed on 10th December 2000 provides that new substances with POP characteristics shall be regulated with the aim of prevention by signatory parties (Articles D2 bis).

With respect the action area to developing substances with better environmental and health properties (see chapter 1), the possibilities for promoting "green chemistry" within the legal procedures for new substances should also be examined. As a first step, the substances which prove safe during the notification procedure (e.g. unclassified according to hazardous properties) should be grouped by application areas and published, along with their names and manufacturers' addresses. The BAuA has already done so for paints with respect to occupational safety. These

"whitelists" could also contain sufficiently tested existing substances which are non-hazardous. A further incentive to market new substances less hazardous for human health and the environment would be to reduce the test requirements in stages 1 and 2 of the notification procedure if favourable properties can be proven during the base stage.

3.4 International activities beyond the EU

The frequent transboundary pollution by chemicals and increasing global trade require international action beyond the EU.

The OECD is an important forum for achieving consensus on chemicals management between industrialized countries. Various committees exchange information and find agreement on important issues in international chemicals management, for example globally harmonising substance classification systems or risk assessment and risk management methods. Synopses of key issues in chemicals safety form an essential basis for a consensual further development of national and European approaches. Hereby, the test guidelines programme is especially important, developing internationally agreed, valid testing procedures as a sound basis for mutual international recognition of substance data and therefore also for risk assessments. International standardisation avoids unnecessary (and in the case of animal experiments, unjustifiable) duplication of tests regarding the same hazardous property. An especially important focus of the programme is on developing procedures for testing effects on the endocrine system (see part II).

Globally, the UNEP, the WHO and the FAO are developing a series of international, legally binding agreements on chemical safety. For example, greenhouse gases like CFC and sulphur hexafluoride are regulated by the Climate Convention, and CFC and other ozone depleters in the Montreal Protocol.

The PIC Convention (prior informed consent) signed in Rotterdam in September 1998 contains a binding procedure which strictly regulates trade with particularly hazardous substances, and places obligations on states which export chemicals that are banned or heavily restricted domestically. Germany currently has ratified the convention to enable it to come into force quickly.
On 10th December 2000, the text of a global POP convention was agreed. Hereafter, a global ban - or at least strong restrictions - is planned on 12 POPs which can cause problems at great distances from their points of emission. Moreover, a procedure is included that new substances with POP characteristics shall be

regulated with the aim of prevention by the parties. In May 2001, this convention is to be signed in Stockholm.

Under the UN ECE convention on long-range transport of air pollutants (LRTAP), a POP protocol was agreed in June 1998 in Århus (Denmark), covering 16 substances. For Europe (including Eastern Europe and Central Asia) and North America, the protocol contains provisions which in parts exceed the provisions required from the POP Convention. Because of the standards already achieved in Germany, only minor adjustment is still needed for legal and formal reasons: Therefore, ratification should soon be performed to enable implementation and entry into force.

As a major industrial chemicals producer, Germany has a special responsibility in international negotiations on chemical safety. In agreement with the other EU Member States, efforts should be made to ensure that the EU continues to take a lead internationally in environmental and health safety. This is also important to guarantee Europe's competitiveness as a location for chemicals production. In particular, the precautionary principle should be anchored bindingly in international agreements (not in preambles only), and environmental conventions must not be subordinated to global trade agreements (WTO/GATT).

Promoting transfer of knowledge and technology is essential for the implementation of international chemical safety agreements, both in Central and Eastern European countries (some of whom are candidates for EU membership) and in the developing world. Some developing countries and countries with economies in transition have no management of chemicals at all, and targeted projects to support them are indispensable. One example for such a project is the GTZ project for producing a PCDD/F emissions inventory in Thailand. The new POP Convention contains provisions for financial and technical support. Therefore, it could be a suitable basis for international management of chemicals.

3.5 Final note

Legal regulation of chemicals cannot be the only instrument used to ensure that chemicals are used safely and without harm to the environment. The high level of proof required for statutory regulation means that only especially hazardous substances can be regulated. In order to effectively substitute harmful substances, soft instruments to modify behaviour indirectly and informational instruments must be used. It is essential that manufacturers and users have sufficient information to be

able to choose the most environmentally sound available alternative (see the following chapter 4).

4. Assessment of and acting on substance flows

Global pollution is increasingly caused by diffuse inputs, in which products (during use and disposal) play a significant role. A wide-reaching reduction in the environmental burdens associated with products is therefore necessary, and life-cycle analysis of substance and energy flows is a crucial instrument for conserving resources and reducing pollution.

Assessing of and acting on substance flows is therefore intimately connected with environmental policy on products. A fundamental principle of integrated product policy (IPP), as formulated in the background document on product-related environmental policy for the EU meeting of environmental ministers in Weimar in 1999 (Umwelt 6/1999, Sonderteil), is "to monitor substance flows from cradle to grave". Meanwhile, the EU Commission has published a greenpaper on integrated product policy which will be a fundamental basis for further discussions.

In view of the variety and rapid change in the cradle-to-grave substance flows caused by production and products, from substance extraction until disposal, monitoring them can be a function of the state only to a very limited extent. The state must directly regulate hazardous substances using chemicals legislation, but problems with overexploitation of resources, for example, or creeping accumulation of hazardous substances in the environment, can only be solved to with non-legal instruments. Most appropriate are instruments for indirectly modifying behaviour and instruments for self-regulation.

The necessary information about chemicals and less polluting alternative chemicals or technical solutions is often available (only) to private actors, who should, mostly on their own initiative, use the information in environmental management of companies, substance flow management across companies, and voluntarily pass it on to consumers and other users, in quality control, product labelling or eco-labelling, for example.
The key to a precautionary, sustainable development lies in innovation which systematically includes the environment in planning, developing and designing products. This kind of innovation requires transparent transfer of information and the

participation of customers and users. The UBA wants to encourage innovation with the handbook ("Was ist Ecodesign?“).

Innovation alliances between actors are required to realise potential for environmental innovation throughout a product's life-cycle and to manage substance flows between companies. Depending on the task in hand, these actors may include research institutes, user groups, consumer associations, environmental groups and trades unions, as well as companies in the substance chain (see the UBA publication "Sustainable Germany", 1997).

A decisive factor in the success of environmental innovation in products and services is knowledge about the environmental importance of the materials and auxiliary substances involved in their production. Based on a description of the desired function, the most resource efficient and low pollution variant can be identified, a process assisted significantly by life-cycle and product line assessments.

There is frequently a wide range of substances to choose from for a specific purpose (e.g. auxiliary agents for textiles), but users are frequently inadequately informed about their impact on the environment or human health. Classification schemes are an appropriate instrument for producing and communicating information for users about the relevant properties of substances or preparations. The UBA has taken up the suggestions by the Enquete Commission on protecting the environment and human health for a classification system for textile auxiliary agents, and commissioned a study to devise a procedure for studying and classifying them ("Konzipierung eines Verfahrens zur Erfassung und Klassifizierung von Textilhilfsmitteln", FKZ 109 01 210). As a result of this work and the pressure it exerted, the chemicals industry, represented by the association for textile and leather auxiliary agents, tanning agents and detergents' raw materials producers (TEGEWA), undertook a voluntary commitment on classifying auxiliary textile agents by their significance for water quality "Selbstverpflichtung zur Klassifizierung von Textilhilfsmitteln (THM) nach ihrer Gewässerrelevanz" in November 1997. They describe a model for classifying the agents which corresponds only in part to the ideas of the UBA. In March 1999, the association presented its first report, grouping the number and quantity of agents in use in Germany in three waste water classes.

The user's guide to requirements for the input of chemicals into water ("Anforderungen an Stoffeinträge in Gewässer - Hinweise für Anwender", UBA-Texte 60/99) had a similar aim, providing the users of chemicals with notes towards a

comparative risk assessment, enabling them to find an environmentally sound process or product.

Because of the fundamental importance of information on the composition and properties of chemical products to environmentally compatible innovation, the question should be examined whether classifying them for other areas of use is also meaningful. As well as classification schemes, "whitelists" are also a way of providing a rapid overview of green alternatives in certain areas of application.

A variety of requirements on products is deducted from the topic indoor air quality, an important area of public health. The German government's 1992 plan for improving indoor air quality contains a detailed examination of possible sources of indoor air pollution, as well as concrete proposals to reduce them. The main goal of the plan is to eliminate, or to permanently reduce, the sources of pollution, which can only be achieved with precautionary measures. Product requirements are especially important, in particular for building materials used indoors, such as paints and varnishes, adhesives, plaster, sealants, putty, grout, preservatives for buildings and furnishing.

In designing and awarding eco-labels, systematic knowledge of the environmental properties of products is also essential, and there are certainly ways of guaranteeing confidentiality for data which are important for competition. The procedure for examining applications for the eco-label for low-pollutant paints demonstrates that this is possible and practical. The LAMBDA database, developed for the UBA, collects, processes and maintains all the data on raw materials, chemical ingredients and addresses needed for the assessment and for processing the application itself. The database guarantees a high level of security.

Assessment of and action on substance flows do not focus primarily on the relative environmental soundness of specific chemicals used in a product. Instead they examine its function, and how this function can be fulfilled with a minimum impact on the environment. The following illustrates the procedure with the example of flame retardants.

Fire damage is among the most serious and far-reaching, and humans has long been trying to reduce the risk of fire. One possibility is to modify flammable materials by adding flame retardants, making them less flammable. Three lines of development in the second half of the twentieth century made this measure for fire safety increasingly important. Firstly, the advent of plastics brought more and more

flammable articles onto the market. Secondly, the spread of electrical and electronic equipment meant that these materials were increasingly used in equipment where a malfunction brought a high fire risk (short circuits, etc.) with it. Thirdly, the chemicals industry greatly extended the range of flame retardants, in particular with the development of organohalogen compounds. The insurance companies and the emergence of technical regulations, e.g. CEN or CENELEC, also encouraged the use of flame retardants in products.

Today, flame retardants based on various kinds of chemicals are manufactured and used:

- *Inorganic flame retardants:* boron, aluminium, antimony, molybdenum or magnesium compounds; inorganic phosphates, elemental (red) phosphorous
- *Organic flame retardants:*
  a. Organohalogen flame retardants: brominated compounds (e.g. polybrominated diphenylethers and biphenyls), chlorinated phosphorous compounds (e.g. tris-(2-chlorethyl)phosphate) or phosphor free chlorinated compounds (e.g. chloroparaffins)
  b. Halogen free organic flame retardants: phosphor (e. g. triaryl phosphates), or nitrogen compounds (e. g. melamine and its derivatives)

These groups of substances cover a large number of individual chemicals - global turnover in the flame retardant market in 1992 was c. 610,000 t/a, about 90,000 t/a in Germany alone, even ignoring substance flows in import/export. In general, organohalogen flame retardants have a greater potential health and environmental hazard than the majority of inorganic products and products free of halogens.

Polybrominated diphenylethers (PBDE) are an important group of substances which is currently heavily and intensely discussed. Persistency is a characteristic of PBDE and, as lipophiles, they have a great potential for geoaccumulation. The question of whether highly brominated members of the group can be debrominated to produce more toxic and bioaccumulating compounds cannot as yet be answered with certainty. The overall goal should be to achieve a ban of the production and use of these persistent xenobiotic substances in the EU in the medium term. It is to be expected that, regardless of the agreed short-term goal of rapidly substituting pentabromodiphenylether, an EU-wide ban on the use of the entire substance group will be hard to achieve. Another approach might be the planned ban on using all polybrominated biphenyls and diphenylethers in the envisaged EU directive on electronic scrap. However, it seems very likely that this directive will be linked to the

results of the risk assessments for existing substances according to the Existing Chemicals Regulation.

The type and extent of flame retardant use is crucially influenced by the basic fire safety philosophy, society's acceptance and weighting of safety risks and the inherent properties of the materials. The legitimate desire to reduce the risk of fire as far as possible has long obscured the concurrent increased risks for public health and the environment. The majority of organohalogen flame retardants in particular, is a group with a high potential of toxicity for humans and the environment, persistence and bioaccumulation. The use of flame retardants on computer keyboards is an example of excessive and unnecessary fire safety: devoid of a high voltage power supply, keyboards present as little fire risk in themselves as the papers and other office materials lying next to them.

A strategy to reduce the health and environmental risks caused by hazardous flame retardants should therefore approach less the substitution of the individual chemicals rather than the basic issue of fire safety measures which are neutral to the environment and human health. In an R&D project on product chain controlling ("Stoffflüsse ausgewählter umweltrelevanter chemischer Stoffe: Produktlinien-Controlling", UBA-Texte 80/96), these broader issues were taken up in an examination of alternatives to flame retardants in personal computers and automobiles, which fell into the following basic types:

- *Using non-flammable materials:* merely substituting flammable with non-flammable materials, e.g. plastic with ceramic circuit boards, can render the use of flame retardants irrelevant.
- *Preventing fire risk by improving design:* Increasing the distances between possible flashpoints and flammable materials may be sufficient.
- *Scrutinising fire safety regulations:* Are existing fire safety regulations genuinely justified, when the risk of fire is weighed against the risks associated with flame retardant chemicals (e.g. keyboards)?
- *Substituting hazardous flame retardants* with products that have less impact on the environment and human health.

In the aforementioned report, these alternative fire safety measures were discussed with important actors in computer and car seat producing industry, to give an impetus to innovations in these directions. It emerged clearly that decisions on environmental innovation require a more or less safe estimate of the future directions in the requirements for handling products and chemicals.

The UBA has commissioned a further R&D project, which is currently working on principles for assessing the merits of substituting flame retardants. The goal is to provide robust information on the major areas of flame retardant use, assess the (eco-)toxicity of selected chemicals and examine options for replacing critical substances.

Similar procedures could be applied to every other environmentally significant substance group, application or technique. Providing information and assessment principles is essential, both for drafting chemicals policy action and to support substance flow management by economic actors. A flexible mixture of instruments, adapted to suit each specific situation is generally required.

In order to take more account of the precautionary principle and sustainability in chemicals and product management measures based on substance flows, the UBA considers the following measures urgently necessary:

- Improving the provision - by industry, associations and authorities - of public and consumer information on the risks of chemicals.

- Optimising the transfer of knowledge with legally based duties for manufacturers and importers.

- Extending the substitution requirement under § 16 par. 2 of the Hazardous Substances Ordinance to cover environmental risks as well as health risks (at present only health risks are covered) to provide an incentive to use substitutes which pose less risk to the environment.

- Extending labelling requirements to include declaring certain product ingredients, e.g. additives in plastics.

- Substance flow analyses of important economic sectors, in order to provide users and consumers with the essential information they need in order to develop less polluting and more resource efficient products and processes.

- Updating the criteria for eco-labelling with a comprehensive, uniform treatment of the issues related with the risks of ingredients, to provide better consumer information.

- Further methodological development of the LCA impact categories for human health and ecotoxicity, to assist product optimisation and comparative advertising.

- Developing comparative risk assessment schemes for users of chemicals:
- Sector specific classification systems for critical product groups
- Voluntary commitments by industrial sectors to develop comparative risk assessment procedures (as in the textiles industry)
- Promoting environmental management systems to reinforce environmentally responsible company practice
- Financial aid for users of products and processes which pose less risk for human health and the environment.

- Subsidies and research funding for the development of chemicals and processes which pose less risk on the environment and human health ("green chemistry").

- Greater integration of environmental requirements - including those on chemicals - in product standards, e.g. for building products (in standards of CEN/CENELEC). Conversely, scrutinising product standards which encourage the use of hazardous chemicals (e.g. brominated fire retardants).

- Consistent consideration of criteria based on environmental and human health issues by the public sector when purchasing and awarding contracts.

Sustainable and Precautionary Risk Assessment and Risk Management of Chemicals

Part II: Chemicals in the Environment which Interfere with the Endocrine Systems of Humans and Wildlife

Chemicals in the Environment which Interfere with the Endocrine Systems of Humans and Wildlife

– Pollution, Effects, Control Strategies –

Presented by: Andreas Gies, Christa Gottschalk, Petra Greiner, Wolfgang Heger, Marike Kolossa, Bettina Rechenberg, Elke Roßkamp, Christa Schroeter-Kermani, Klaus Steinhäuser, Christine Throl

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1. Introduction

In 1995, the Federal Environmental Agency (UBA) hosted the first symposium on endocrine disrupters in the environment (UBA-Texte 65/95). Since then, an intense debate has been conducted in Germany on the related mechanisms, pollution levels and resulting risks to public health and the environment. Opinions on these substances and their endocrine effects are still strongly divided, not only among the various interest groups, but also among experts themselves. An international register of current research projects in this field shows Germany to be the most active country in Europe, with 50 current projects. Both the intensive research and the debate on risk assessment have meant that – despite the large gaps in our knowledge which remain – the importance of this problem in Germany can be assessed in far greater detail than ever before.

In addition, the European Parliament, European Commission and many national governments in the EU have come to recognise the importance the issue of endocrine disrupters, and are asking for more activity with a greater integration into the chemicals safety programme. A key document is the Commission's 17/12/1999 communication on a community strategy for endocrine disrupters (COM 99/706), which sets out the necessity of further research, informing the public and taking political action. Short-term proposals are prioritising the various substances, primarily with respect to the risks associated with their hormonal effects, applying existing legal regulations (e.g. assessing high-priority substances according to the Existing Substances Regulation (EC 793/93)) and deciding on monitoring programmes, international co-ordination and information for the general public. In the medium term, xenobiotic endocrine disrupters should be determined and assessed, and impetus given to research and development into improved evaluation of the consequences. This has already begun. In the long term, the EU legal framework on chemicals, crop protection agents and biocides may require adjustment.

In August 1999 a government decision in the German Bundestag called for a staged but drastic reduction in discharges of proven endocrine disrupters (14/1471 of 4/8/2000), drawing on the similar decision by the European parliament on 26th January 1999. Furthermore, it asked that those chemicals which can also reach ground water and drinking water supplies, and which can regularly be shown to have done so, should be banned, and limits for drinking water should be determined. The use of environmental chemicals should also be reduced where there is reason to suspect that they are endocrine disrupters. Domestically, special measures should be taken for alkylphenol(ethoxylate)s, phthalates and tributyltin compounds. In a decision on 26th October 2000, the EU parliament once again called upon the

Commission, in the strongest terms, to take rapid action to reduce the risks from endocrine disrupters, rather than waiting for further tests.

The greater emphasis on precaution, expressed in e.g. the EU Commission's 2/2/00 white paper on the precautionary principle (COM 2000 (1)), makes it necessary to examine whether our current state of knowledge about environmental chemicals which disrupt the endocrine system calls for precautionary reduction measures.

In this context, the following report

- assesses existing epidemiological knowledge on detriments to human health,
- briefly outlines the levels of pollution by important endocrine disrupters in the environmental media,
- describes the current state of development in procedures for testing the endocrine effects ,
- lists the environmental chemicals currently considered by the EU to be endocrine disrupters, and assesses the need for regulation
- proposes measures to influence public behaviour directly and indirectly, improve our knowledge and reduce risks.

2. Assessing existing knowledge on detriments to human health

It is undisputed that a number of substances are able to disrupt endocrine processes, with the potential for impairing development and reproduction or increasing the risk of cancer[1]. However, to fully evaluate the risks, we must assess the probability that biologically significant concentrations of such substances may be present now or in the past in foods, drinking water or environmental compartments, i.e. whether they could, under realistic conditions, in fact trigger harmful effects in humans and animals. To answer this question, information on a potential endocrine disrupter must be available, both as to its activity, i.e. dependency on dosage or concentrations, and as to the actual concentrations, i.e. human and animal exposure.

However, even today there are no reliable data (which can be extended to different animal species or humans) on the potential of known endocrine disrupters for triggering significant effects. Results from *in vitro* testing of isolated hormone receptors or cell cultures, as are available for many xeno-estrogens, are inadequate for a number of reasons.[2]

It is therefore surprising that in 1999 the BUA (GDCh-Advisory Committee on Existing Chemicals) and subsequently the German Council of Environmental Advisors (in its 1999

special report on environment and health) expressed the view that "the significance of endocrine disruptors for human health has been exaggerated"[3].

The following details the important aspects in assessing significant harm to humans associated with the effects of endocrine disrupters.

2.1 Male reproductive functions

2.1.1 Sperm quality

The debate on the possibility of human health being harmed by substances with effects on the endocrine system was initiated by a supposed reduction in men's sperm quality in industrialised countries. A meta-analysis by Carlsen et al.[4] originally concluded that the sperm count in the ejaculate from test subjects has fallen by c. 50% between 1938 and 1990. There followed a detailed discussion in the scientific literature[5] as to the significance of the results and the likelihood that environmental pollutants had played a role in this development. Taking this criticism into account Swan et al.[6] re-evaluated the data, confirming a fall in sperm count in Western Europe and North America (but not elsewhere) and excluding the possibility of statistical errors in the sampling and analysis. As the authors nonetheless admitted, "We have not addressed the cause(s) of this decline or assumed an environmental aetiology", stating in later work: "Although few of these trend studies have examined possible causes, common environmental exposures are plausible."[7] Other writers studying the phenomenon of falling sperm counts also discuss cultural, socio-economic as well as environmental factors as potential causes. A study co-ordinated between Finland, Scotland, Denmark, France and Japan has now shown that sperm quality varies geographically[8,9], making the findings here especially important in assessing the situation for Germany. There are now three studies in Germany, examining sperm quality trends in thousands of test subjects from fertility advice centres. The tests in Hamburg[10], Leipzig[11] and Magdeburg[12] revealed significant falls in sperm quality parameters, shown relative to Swan's calculations for western Europe in Fig. 1.

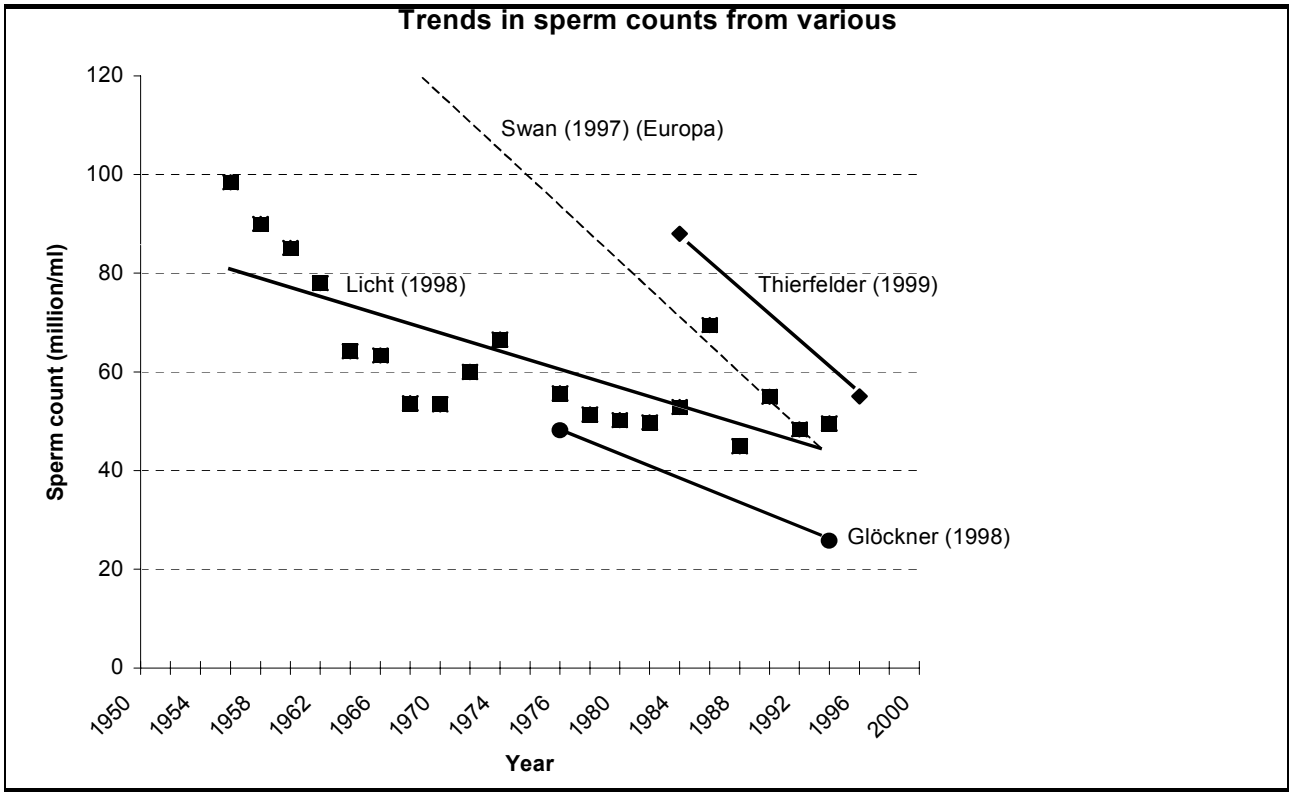

Figure 1: Linearised graph of trends in sperm counts from various German studies. Sources: see text.

In interpreting these observed results, the following should be noted:

- The studies each comprised several thousand test subjects. They are among the largest in the world, and can be considered correspondingly reliable. The men tested had sought advice on fertility problems, and are therefore not typical for the entire population. Nonetheless, similarly large-scale surveys in France, for example, where the sample was more representative of the population as a whole, show similar results[13]. In Thierfelder's study at least, the sperm characteristics of men where no results were found relating to the causes of their infertility were considered separately.

- The fall in sperm quality can be found in both of the former German states, but appears to set in earlier in the west than in the east. For the past 10 years, the data from Hamburg show stabilisation at a low concentration, around the 20 mil./ml described by the WHO as critical for fertility. A new study of not preselected recruits in Denmark[14], shows similar concentrations to those in Hamburg. This also implies that the data collected from German men with fertility problems are indicative for the entire population.

- The reduction of sperm counts appears to depend more on date of birth than on the date the tests were made. This means that, surprisingly, older men have better sperm counts than younger men, making it likely that the damage occurs before birth or during development.

- Wearing tight trousers, or eating soya-based meals rich in phytoestrogens, both proposed explanations - which were not substantiated by studies[3] - appear less able to explain the observed phenomena[3], as these lifestyle factors did not apply in the former GDR. However, other - equally controversial - possible causes are being considered: consumption of alcohol, cigarettes, caffeine, etc. (which were equally prevalent in the GDR).

- The geographical variance observed in western countries could imply the influence of still unknown lifestyle or environmental factors.

- This raises the question of how far falling sperm counts affect the fertility of the German male population. WHO guidelines define a sperm count below 20 mil./ml as abnormal[15], a significant reduction on the previous norm[16] of 40 mil./ml. Danish tests on the connection between sperm count and fertility have shown that male fertility is impaired if the sperm count is below 40 mil./ml.[17]

- Overall, the hypothesis that the cause lies in chemical effects has become increasingly likely.

Assessment:

Are there changes in sperm quality in Germany which could be caused by environmental factors?

Yes. Several independent studies have found a significant deterioration in the quality of sperm in men from western and eastern Germany.

Is there evidence that similar phenomena have occurred in the sons of women who took DES (diethylstilbestrol), an artificial estrogen, during pregnancy?

Yes. Several studies have found sperm counts about one third lower than in the control population in the sons of women treated with DES[18].

Have epidemiological studies or animal experiments provided evidence that the development could have been caused by phytoestrogens?

No.[19]

Have epidemiological studies or animal experiments provided evidence that the development could have been caused by industrial chemicals or pesticides?

Yes. Animal experiments have shown that low doses of xeno-estrogens (e.g. bisphenol A[20]) and antiandrogens (e.g. dibutylphthalate[21]) disrupt sperm production, although the results and design of the experiment are a matter of heated discussion.

2.1.2 Testicular cancer

The incidence of testicular cancer standardised for age is obviously rising continuously. Although testicular cancer is still not a frequent form of cancer, it can occur in younger men, which gives it a high importance for society. It is supposed that lifestyle and environmental factors, as well as genetic predisposition and workplace conditions, play a role in the development of testicular cancer. This is indicated by the increased incidences and the significant geographical variance[22]. In Denmark, for example, the incidence rose by c. 2.6% annually between 1943 and 1996. However, the increase has tended to fall recently (since c. 1985), especially in men born after 1963. In the USA, however, the incidence of testicular tumours has risen in white, but not black men. This may imply a significance for genetic predisposition.[23]

The development of sexual organs is hormone-dependent, and it is therefore plausible that affecting the hormonal influence on this development could also affect the development of testicular cancer. There is no experimental proof, as there is no suitable animal model for the most frequent form of testicular cancer in men (seminoma). On the other hand, a meta-analysis by Toppari et al.[24], implies that prenatal exposure to therapeutic DES is a significant risk factor for testicular cancer: the risk of testicular cancer was 2.6 times higher for the sons of women who were treated with DES than for the population as a whole.

Recent studies, such as those by Moller[25] and Jacobsen[26], suggest a common aetiology for deteriorating sperm quality and the risk of testicular cancer. The authors present the following evidence:

- Men who have fathered children are at a significantly lower risk of developing testicular cancer.
- Men with poor sperm characteristics have a higher risk of testicular cancer.
- Men with a low relative fertility (i.e. who have fathered less than the average number of children for their age group) have twice the risk of getting testicular cancer.
- However: while low relative fertility can be related to testicular cancer, the cancer risk is not lower for men with above-average fertility.
- Men in marriages with fertility problems have a high probability of developing testicular cancer.

- Low sperm count and mobility, and an increased level of abnormally shaped spermatozoa correlate to an increased risk of testicular cancer.

In the view of this report, these data are consistent with the hypothesis that male subfertility and poor sperm have aetiological factors in common with testicular cancer.

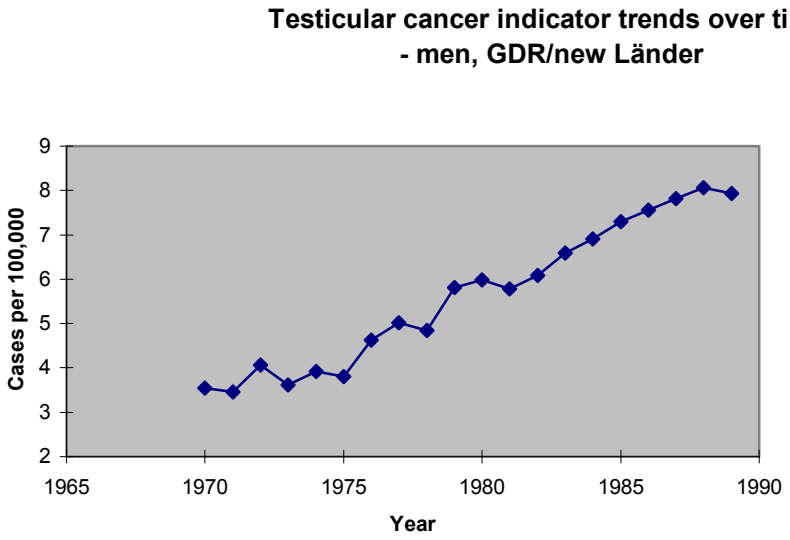

Figure 2: Incidence of testicular cancer in the GDR, grouped by age.

Source: Cancer Atlas of the GDR[27]

The aforementioned pilot study[22] traces the incidence of testicular cancer in the GDR between 1961 and 1989 on the basis of the "Cancer Atlas of the GDR". The incidence, grouped by age, quadrupled steadily over the 28 years, from 2 to 8 cases per 100,000, an annual increase of 5%. Urban districts were found to have a 25% higher risk of illness than rural districts.

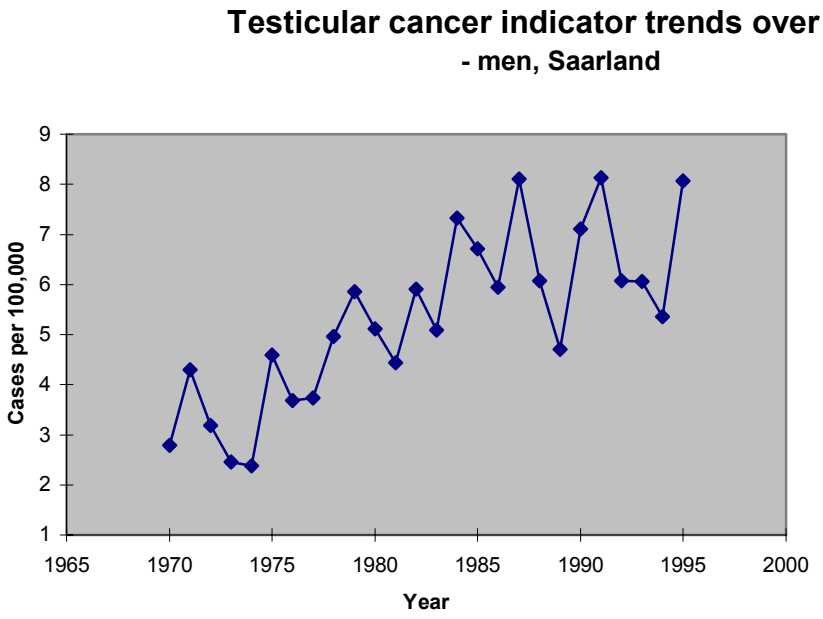

Figure 3: Incidence of testicular cancer in Saarland, 1970-1995, grouped by age. Source RKI

The Saarland cancer register shows an increase in new cases of testicular cancer from 2.8 to 8.1 cases per 100,000 between 1970 and 1995.

Assessment:
As in most industrialised countries, Germany is also experiencing an increase in new cases of testicular cancer cases. Recent studies suggest that deteriorating sperm quality and increased testicular cancer could have a common aetiology. The relevance of estrogenic substances appears plausible, due to the increased risk of testicular cancer found in men who had been exposed to DES *in utero*. However, the lack of prospective studies, the long latency period of the illness after prenatal exposure and the lack of animal models for this form of cancer make it impossible to prove causality.

2.1.3 Prostate cancer

The incidence of prostate cancer in the GDR doubled between 1961 and 1989, from 12 to 24 cases per 100,000. In Saarland, the rate of new cases per 100,000 rose from 33 to 62.

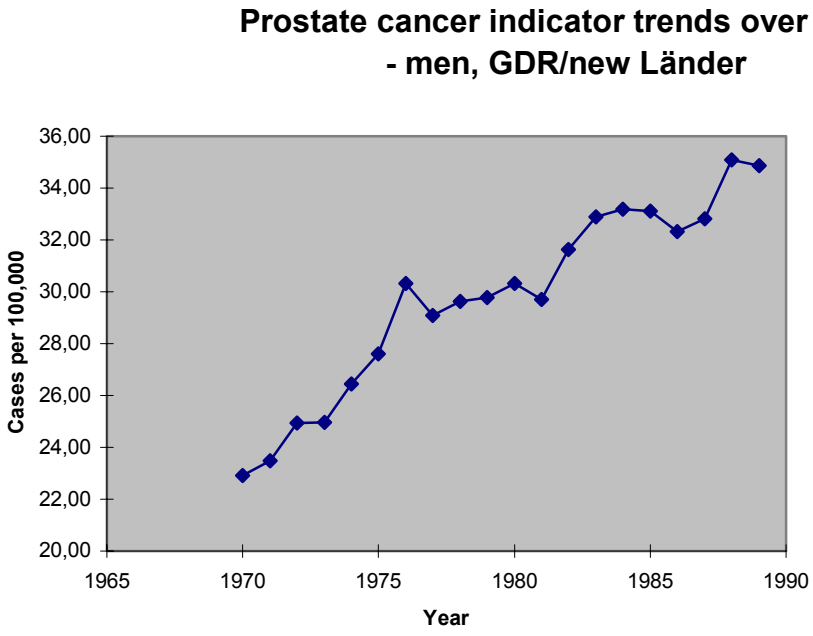

Figure 4: Incidence of prostate cancer in the GDR, 1961-1989, grouped by age

Source: Cancer Atlas of the GDR[27]

The increased incidence is also confirmed by the other German cancer registers[28]. Increases in incidence and mortality can be found internationally for the illness, although there is very great variance in the rates[29]. Regions where there is a high incidence of prostate cancer in men correlate with high levels of breast cancer in women[30]. Several epidemiological studies describe how users of pesticides have a significantly increased risk of developing prostate cancer[31,32,33,34]. This can be partially traced back to the endocrine effects of pesticide use, although the actual pesticides are unknown[35].

There is also a connection between increased levels of estrogen in mothers during pregnancy and neoplastic development in the prostates of male children. Cellular change in the prostate during pre- and perinatal development can make these cells especially sensitive to the neoplastic effects of testosterone and estrogen later[36]. This would form a plausible explanation for a connection between xeno-estrogen and increased incidence of illness.

Assessment:
There is currently no evidence for a causal connection between exposure to endocrinally active substances and an increased incidence of prostate cancer. However, this increase could hypothetically be explained by the effects of endocrine disrupters.

2.1.4 Malformation in male genitals

A number of authors[24] has postulated a connection between the occurrence of genital malformation - in particular cryptorchidism and hypospadias - and the prenatal exposure to endocrine disrupters. A Spanish epidemiological study points to a possible connection between pesticide use and the frequency of male genital malformation[37]. In order to clarify whether existing studies and observations in Germany exhibit a trend in the frequency of genital malformation over time, the UBA commissioned a pilot study to summarise and evaluate the data on the prevalence of genital malformation, and produce hypotheses as to the causes[22], the results of which are now available. Genital malformation has been selected as a symptom, as there is a short time span between possible external factors and the symptom, and therefore a correlation between exposure and its effects is most likely to be found.

However, the pilot study could prove no uniform trends in the incidence of genital malformation over time. The data collection methods within Germany and across Europe are not uniform and not suited to the issue under examination. The frequencies determined by the different institutions vary hugely. The study's authors plead for a uniform nation-wide register of malformations to register regional and temporal trends, and also point to the possibility of using existing precautionary examinations of children.

Assessment:
Currently available surveys do not permit a final judgement as to whether genital malformations are occurring more frequently in new-born males than earlier. As yet there is no malformation register to record these abnormalities uniformly and with the necessary precision. Such a register would be highly desirable, not least because connections between increased malformation and pollution are being made more and more often.

2.2 Female health

2.2.1 Breast cancer

Breast cancer is the most frequent form of cancer in women, and exposure to estrogen is one risk factor in its incidence. However, a distinction can be drawn between estrogen-sensitive breast tumours and others. According to Glass and Hoover[38], the incidence of estrogen-sensitive tumours has risen significantly faster in recent decades than that of other breast cancers. Since the publication of a study by Wolff in 1993[39], which linked levels of DDT and its metabolites in the body with the incidence of breast cancer, there has been a heated debate as to the significance of xeno-estrogens in the development of breast cancer. Years or decades may pass between exposure and the incidence of the illness, and retrospective studies therefore have great difficulty in identifying a connection between exposure and increased incidence. Since personal factors, for example nutrition or hormone levels in various phases of life, also affect cancer development, designing suitable studies is even more difficult.

Neither the larger retrospective studies nor more recent prospective studies have been able to reinforce the suspected link between exposure to DDT and the frequency of breast cancer[40,41,42,43,44]. The same applies for studies of PCB and breast cancer.

Apart from these two groups, there have been few studies of the effects of endocrine disrupters on incidence of breast cancer. Two recent prospective studies from the USA[43] and Denmark[42] show that hexachlorobenzene and dieldrine may be risk factors in the development of breast cancer.

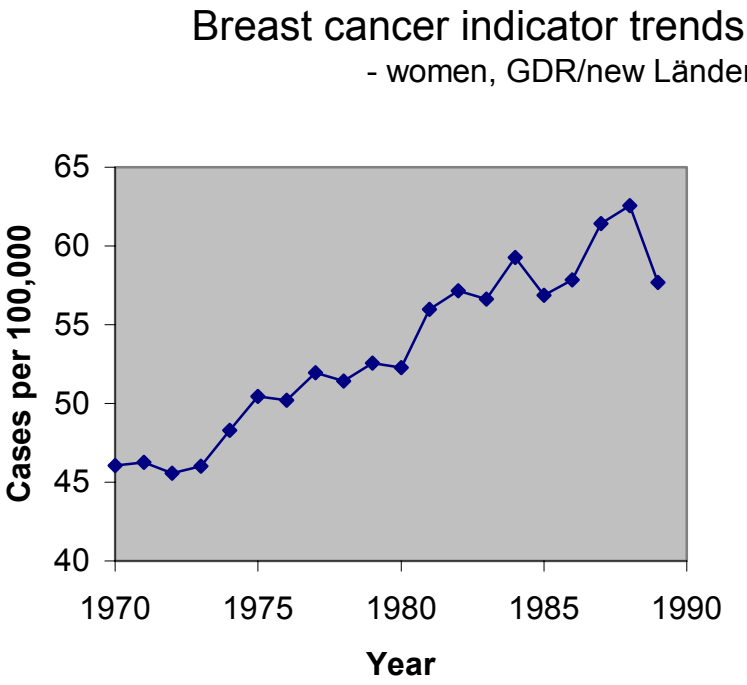

Figure 5: Incidence of breast cancer in the GDR, 1961-1989, grouped by age.

Source: Cancer Atlas of the GDR[27]

An upward trend in new cases of breast cancer is emerging in Germany. In the former GDR, this rise was from 27 cases per 100,000 in 1991 to 45 in 1995.

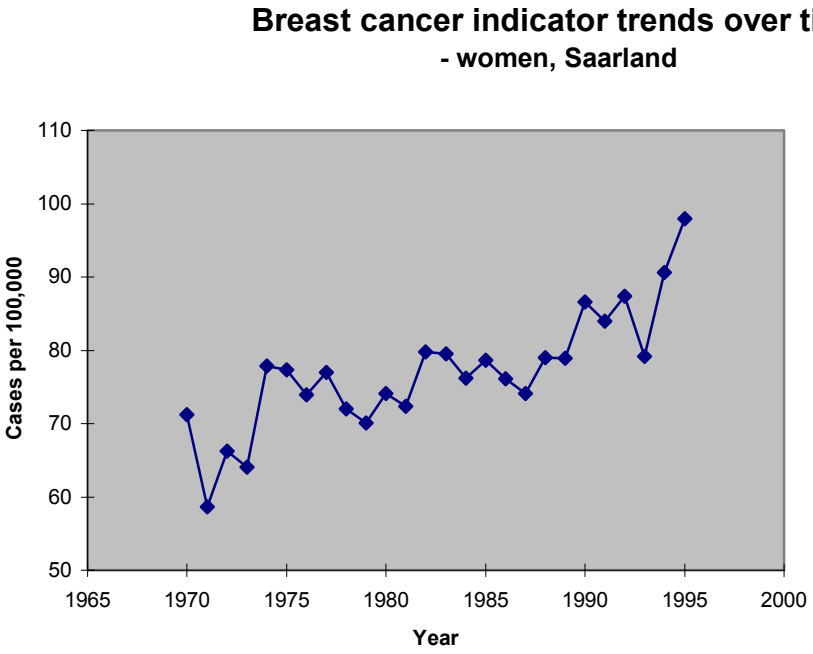

Figure 6: Incidence of breast cancer in Saarland, 1970-1995, grouped by age. Source RKI

The Saarland cancer register shows a rise from 71 cases per 100,000 in 1971 to 98 in 1997.

However, there is no disputing that factors such as genetic predisposition and western industrialised lifestyles (nutrition, tobacco and alcohol use and lack of physical activity) play a major role in the development of breast cancer. Other important factors are the time of first menstruation and the onset of menopause, the number of children born and at what age, as well as specific hormone treatments.

Assessment:
Studies to date have restricted themselves more or less exclusively to the links between DDT and breast cancer. According to the vast majority of the studies (in particular the better studies), there does not appear to be such a link. The discovery in recent prospective studies of positive links with other pesticides make further studies desirable.

2.2.2 Early Puberty

There are very few studies of the question as to whether an early start into puberty may be linked to exposure to chemicals. In an article in "Nature", Howdeshell et al. note that the estrogenic industrial chemical bisphenol A given in very low perinatal doses leads to an earlier occurrence of puberty in laboratory animals[45], although there is no precise description of the experiment. In Central Europe the menarche has been observed to occur on average three months earlier per decade.

2.3 Other changes related to reproduction

2.3.1 Gender ratio

The gender ratio in newborns is known to be 106 male to 100 female[46]. This ratio is maintained by hormone concentrations in the parents at the moment of conception. Changes in the levels of gonadotropine or steroids can produce a change in this ratio. It is known that men exposed to dioxins have a significantly lower level of testosterone and a higher level of gonadotropine.[47] Tests of the population affected by the accident at Seveso in 1976 have shown that females are significantly overrepresented in the offspring of those exposed to high levels of dioxins[48]. Similar shifts towards female births were observed where the fathers had been exposed to high doses of the antiandrogenic pesticide vinclozoline[49] or organo-chlorinated pesticides[50].

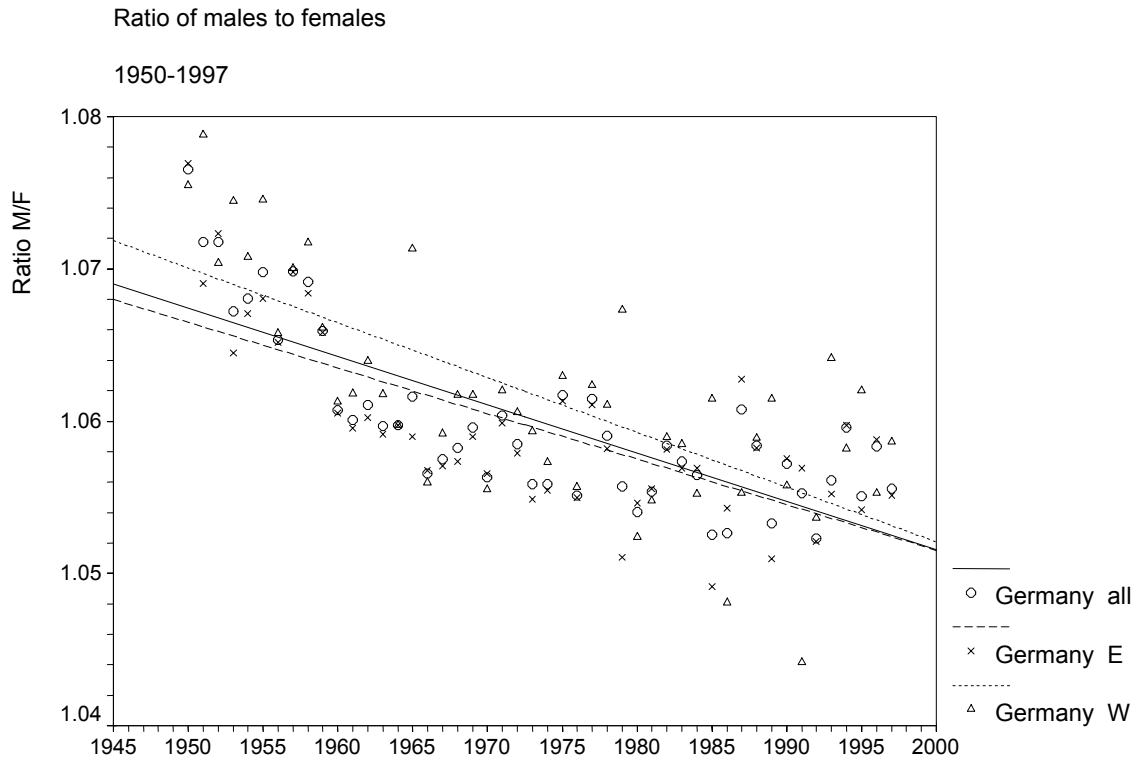

Figure 7: Gender ratio in Germany. Linearised trends in the whole of Germany, the new Länder and western Germany. Source: Rösch et al.[22]

A rising trend in the relative numbers of new-born females has been observed in many industrial countries[51], although geographical differences have been reported here too. Astolfi and Zonta have found a fall in male births in Italian conurbations, while on the other hand, more males are being born in rural areas. The Magdeburg pilot study has evaluated the statistics on the gender of new births.[22] A highly significant fall in the number of male births can be shown, both in Germany as a whole and in eastern or western Germany. Between 1950 and 1997, the ratio of male to female births fell from 1.08 to 1.05. This shift clearly began in the 1950s and is continuing. Vartiainen et al. have studied live births in Finland since 1751. While there was an increase in the proportion of male births until 1920, there has been a steady decrease since the 1940s, interrupted only by peaks before and after the two world wars. The shift began before intensive industrialisation and before the widespread introduction of pesticides and hormone-based medicines, leading the authors to conclude that a causal connection is less likely.[52] Similar analyses are not yet available for Germany.

Assessment:
Although a shift towards females in the birth ratio cannot automatically be termed a negative effect on human health, this parameter is a sensitive indicator for the hormonal environment in early pregnancy. The shift indicates changes in this environment. However, hypothesising an influence from endocrine disrupters does not explain the pre-industrial shift.

2.4 Behavioural change and endocrine disrupters

A summary of the key discoveries as to the influence of PCB on behavioural parameters in new-born babies and children can be found in a recent article by Winneke[53]:

"PCB can enter the placenta and therefore expose the human foetus to contaminations of the maternal fatty tissue. After birth, the baby is exposed to relatively high concentrations of PCB through maternal milk. As a potential hazard in development, these concentrations of PCB in lactate have received significant attention. After the ban on producing and using PCB, concentrations in human milk have fallen steadily since the mid-1980s, albeit more slowly than those of other organochlorine compounds. As for the range of biological effects – enzyme induction, immunotoxicity, reproductive toxicity and thyroid subfunction – experimental and epidemiological results imply that the compounds' neurotoxicity with respect to development plays a prominent role[54]. There are estimates that increases in environmental concentration can have a toxicological significance for the developing nervous system in the upper 10% of a typical distribution of the general public [55].

The significance of PCB pollution's toxicity to the developing human nervous system is principally supported by the results from the Michigan study[56,57,58], a cohort in North Carolina[59,60], the outcome of a toxic incident in Taiwan[61,62] and two cohorts in the Netherlands[63,64]. Although all the studies describe negative effects on neurological or cognitive development as a result of early exposure to PCB, the findings are by no means consistent in many important aspects, particularly the spectrum and persistence of observed deficits[65].

Because of these inconsistencies, a Europe-wide study co-ordinated by the MIU [Med. Institute for Environmental Hygiene at Düsseldorf University – ed.] and involving in addition to the Düsseldorf group two groups from the Netherlands and one from Denmark, was begun with support from the EU. The project was funded from 1993 to 1999, and studied the neurological and cognitive/motor development of new-born infants of various ages, and first publications are now available[66,67,68,69]. The results may be summarised as follows: negative consequences from pre- or perinatal PCB pollution are not pronounced up to an age of 18 months, except in isolated cases [which still lie within normal bounds – ed.], while clearer links between poor motor and mental development and early exposure to PCB can be shown for ages between 30 and 42 months.

Alongside their neurotoxicity, PCB's potential for interaction with the endocrine system has recently been receiving more attention[70]. As well as effects on thyroid hormones, which are

under discussion as a possible cause of the developmental neurotoxicity, other forms of interaction with sexual hormones are clearly also especially significant. New animal experiments, conducted by Lilienthal and co-workers within a PUG-funded project (Project Environment and Health – ed.), were able to show significant and persistent antiandrogenic effects of PCB on both the endocrine system and the behaviour of rats[71]. Comparable results in humans are scarce, one of the few being the findings of the Taiwan study, where it could be shown in a matrix test with matched control children that boys exposed to PCB were considerably more seriously affected than girls. The authors take this result to be an indication of estrogenic or anti androgenic effects from PCB during early development of the brain. Further (weak) evidence of PCB interaction with sexual steroids are the shorter penises of the exposed boys in the Taiwan cohorts, as well as the positive link, observed by Lanting[66], between maternal exposure to PCB and the quantities and fat content of their lactation."

Assessment:
The link between PCB in maternal milk and children's' cognitive abilities can be considered proven in Germany as well. The findings are significant, but the deviations are within normal parameters. The role of PCB in obstructing transplacental transport of thyroid hormones is being debated, and animal experiments support the hypothesis. These findings require special attention to substances which affect the thyroid hormone system. Links to other xeno-estrogens are unknown.

2.5 Final assessment of the results on harm to human health

In Germany, the factors discussed above indicate that endocrinally active substances do affect the health and development of humans, although there is as yet no proof of causality. Research projects are attempting to collect quality *in vivo* data (including pharmacokinetics) on at least a few synthetic substances and selected phytoestrogens, to support an evaluation of the causality and the risks.

In principle, however, the changes discovered are consistent with the hypothesis that endocrine disrupters have played a part. Methodological problems, especially the long latency between exposure and effects and the complicated modes of exposure (present, past, *in utero*) make determining potential causality difficult. In addition, the effects of simultaneous exposure to estrogens and anti estrogens, for example, cannot be assessed at present.

Many of these unanswered questions reveal that the instruments for observing the environment and public health in Germany are inadequate.

In particular, there is no perinatal archive, which would make it possible to study the exposure of new-born babies retrospectively. Alongside environmental and health surveys of adults and children, there is no program to record data on umbilical blood or placenta samples or on human lactate, in order to study the exposure of new-born babies prospectively or

retrospectively. The Environmental Specimen Bank could be extended with such a perinatal archive.
The study by Rösch[22] has shown the importance of a nation-wide malformation register for new-born babies, with validated and detailed records of malformations. Monitoring the early phases of life makes it easier to discover the potential causal environmental exposure.

3. Contamination of environmental media and harm to ecosystems from endocrine disrupters

3.1 Harm to aquatic ecosystems

The majority of information as to chemical disruption of the endocrine systems of wildlife in Germany is from aquatic ecosystems. This is due to the fact that most research projects have concentrated on this medium. But there is no reason to suppose that there is no impact on terrestrial ecosystems.

Invertebrates:
The increased incidence of certain disruptions in the fertility and development of marine and limnetic molluscs, such as imposex and intersex formation in prosobranch gastropods, or shell malformation and disruption of larval development in oysters, are considered the direct effects of aquatic pollution by organic tin compounds, especially tributyltin (TBT). TBT is a non-steroidal compound which is used in, for example, antifouling paint for ships. Direct correlations between the imposex and intersex stages and TBT pollution in those areas were found above all in the vicinity of harbours[72,73].

Using the areas of ship's hull coated with antifouling paint in the German merchant navy and a leaching rate of 1 mg/cm^2/d TBT as a basis, it was estimated that 45 tonnes of TBT are discharged into the North Sea per annum. Assuming even distribution, this would therefore produce in theory a total concentration of c. 0.24 ng/l. Measured concentrations of organic tin in German Bight were in fact 1.2 ng/l, in coastal waters 7.6, 6.0 and 2.6 ng/l and in the central North Sea between $\geq$ 1 and 0.5 - 0.7 ng/l[74].

The biological effect is expressed through indirect androgen mechanisms preventing the formation of estrogen and inducing male characteristics in female snails. This effect, associated with a significant increase in endogenous testosterone content, can be shown at TBT concentrations of 5 ng/l (as Sn).[75] Depending on the level of toxicity, the animals' reproductive function may be impaired due to anatomical malformation or the animals may become completely sterile.

The periwinkle *Littorina littorea* and dogwinkle *Nucella lapillus* (North Sea), and the mud snail *Hydrobia ulva* (Baltic Sea) are being observed as indicator organisms. Imposex formation occurs in *Nucella lapillus* at concentrations as low as 1 - 3 ng TBT/l.[76]

The seriously threatened stocks of the common whelk *(Buccinum undatum)* in the North Sea[77], which occur predominantly in sediment in open seas, appear to be recovering slowly, as a consequence of the restriction in the use of organic tin compounds[78]. The lowest NOEC for this species is for reproductive functions, at 8.3 ng TBT/l (measured over 8 months, based on imposex formation)[79].

On the basis of the framework provided for quality standards in the proposed EU water framework guideline, the existing ecotoxicological data were evaluated and the target set for the protection of aquatic habitats from harm from tributyltin compounds at 0.1 ng/l, in terms of tributyltin cations[80].

Samples of *Nucella lapillus* with pronounced imposex collected in 1993-1995 from Norwegian coastal waters contained 48-1096 ng Sn/g TS. Here too, there was a direct correlation between TB content in the animals and the extent of imposex formation. The NOEC at which no malformation could be found was below the discernible limit of 7 ng Sn/g dw, and was determined graphically as 4 ng Sn/g dw[81].

Over 70 marine species are affected by this phenomenon around the world[82].

Summary:
Limnic and marine mollusc species in Germany are exposed to triorganic tin concentrations which give reasons to fear significant harm. Stocks of these species have fallen drastically in recent decades. Contamination by TBT must therefore be assumed to be the cause.

Vertebrates:
Tests on fish from German inland and coastal waters show increased incidence of high concentrations of vitellogenin (preproduct of vitellus) in their blood, regardless of their gender or the time they were caught. Vitellogenin is an indicator for contamination by estrogens and substances with estrogenic effects.[83]

Organisms which are induced to synthesise vitellogenin by external estrogenic stimuli also exhibit other more or less pronounced negative effects, including, among others, a shift in steroid metabolism, atrophy of the liver, delayed testicle growth with frequent occurrence of ova in male testicles (ovotestis) in juvenile and adult males, as well as disruption of gamete production associated with reduced reproductive success[84,85,86]. Since male organisms lack the

target organs for vitellogenin, it is retained in the blood, which can cause damage to the kidneys and calcium deficiency. In addition, this additional abnormal biosynthesis, especially where the fish is exposed to a high level of estrogenic stimulants, depletes the energy and disrupts the hormonal equilibrium in the animal's body [87,88,89,90]. In females, excessive levels of estrogens and estrogenic substances cause prematurity and abnormal development of ovaries and ova, reducing the likelihood of eggs hatching successfully[91].

Another indicator for excessive levels of estrogen or estrogenic substances under discussion is a shift in the gender ratio towards females in fish populations, as well as the increased occurrence of ova in male testicles (ovotestis).

Although the phenomenon of ova forming in fish testicles can frequently be observed both in fish farms and in the wild, carefully designed studies have shown that increasing concentrations of estrogens or estrogenic pollutants can increase the number of hermaphrodites, including fully developed female sexual characteristics[92]. This is also exploited in fish farms, in order to produce faster growing female fish.

Long term exposure of adult male trout and carp to gradually increasing amounts of domestic waste water from a Berlin sewage treatment plant demonstrated a quantitative connection to induced synthesis of vitellogenin in the blood. The spawn from this test series was exposed to the same pollution as the parent fish for a further 12 months after the larvae hatched. The sexual characteristics of the offspring shifted increasingly towards almost complete feminisation where the waste water concentration was at 40 %[93,94]. This level of concentration is certainly possible in Berlin surface water during the summer months.

Studies of fish stocks in Berlin's water bodies conducted by the fisheries agency between 1985 and 1995 have found shifts in gender ratios among certain species (perch-pike, roach, asp), while other species seemed scarcely affected. The catches were made during stock management, aimed primarily at screening out fast-growing and less profitable species. It is therefore possible that the generally larger females were caught in the study . On the other hand, analysis of the catch data in terms of water pollution, using perch-pike caught in 1998 as an example, showed a significantly larger proportion of females in more heavily polluted regions.[95]

However, a study of the gender ratios and gonad structures of roach *(Rutilus rutilus)* and common perch *(Perca fluviatilis)* from the Spree and the Havel, made in the same year, showed no abnormal results[95].

In North Rhine-Westphalia, bream from the Rhine were compared with a related species from the Wahnbach reservoir. A histology of the testicles found ovotestis in only three out of 59 fish from the Lower Rhine, and none at all in the bream from the reservoir. The gender ratio of both catches was balanced. On the other hand, the vitellogenin content of blood plasma was four times as high in male bream from the Rhine as in those from the Wahnbach reservoir (980 and 225 µg/l)[96]. The levels of vitellogenin in the reservoir fish were also raised, which implies some contamination through estrogen-like chemicals.

Vitellogenin tests in male bream from polluted sections of the Elbe showed only slightly higher levels up to 200 µg/l, i.e. comparable levels to those found in the Wahnbach reservoir. Of 97 male fish examined, only 5 had oozytes[97,98].

These results permit us to conclude that increased vitellogenin levels in the blood of fish or shifts in the gender ratio of populations can be used as biomarkers for estrogenic contamination, although a combination of vitellogenin levels and other parameters (e.g. histological change, induced mixed function oxidases or concentrations of steroids) is recommended for evaluating specific pollution situations[98,99].

Summary:
The data show that there is widespread pollution by estrogenic substances in Germany's surface water, which lead to negative change in fish. Induced vitellogenin synthesis can be used as a biomarker for these adverse effects.

3.2 Incidence of endocrine disrupters in water bodies

In the publication" Substanzen mit endokriner Wirkung in Oberflächengewässern", UBA Texte 46/97 knowledge in the literature on over 200 suspected endocrinally active substances in the environment was collated. Their endocrinal effects were evaluated, as well as their actual importance for water quality, using measurements from a survey of German Länder, databases at the UBA and from local authorities, and information about the production and environmental behaviour of the chemicals. However, the importance of the substances for water quality proved difficult to assess, as for most substances there are no measurements, and the relative potency of the substances is unknown.

The following chemicals appear to have a special relevance:

1 Alkylphenol ethoxylates and their metabolites and decomposition products
Nonylphenol and octylphenol, as well as the decomposition products of nonylphenol ethoxylates, NP1EO and NP2EO induce vitellogenin synthesis in male

and female fish. The lowest observed effect concentration (LOEC) for octylphenol is 5 µg/l, for nonylphenol 20 µg/l, for NP1EO and NP2EO approximately 30 µg/l. Analytic studies have shown that nonylphenol concentration in unpolluted stretches of river are between $\leq$ 0.01 and 0.1 µg/l. Downstream from sewage treatment plants, and depending upon population density and industrial structure, concentrations between 0.7 and 16.5 µg/l nonylphenol are found. The sediment of these stretches contains concentrations of 1 to 156 mg/kg. Concentrations of octylphenol and NP2EO, even in water with a heavy load of sewage, are generally an order of magnitude below their LOEC, although peak concentrations of NP1EO have been measured in the range of its effect concentration. The tests were random samples, and the results cannot therefore be used to determine a general trend in pollution levels. Tests between 1988 and 1991 in Bavaria nonetheless showed an average 50 % decrease in water pollution[100].

2 The effects of tributyltin (TBT), an androgenic substance, have been observed on water snails in field studies. Laboratory tests have shown that the development of male sexual organs in female snails (pseudohermaphroditism or imposex) is triggered by a rise in the testosterone titre resulting from disruption of the hormone synthesis by TBT (LOEC 0.005 µg/l TBT Sn for marine snails, 0.08 µg/l TBT Sn for limnic snails). TBT is used predominantly as a biocide in antifouling paints for ships. Its use has been banned, but only for boats under 25 m, since 1990. Elevated concentrations of TBT are still being found in sediment and suspended matter in German rivers. Between 1987 and 1990 an UBA research project found maximum concentrations of c. 1 µg/l tributyltin (0.41 µg/l TBT Sn) in various marinas on the Bodensee, in Berlin, Hamburg and Kiel. Median concentrations in fresh water were 0.025 µg/l (0.010 µg/l TBT Sn), in the Baltic c. 0.150 µg/l (0.06 µg/l TBT Sn) and in the North Sea c. 0.080 µg/l (0.033 µg/l TBT Sn)[101]. A number of tests conducted on suspended matter by the *Länder* and local authorities showed high concentrations within the range of effect concentrations, the Elbe and its tributary the Mulde proving most heavily polluted. Also of note were the high concentrations of other butyltin compounds, caused by industrial discharges. The target for protection of aquatic habitats is 0.1 TBT Sn ng/l in water and 2 µg/kg TBT Sn in suspended matter. Every measuring station on the Elbe and Mulde where the analysis was sufficiently sensitive showed concentrations in excess of these targets.

Samples of bream (*Abramis brama*) and zebra mussels (*Dreissenia polymorpha*) collected between 1992 and 1998 for the Environmental Specimen Bank from the Rhine, Elbe, Saar, Mulde, Saale and the Belauer Lake (Bornhöved Lake District)

were tested for organic tin compounds in a research and development project (Tab. 1 and 2)[102]. Increased levels of tetrabutyltin (TTBT), tributyltin (TBT), dibutyltin (DBT), monobutyltin (MBT) and triphenyltin (TPhT) were measured. Levels of monooctyltin (MOT), diooctyltin (DOT) and tricyclohexyltin (TCxT) were generally below the analytical detection limit. In the Elbe and the Rhine, the concentrations increase in downstream samples. The highest TBT concentration was found in samples from the sample point Blankenese/Elbe. Samples from the Saar were relatively uncontaminated, relatively high concentrations of TPhT were found in muscle tissue from bream samples from the Belauer Lake.

Tab. 1: Organic tin compounds in zebra mussels from the Elbe, Rhine and Saar (Environmental Specimen Bank, in µg Sn/kg round weight)

River		MBT	DBT	TBT	TTBT	TPhT	Σ Sn
Elbe	(1996) (1 PNF)	8	4	385	4	5	408
Rhine	(1996) (4 PNF)	<1-2	<2	2-6	<1	<2-4	4-9
Saar	(1995)(2 PNF)	<1/2	<2/<2	3/6	<1/<1	<2/<2	5/6

Tab. 2: Organic tin compounds in brace muscle tissue from the Elbe, Saale, Mulde, Belauer Lake, Rhine and Saar (Environmental Specimen Bank, in µg Sn/kg round weight)

River		MBT	DBT	TBT	TTBT	TPhT	Σ Sn
Elbe	(1998) (3 PNF)	<1	2-11	12-168	7-13	<2-26	14-217
Saale	(1998) (1 PNF)	<1	<2	18	<1	<2	18
Mulde	(1998) (1 PNF)	<1	4	32	8	6	50
Belauer Lake	(1997)	<1	<2	1	<1	9	10
Rhine	(1998) (4 PNF)	<1	<2	5-10	<1	<2-18	5-32
Saar	(1995)(2 PNF)	<1	<1	6/7	<1	<2	6/7

Between 1993 and 1998, an average downwards trend was found in TBT concentrations in bream from inland river sample points. This does not apply to the mouth of the Elbe (Blankenese), where they remain consistently high, presumably due to the influence of the docks and merchant shipping. In contrast, a rise in TPhT concentrations was found everywhere but at Blankenese, indicating greater use of TPhT as a crop protection agent.

Organic tin compounds were also measured in water and sediment from selected rivers[103]. High concentrations were found in the Elbe, Mulde and Rhine. The sedimentary concentrations in the most notable river sample points are shown in Table 3.. Concentrations of TTBT appear to be falling between 1994 and 1996, while concentrations of TBT and TPhT remain almost unchanged. The data for water samples are sporadic, the range of TBT concentrations measured at Ems-Herbrum in 1996 was between < 0.002 and 0.002 µg/l. This was a cause for concern, as the target maximum for protecting aquatic habitats (2 ng/l) is exceeded by a factor of 20.

Tab. 3: Organic tin compounds in sediment from the Elbe, Rhine and Saale (in µg/kg dry weight)

River		TBT	TTBT	TPhT
Elbe	(1996) Schnackenburg	<1-80	<1-140	<1
Saale	(1995)Groß Rosenburg	4-53	<1-57	<1
Mulde	(1996) Dessau	73-427	240-2420	<1
Rhine	(1996)Kleve-Bimmen	12-85	<2	<2-7,3

Samples from the Environmental Specimen Bank of bladderwrack (*Fucus vesiculosus*), blue mussels (*Mytilus edulis*), eelpout (*Zoarces viviparus*) and herring gull (*Larus argentatus*) eggs, collected from areas along the North Sea and Baltic coasts, were tested for organic tin compounds in a research and development project[102] (Tab. 3 and 4). Elevated concentrations of tributyltin (TBT), dibutyltin (DBT), monobutyltin (MBT), diphenyltin (DPhT), and triphenyltin (TPhT) were found. Levels of monooctyltin (MOT), diooctyltin (DOT) and tricyclohexyltin (TCxT) were generally below the detection limit of the study. Tables 4 and 5 show only the levels in marine mussels and eelpout muscle tissue, as herring gull eggs and bladderwrack contain relatively low levels of organic tin compounds.

Tab. 4: Organic tin compounds in blue mussels from the North Sea (Eckwarderhörne) and the Baltic Sea (Darßer Ort) (Environmental Specimen bank, in µg Sn/kg round weight)

	MBT	DBT	TBT	DPhT	TPhT	Σ Sn
North Sea (1996)	2	<2	8	<1	3	14
Baltic Sea (1996)	3	<2	7	<1	<2	10

Tab. 5: Organic tin compounds in eelpout muscle tissue from the North Sea (Jadebusen) and the Baltic Sea (Darßer Ort) (Environmental Specimen bank, in µg Sn/kg round weight)

	MBT	DBT	TBT	DPhT	TPhT	Σ Sn
North Sea (1998)	<1	<2	4	<1	2	6
Baltic Sea (1998)	<1	<2	18	<1	<2	18

Over the years, TBT concentrations have remained more or less constant in marine mussels (1985-96) and eelpout (1994-98). The source of TBT is presumably merchant shipping. In contrast, TPhT concentrations have fallen by at least a half.

There is evidence for alarmingly high concentrations of organic tin compounds in marine mammals. High levels of TBT have been found in the blubber and livers of dolphins and whales (e.g. the finless porpoise *Neophocaena phocaenoides*: 770 µg TBT/kg round weight).[104] A fall of concentrations from the coast to the open seas has been noted. Apart from the levels of TBT found in blubber and liver, the substance also appears to accumulate in the animals' central nervous system (brain).

High concentrations of organic tin compounds are found particularly in the vicinity of dischargers such as harbours. After the ban on organic tin compounds in antifouling paint, a clear fall in TBT levels was observed (presumably because leisure boats were the primary source). However, although levels in areas far from emittants are significantly lower, organic tin compounds can be found in organisms in the remotest high sea and deep sea areas.[105].

- Bisphenol A
  Bisphenol A is a chemical with estrogenic effect. Its feminising effect has also been shown in male trout. Significant quantities (1995: 210,000 t) are produced in Germany, primarily for use in plastics manufacture. At the time of the study there were no data on its incidence in German waters, and specific tests conducted in various *Länder* showed pollution of surface waters of < 1 µg/l (frequently < 10 ng/l, in the Elbe and the Saale c. 100 ng/l).

- Phthalic acid esters
  Because of their widespread use as plasticizers in PVC, phthalates are ubiquitous. Extensive data on their incidence in the environment have been published by the UBA in the report "Action Areas and Criteria for a Precautionary, Sustainable Substance Policy Using the Example of PVC" (in English: March 2001).

- Gamma-HCH
  A follow-up study showed that vitellogenin synthesis in juvenile fish was stimulated by Gamma-HCH at concentrations in excess of 0.1 mg/l or 0.18 mg/l[106]. The maximum concentration measured between 1993 and 1996 in the LAWA measuring network was 0.6 µg/l[107]. The target set by International Commission for the Protection of the Rhine (ICPR) for Gamma-HCH is 0.1 µg/l, according to current knowledge, the substance's toxic effects are greater than its endocrine effects[108].

The above discussion concentrates on a number of important synthetic substances. To assess the total contamination of waters with endocrine disrupters, naturally excreted hormones (form humans and animals) and synthetic hormones must also be considered (Chapter 4.3).

4. Endocrine disrupters in the environment and possibilities for identifying them

4.1 Procedures for testing endocrine effects

Much work is still in progress within the OECD on validating and standardising testing procedures to determine the endocrine effects of chemicals. The present information on the endocrine effects of chemicals is gathered from:

- *in vitro* tests of organs, cells or subcellular structures,
- *in vivo* tests using standard experimental methods,
- *in vivo* tests using standard procedures on e.g. reproduction, whose goals are not the investigation of hormonal mechanisms, but which can provide indirect hints as to these effects.

The following basic requirements are essential for procedures to investigate the endocrine activity of chemicals:

- suitability for identifying effects on the endocrine system,
- meaningfulness for intact organisms,
- relevance of the results for other organisms,
- reproducibility of results.

In vitro tests examine the effects of chemicals on cells, subcellular structures or certain organs or tissue types. Such relatively simple procedures are useful in determining effects (e.g. binding to hormone receptors, egg maturation or induced synthesis of certain endocrinally regulated proteins or RNA). However, extrapolating the results to endocrine effects on the organism as a whole is not possible, as the procedure ignores resorption, distribution and the possible metabolisation or excretion of the substance.

There is therefore a consensus in Europe that no final assessments of chemicals should be made on the basis of *in vitro* tests when drafting regulations.

The utility of *in vitro* tests in screening is also disputed by experts, as expressed in the OECD's "Draft Detailed Review Paper: Appraisal of Test Methods for Sex-Hormone Disrupting Chemicals", for example. In general, *in vitro* tests could be suitable for priority-setting, i.e. identifying substances which are then subjected to more detailed examination in *in vivo* assays. Apart from producing reproducible results, the tests should also meet the following requirements:

- Few false positive results, i.e. a positive result should be associated as strongly as possible with an endocrinal mechanism.

- Few false negative results, i.e. a high percentage of suspect substances should be identified with sufficient sensitivity. As there are several mechanisms by which chemicals can affect the endocrine system, this requirement cannot be met by a single test, but only by a battery of tests.

Further information on toxicokinetics discoveries (absorption, excretion, distribution, metabolism) can then justify further tests. For priority-setting, therefore, the UBA considers further development and validation of *in vitro* assays for substance testing to be sensible.

Excursion: Combining *in vitro* tests with chemical analysis:

A method developed by B. Hock (TU Munich), "effect analysis", could help in identifying high-priority substances. Suspect substances in natural water samples are allowed to bind to fixed estrogen receptors, isolated, analysed and quanitified.[109] The method is suitable for recognising potentially estrogenic or antiestrogenic substances which are present in the environment, and which can then be further tested and evaluated.

Numerous already standardised *in vivo* testing procedures (e. g. OECD, US EPA, FIFRA, IOBC and EPPO testing guidelines) are not directly conceived for endocrine effects, but may provide indirect evidence::

Mammals:
- Subacute toxicity (28 days exposure)
- Subchronic toxicity (90 days exposure)
- Chronic exposure (18 or 24 months exposure) usually of 2 species
- Multigeneration study
- Teratogenicity test on 2 species

Birds:
- Reproduction studies of quails

Fish:
- Early life-stage test (e.g. *Danio rerio)*
- Full life-cycle test (e.g. *Danio rerio*)

Aquatic invertebrates:
- Daphnia reproduction test

Sediment organism tests on chironomides (larval development)

Terrestrial invertebrates:

Aleochara bilineata (rove beetle): reproduction

Aphidius rhopalosiphi (parasitic wasp): reproduction

Chrysoperla carnea (green lacewing): fertility

Coccinella septempunctata (7-spotted ladybird): fertility

Folsomia candida (springtail): reproduction

Poecilus cupreus (ground beetle): larval development

Syrphus corollae (hover fly): fertility

Trichogramma cacoeciae (egg parasitoid): parasitic performance and fertility

Typhlodromus pyri (predatory mite): fecundity and fertility

Eisenia foetida (compost worm): reproduction

However, the most valuable tests are *in vivo* tests that deliberately set endpoints connected with endocrine activity, to investigate phases of life which are expected to be especially sensitive. Numerous substances now considered as endocrinally active have been identified in such tests, which are valid, if not yet standardised. These include reproduction studies in Collembola and lacewing, levels of vitellogenin synthesis in fish, metamorphosis in amphibians, as well as numerous studies on mammals. Some particularly suitable tests have been selected for standardisation by the EDTA (Endocrine Disrupter Testing and Assessment) working group, a task force set up as part of the OECD test guidelines programme.

A Validation Management Group (VMG) was set up in 1998 to validate new and redesigned methods for testing endocrine effects on mammals. Work is currently focused on validating two short-term tests for identifying estrogenic and androgenic effects (Uterotrophic and Hershberger Assay), as well as an extended 28-day test on oral toxicity to rats under repeated doses (enhanced TG 407). A date for the conclusion and evaluation of the extensive tests cannot yet be set.

For ecotoxicity testing methods, the EDTA Task force is focusing on endocrine effects on fish, although progress in test guidelines for bird reproduction are in prospect. To co-ordinate further development and validation, a “VMG-eco”, similar to the “VMG-mammalian”, has recently been decided upon. The second OECD meeting of fish experts recommended developing and validating a short-term test for young and adult fish, a test in early life-stage (based on the OECD 210 test), a reproduction test and a full life-cycle test. Germany is playing an active role here. Work on bird reproduction is waiting upon the conclusion of a comparison between the sensitivity of various quail species. In the medium term, the need for and suitability of amphibian tests (e.g. African clawed frog test) will be examined.

With a research project, on developing a biological test on *Marisa cornuarietis* (Gastropoda: Prosobranchia) to determine endocrine disrupters in the environment, the UBA has given impetus to the development of such tests. Results to date point to the potential high sensitivity of such testing systems, and not only to triorganic tin compounds. It should be noted that the validation requirements have not yet been met for these results, and the data cannot therefore be used for regulatory purposes as yet.

4.2 Endocrine disrupters in the environment

Gülden et al. have published a list of substances in surface waters suspected of being endocrine disruptors[2]. This list of over 200 substances contains many for which a definitive judgement is impossible, due to a lack of valid *in vivo* studies.

It should be emphasised that even substances definitively classed as endocrine disrupters are more or less a random selection, as systematic, large-scale testing programmes are lacking (also a consequence of there being no standardised methods). Furthermore, the endocrine disrupters do not possess a limited set of clearly describable structural characteristics, making a prognosis as to the total number of disrupters impossible at this time

In June 2000, BKH Consulting Engineers Delft and TNO Nutrition and Food Research Zeist, in the Netherlands, published a report commissioned by the EU Commission (DG ENV): "Towards the establishment of a priority list of substances for further evaluation of their role in endocrine disruption". These results were presented by the EU Commission at the Joint Meeting of the Competent Authorities (DOC/ENV/D 720257/00 NOTIF/23/2000) on 31/5/2000. A four-tier selection procedure on 564 substances identified 60 high-priority substances, which had been proved endocrinally active in at least one *in vivo* study, are considered either persistent or substances with a high production volume, and where exposure of humans or the environment can be presumed. On 8th and 9th November 2000, an expert meeting considered these results, and asked the Commission to rapidly develop a schedule for further steps, and especially to complete the data on substances which are as yet only classified as potential endocrine disrupters, in order to classify their priority as fast as possible. The substances are listed in the following Table 6.

Table 6: High priority endocrine disrupters

No	Substance name	CAS No
1	Chlordane	12789-03-6
2	Chlordane (cis- and trans-)	57-74-9
3	Kepone (Chlordecone)	143-50-0
4	Mirex	2385-85-5
5	Toxaphene = Camphechlor	8001-35-2
6	DDT (technical) = clofenotane	50-29-3
7	p,p'-DDT = clofenotane	50-29-3
8	Tetrachloro DDT = 1,1,1,2-Tetrachloro-2,2-bis(4-chlorophenyl)ethane	3563-45-9
9	Vinclozoline	50471-44-8
10	Maneb	12427-38-2
11	Metam Natrium	137-42-8
12	Thiram	137-26-8
13	Zineb	12122-67-7
14	Gamma-HCH (Lindane)	58-89-9
15	Linuron (Lorox)	330-55-2
16	Atrazine	1912-24-9
17	Acetochlor	34256-82-1
18	Alachlor	15972-60-8
19	Styrene	100-42-5
20	Hexachlorobenzene (HCB)	118-74-1
21	Butylbenzylphthalate (BBP)	85-68-7
22	Di-(2-ethylhexyl)phthalate (DEHP)	117-81-7
23	Di-n-butylphthalate (DBP)	84-74-2
24	2,2-Bis(4-hydroxyphenyl)propan = 4,4'-isopropylidenediphenol = Bisphenol A	80-05-7
25	PCB	1336-36-3
26	PCB 153 (2,2',4,4',5,5'-Hexachlorobiphenyl)	35065-27-1
27	PCB 169 (3,3',4,4',5,5'-Hexychlorobiphenyl)	32774-16-6
28	PCB 47 (2,2',4,4'-Tetrachlorobiphenyl)	2437-79-8
29	PCB 77 (3,3',4,4'-Tetrachlorobiphenyl)	32598-13-3
30	PCB Aroclor 1242	53469-21-9
31	PCB Aroclor 1248	12672-29-6
32	PCB Aroclor 1254	11097-69-1

33	PCB Aroclor 1260 (Clophen A60)	11096-82-5
34	PBBS = Brominated Flame retardants = PBB (mixed group of 209 Congeners)	59536-65-1
35	1,2,3,7,8-Pentachlorodibenzodioxin	40321-76-4
36	2,3,7,8-Tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD)	1746-01-6
37	2,3,7,8-TCDF	51207-31-9
38	Tributyltin compounds	
39	Tributyltin hydride	688-73-3
40	Tributyltin oxide = bis(tributyltin) oxide	56-35-9
41	2-propenoic acid, 2-methyl-, methyl ester = Stannane, tributylmethacrylate	26354-18-7
42	Methoxyethylacrylate tributyltin, copolymer	26354-18-7
43	Phenol, 2-[[(tributylstannyl)oxy]carbonyl]-	4342-30-7
44	Stannane, (benzoyloxy)tributyl-	4342-36-3
45	Stannane, [1,2-phenylenebis(carbonyloxy)	4782-29-0
46	Tributyltin naphthalate	36631-23-9
47	Stannane, tributyl-, mono(naphthenoyloxy)	85409-17-2
48	Stannane, tributyl[(1-oxo-9,12-octadecadienyl)oxy]-, (Z,Z)-)	24124-25-2
49	Stannane, tributyl[(1-oxo-9-octadecenyl)oxy]-, (Z)-	3090-35-5
59	Stannane, tributyl[[[1,2,3,4,4a,4b,5,6,10,10a-decahydro-1,4°-dimethyl-7-(1-methylethyl)-1-phenanthrenyl]carbonyl]oxy]-, [1R-(1.alpha., 4a.beta., 4b.alpha.,10°.alpha.)]-	26239-64-5
51	Stannane, tributylfluoro-	1983-10-4
52	Tributyl[(2-methyl-1-oxo-2-propenyl)oxy]stannane	2155-70-6
53	Tributyltincarboxylate	
54	Tributyltinnaphthalate	26636-32-8
55	Tributyltinpolyethoxylate	
56	Tri-n-propyltin (TPrT)	2279-76-7
57	Triphenyltin compounds	
58	Fentin acetate = triphenyltin acetate	900-95-8
59	3,4-Dichloroaniline	95-76-1
60	Resorcinol	108-46-3

While the significance of these substances as endocrine disrupters - i.e. their inclusion in Category I - is more or less clear, the exclusion of six Category I substances because of presumed low exposure levels has no reasonable justification. Listed in Table 7, these substances should continue to be considered high-priority.

Table 7: Category I substances which, because of presumed low exposure, are not considered priorities		
1.	Amitrol	61-82-5
2.	4-tert. Octylphenol	140-66-9
3.	4-Nonylphenol	25154-52-3
4.	Nitrofen	1836-75-5
5.	Tetrabutyltin	1461-25-2
6.	4-Nitrotoluene	99-99-0

Also, the following substances should be considered as essentially high-priority (category I):

Alkylphenolethoxylates (APEO)	decompose to Nonyl-/Octylphenol
Diuron	decomposes to 3,4-Dichloroaniline
Phenanthrene, Chrysene, Benzanthracene, Dibenz[a,h]anthracene	there is a positive *in-vivo* test (Allen-Doisy-Test: estrogenicity in rodents) for these PAH. [110]

Further discussion of these 70 substances should first examine the extent to which there is a need for any action at EU level. This is not the case for substances which are either already banned (e.g. Chlorodane, Mirex, DDT and its metabolites, PCB) or whose emission as unintentional by-products is already widely restricted (e.g. polychlorinated dioxins and furanes, or polycyclic aromatic hydrocarbons, PAH). Table 8 lists the remaining substances or substance groups and their main areas of application.

Table 8: Regulatory status of remaining Category I substances			
No	**Substance name**	**Key area(s) of application**	**Regulatory status**
1	Vinclozolin	crop protection agent	EC-Reg. 3600/92; decision open. Permitted in Germany until 2002
2	Maneb	crop protection agent	EC-Reg. 3600/92; Monograph to be finished. Permitted in Germany until 2008
3	Metam-Sodium	crop protection agent	Not permitted in Germany (App 3 of the Crop Protection Agent Use Ordinance)

4	Thiram	crop protection agent	EC-Reg. 3600/92; decision open. Permitted in Germany until 2007 (as stripper)
5	Zineb	crop protection agent	EC-Reg. 3600/92; Monograph to be finished. Not permitted in Germany
6	Gamma- HCH (Lindane)	Crop protection and pest control agent	*crop protection agent:* EC-Reg. 3600/92; Proposed decision: No inclusion in App. 1; Not permitted in Germany (App 3 of the Crop Protection Agent Use Ordinance); *pest control agent:* permitted under § 18 InfSchG
7	Linuron (Lorox)	crop protection agent	EC-Reg. 3600/92; decision open. Not permitted in Germany
8	Atrazine	crop protection agent	EC-Reg. 3600/92; decision open. Not permitted in Germany (App 1 of the Crop Protection Agent Use Ordinance)
9	Acetochlorine	crop protection agent	Not permitted in Germany
10	Alachlorine	crop protection agent	EC-Reg. 3600/92; decision open. Not permitted in Germany
11	Styrene	industrial chemical (polymer pre-product)	1st priority list under EU-Existing Substance Regulation 793/93/EC
12	Butylbenzylphthalate (BBP)	industrial chemical (plasticizer)	3rd priority list under EU-Existing Substance Regulation 793/93/EC
13	Di-(2-ethylhexyl)phthalate (DEHP)	industrial chemical (plasticizer)	2nd priority list under EU-Existing Substance Regulation 793/93/EC
14	Di-n-butylphthalate (DBP)	industrial chemical (plasticizer)	1st priority list under EU-Existing Substance Regulation 793/93/EC
15	2,2-Bis(4-hydroxyphenyl)propan = 4,4'-isopropylidenediphenol = Bisphenol A	industrial chemical (oxidation inhibitor, plastics additive)	3rd priority list under EU-Existing Substance Regulation 793/93/EC
16	PBBS = Brominated Flame retardants = PBB (mixed group of 209 Congeners)	industrial chemical (flame retardant)	Polybrominted biphenyls no longer produced in Europe. a)
17	Tributyltin compounds	biocide (antifouling)	Banned for boats < 25 m long under Chemicals Prohibition Ordinance; comprehensice domestic ban under discussion
18	Tributyltin hydride	biocide (antifouling)	see above
19	Tributyltin oxide = bis(tributyltin) oxide	biocide (antifouling)	see above
20	2-propenoic acid, 2-methyl-, methyl ester = Stannane, tributylmethacrylate	biocide (antifouling)	see above

21	Methoxyethylacrylate tributyltin, copolymer	biocide (antifouling)	see above
22	Phenol, 2-[[(tributylstannyl)oxy]carbonyl]-	biocide (antifouling)	see above
23	Stannane, (benzoyloxy)tributyl-	biocide (antifouling)	see above
24	Stannane, [1,2-phenylenebis(carbonyloxy)	biocide (antifouling)	see above
25	Tributyltin naphthalate	biocide (antifouling)	see above
26	Stannane, tributyl-, mono(naphthenoyloxy)	biocide (antifouling)	see above
27	Stannane, tributyl[(1-oxo-9,12-octadecadienyl)oxy]-, (Z,Z)-)	biocide (antifouling)	see above
28	Stannane, tributyl[(1-oxo-9-octadecenyl)oxy]-, (Z)-	biocide (antifouling)	see above
29	Stannane, tributyl[[[1,2,3,4,4a,4b,5,6,10,10a-decahydro-1,4°-dimethyl-7-(1-methylethyl)-1-phenanthrenyl]carbonyl]oxy]-, [1R-(1.alpha., 4a.beta., 4b.alpha.,10°.alpha.)]-	biocide (antifouling)	see above
30	Stannane, tributylfluoro-	biocide (antifouling)	see above
31	Tributyl[(2-methyl-1-oxo-2-propenyl)oxy]stannane	biocide (antifouling)	see above
32	Tributyltincarboxylate	biocide (antifouling)	see above
33	Tributyltinnaphthalate	biocide (antifouling)	see above
34	Tributyltinpolyethoxylate	biocide (antifouling)	see above
35	Tri-n-propyltin (TPrT)	Unclear	
36	Triphenyltin	crop protection agent, earlier: biocide (antifouling)	EC-Reg. 3600/92; decision open. Permitted in Germany until 2003
37	Fentin acetate = triphenyltin acetate	crop protection agent	EC-Reg. 3600/92; decision open. Not permitted in Germany
38	3,4-Dichloroaniline	Decomposition product of several PSM agents, industrial chemical (intermediate)	1st priority list under EU-Existing Substance Regulation 793/93/EC (risk assessment skipped)
39	Resorcinol	industrial chemical	
40	Amitrol	crop protection agent	
41	4-tert. Octylphenol	industrial chemical, pre- and decomposition product of emulsifiers and detergents, above all	
42	4-Nonylphenol	industrial chemical, lubricant, pre- and decomposition product of emulsifiers and detergents, above all	1st priority list under EU-Existing Substance Regulation 793/93/EC
43	Nitrofen	crop protection agent	Not permitted in Germany (App 1 of the Crop Protection Agent Use Ordinance)
44	Tetrabutylzinn	industrial chemical (intermediate for Tri-, Di- and Monobutyltin comp.)	
45	4-Nitrotoluene	industrial chemical (intermediate)	
46	Diuron	crop protection agent	Permitted in Germany until 2008 (App 1 of the Crop Protection Agent Use Ordinance)

47	Alkylphenolethoxylate	industrial chemical (emulsifier, detergent)	Nonylphenolethoxylate covered by risk assessment of 4-Nonylphenol.

a) The most important examples of structurally similar polybrominated diphenyl ether (PBDE), Penta-, Octa- and Decabromodiphenyl ether, are currently given priority in the European Existing Substances Programme under the EU Existing Substances Regulation 793/93/EC.

Where closer examination of these substances reveals significant exposure, they should be assessed rapidly, and regulated where necessary. The last column of Table 8 shows whether a risk assessment is already provided for in Directive 91/414/EWG or Regulation 793/93/EG. The assessments should include results about endocrinal activity.

However, the endocrine effect is not necessarily the decisive factor in the assessment. Some of the estimated (or calculated) exposure concentrations are far below the corresponding LOEC, and other toxic or ecotoxic effects may be more significant. Under the current guidelines, a substance's endocrine effects then have no influence on the result of the assessment, nor therefore on any necessary reduction measures. 4-octylphenol, resorcinol, tri-n-propyltin (compounds) and nitrotoluene are not currently on any priority assessment list. It is uncertain whether tripropyltin compounds (which are very similar to tributyltin) are technically significant at all. With respect to 4-octylphenol (and the related octylphenol ethoxylates), the UK's development of a risk reduction strategy of 4-nonylphenol will include a targeted risk assessment of octylphenol and its derivatives. It is expected that the result will be an extension of measures provided for nonylphenol to cover octylphenol and its derivatives. What remains is the need to assess resorcinol and 4-nitrotoluene as a priority. The ICCA (International Council of Chemical Associations) programme on assessing priority substances is not suitable for evaluating the risks from endocrine effects, as the appropriate endpoints are not a requirement in the programme. However, the inefficiency of the European Existing Substances Programme should by no means be forgotten. Any possibility for speeding up the procedure should be exploited in the case of the industrial chemicals listed in Table 8 (see part I). To avoid delays, a targeted risk assessment, focusing on endocrine effects, should be initiated in cases where a comprehensive assessment is not expected in the foreseeable future.

Excursion: Are endocrinal effects *per se*, i.e. regardless of LOEC, hazardous?

In part I of this report, substance-related action targets are described, the second of which was: *"The irreversible input of xenobiotics with carcinogenic, mutagenic and reproduction toxic effects (CMR substances) into the environment must be avoided completely. This applies also to substances whose metabolites exhibit these properties."* Since such substances are capable of causing irreversible changes in organisms and ecosystems, a risk exists, regardless of the level of exposure, and this should be minimised. Scientific opinion is divided as to whether endocrine disrupters should also be included in this category: it is often pointed out that

endocrine mechanisms are generally triggered when a threshold dose is exceeded. However, Sheehan et al. were able to show that even very low doses of exogenic estradiol (and hydroxylated PCB), when applied to the eggs of the red-eared slider (Trachemys scripta elegans), a turtle, could cause a gender shift, and no threshold value could be determined (Sheehan, 1999).[111] An already active system is being influenced, which would mean that endocrine disrupters should be treated like genotoxic substances, for example. Endocrine effects at low doses have been shown for only very few substances as yet. Completely abandoning the idea of comparing exposure and effect in describing risk is not sufficiently justified in the case of endocrine disrupters. There is currently good reason to examine effects at low doses especially thoroughly.

The following arguments also favour particular care when assessing endocrine mechanisms:

- Hormonally transmitted effects are frequently especially pronounced in certain stages of life, e.g. prenatally. This has not necessarily been considered in the tests conducted to date.
- There are indications that the relationship between concentration (dosage) and effect does not always rise monotonously in the case of endocrinal effects, i.e. effects can be found at concentrations below those where there was no effect (U shaped curve). Such relationships are not uncommon in pharmacology. Nonetheless, there are few data as yet to confirm this type of chemical effect. It is assumed that U shaped curves are due to multiple mechanisms such as homeostasis, or compensatory or protective reactions being activated.[112] The effects of TCDD on the thyroid gland and estrogenic activity of bisphenol A are examples of this form of dose-effect curve.

- Synergistic effects, i.e. mutually reinforcing, rather than merely additive, effects could be widespread among endocrine disrupters, although McLachlan's[113] withdrawal means that there is no conclusive evidence that endocrine effects are significantly different to other types of effect. Nevertheless, additive effects are likely where the mechanisms are identical, which means that even substances at below their LOEC can contribute to an overall effect.

In view of our currently sketchy knowledge of endocrinal mechanisms, the following differentiated approach to assessment is appropriate,:

- Substances which are both hormonally active and persistent present a hazard when discharged into the environment, regardless of exposure levels. In view of the uncertainty of assessments, persistence in the environment and long-term consequences cannot be ruled out. Corresponding action targets in part I concerning the characteristic combinations

persistent/bioaccumulating and persistent/highly mobile are supplemented by this approach.

· Substances which are hormonally active but not persistent may be hazardous, depending on the measured or calculated exposure. The open questions in assessment do nevertheless give good cause for using greater margins of safety (MOS) when deriving PNEC or TDI values.

There is currently insufficient evidence to justify a total abandonment of exposure-effect comparisons, as in the case of genotoxic substances.

The assessment schemes described above will be proposed in further discussion of European assessment guidelines (e.g. TGD).

4.3 Hormonal pharmaceuticals

Hormone-based medication is discharged into the environment, just as xenohormones are, especially estrogens, which are prescribed to humans and animals as contraceptives or hormone therapies.

The basic issue of environmental discharges of drugs has received increasing attention in recent years. Pharmaceuticals are appearing in concentrations of c. 0,01 µg/l up to over 1 µg/l in sewage treatment plants and small tributaries, synthetic estrogen 17α-ethinylestradiol in particular has been found in treatment plant effluents and surface water, as well as in sewage sludge and fish. The 51st German Conference of Environmental Ministers in 1998 decided that pollution by drugs and the key discharge paths should be investigated in a nation-wide testing programme, run by the individual *Länder*. The programme will probably cover three natural and three synthetic estrogens.

There are currently no representative data on the quantities of hormone-based medication prescribed to humans and animals. The quantities of 17 α-ethinylestradiol prescribed in Germany are estimated to be no more than c. 50 kg/a.[114]

Collating measured concentration data on estrogenic medicinal agents in sewage treatment effluent provides an average level of c. 1 ng/l; a maximum of 70 ng/l was found for estron, a natural estrogen.

In a study covering 15 surface water systems, only estron, at a level of max. 1.6 ng/l, was found.[115] The as yet not fully published study of the effects of estrogenic substances (17β-estradiol, ethinyl estradiol) by the Fraunhofer Institute in Schmallenberg, part of multigeneration tests at significant concentrations has produced the following results for reproduction in *Danio rerio* (zebra fish): while concentrations of ethinyl estradiol had practically no effect on embryo survival, hatching or gender ratios, a significant fall in the rate of fertilisation, due to disruption of physiological processes in male animals, was observed at 1.1 ng/l. An NOEC of 0.3 ng/l was determined for this most sensitive endpoint identified.[116]

From these preliminary results we can conclude that the relatively low concentrations of ethinylestradiol, only a few ng/l, are frequently already above the NOEC observed above for reproduction in fish. It is therefore likely that the effects detailed in Chapter 3 will be clearly influenced by steroids, even if the effect is not yet quantifiable. It is also to be expected that different organisms will react very differently. For example, female goldfish excrete the estrogen 17α, 20β-dihydroxy-4-pregnen-3-on into water to attract males (Urich, 1990).[117]

Based on current environmental regulations for licensing pharmaceuticals, no emissions reduction measures can be expected in the medium term, at least for human medicines, because regulation would be impracticable, or because revoking the licences of contraceptives or hormone therapies for environmental reasons would be unrealistic. It is more realistic to look at changing and developing the forms, dosages, etc. of environmentally hazardous drugs, in order to reduce discharges to the environment. Another avenue to explore is whether developing and using modern waste water purification technologies could eliminate hazardous substances more effectively.

4.4 Phytoestrogens

Phytoestrogens occur naturally in plants, via which they can be ingested. Vegetable estrogens can be split into two substance groups: flavonoids (e. g. genisteine, coumestrol etc.) and lignanes. Soya products, a common source of protein in the foodstuffs industry, including milk substitutes in baby foods, are by far the largest source of vegetable estrogens.

It is known that some phytoestrogens, e.g. isoflavons, have an anti carcinogenic, i.e. positive, effect on human health. Until recently, little was known about the effects of human exposure to phytoestrogens such as coumestrol or genisteine as foods during pre- and perinatal development or childhood. A new study[118] has now shown that the sons of women who kept to a vegetarian diet during pregnancy have five times the risk of being born with genital malformation than the sons of women with a mixed diet. The authors take these findings as

reinforcement for the hypothesis that phytoestrogens have harmful effects on the development of male genitals. Further study in this area is urgently required.

Many agricultural cases have been documented, where wrongly mixed livestock feed or free-range grazing has led to considerable losses due to excessive consumption of phytoestrogens. For example, female sheep in Australia and New Zealand, Finland and in Israel are known to have suffered reproductive harm which was traced back to feeding on plants with a high phytoestrogen content (e.g. red clover). How these data relate to humans in still unclear.

The more active mating period which sets in after livestock which have been kept in stalls during the winter begin grazing, the higher rate of conception and lactation, are thought to be encouraged by phytoestrogens in certain legumes and grasses. On the other hand, cabbage and marsh horsetail lead to fertility disorders in female cattle if used as feed for lengthy periods.[119]

The public debate on risk assessment for endocrine disrupters in the environment often makes reference to daily consumption of phytoestrogens. Some scientists maintain that the quantities and effects of endocrine disrupters in the environment can be ignored when compared to phytoestrogens (on the basis of their relative endocrinal activity *in vitro*). It should be noted that a comparison of the relative estrogenicity *in vitro* is insufficient for a quantitative risk assessment of environmental endocrine disrupters and phytoestrogens. Exposure must be examined in more detail, and the quantity consumed or adsorbed is merely one variable in the equation. A comparison of *in vitro* potency and daily consumption rates alone is therefore scientifically meaningless.

A risk assessment must consider the necessary *in vivo* exposure and effect data, which can vary widely. This makes universal statements about entire substance groups impossible, especially since important aspects of exposure to and the effects of phytoestrogens are themselves heterogeneous.

A comparative assessment must consider the following exposure factors: sources and incidence in the environment, exposure paths, quantities absorbed, concentrations in the environment and in organisms, decomposition, bio- and geo-accumulation.

As for effects, studies should consider the strength and mechanism of the effect, bioavailability, metabolisation, paths and rates of excretion, storage and toxicodynamics. The major arguments against a simple comparison of the risks from xenoestrogens to phytoestrogens are:

– In contrast to certain industrial chemicals, there is no evidence for geo- or bio-accumulation of coumestrol or genisteine. On the contrary, they are metabolised very easily.

– In respect of decomposition/degradation, there is no evidence that phytoestrogens are environmentally persistent, in contrast to many endocrine disruptering chemicals.

– The mechanisms by which phytoestrogens and xenoestrogens function are not always the same, and therefore even comparing concentrations in the body is inadequate, due to their varying degrees of binding to hormone receptors.

As far as is known today, however, the possibility that phytoestrogens appear in food and the environment within the range of effect concentrations cannot be ruled out. This is especially true for people with special diets (e.g. vegetarians who eat a lot of soya products) or whose work exposes them to phytoestrogens (e.g. hops pickers). Also, detrimental effects in habitat-bound aquatic organisms, triggered by significant concentrations of estrogens in the waste water from pulp works, for example, have been well documented.

To sum up, the incidence and effects of phytoestrogens in the environment and in foodstuffs require further careful observation, but assessing the estrogenic potential of xenobiotics by way of a simple comparison of their effects with those of phytoestrogens is not scientifically meaningful.

5. Measures

In part I, proposals for structuring EU chemicals assessment and management more efficiently and orienting it more closely around the precautionary principle. The following aspects are particularly important for endocrine disrupters:

- Where a suspicion is sufficiently well-founded, the necessary regulations should be introduced, temporarily if necessary, even where some questions remain open.

- The substitution requirement under § 16 par. 2 GefStoffV (Hazardous Substances Ordinance) should be extended to cover environmental risks.

- “Blacklists” of especially critical substances which are not yet the subject of regulations should be used to inform users, consumers and the general public.

- Basic data on substances whose production/sales volume exceeds 1000 t/a (subsequently also at lower sales volumes) are to be made available at predetermined times. They should include any significant information on endocrine effects. (This should also be required for biocide products, under EU Regulation 1896/2000).

- Where possible, substances should be grouped by structure-activity relationships, to enable assessment and any subsequent measures to apply for the group as a whole.

- Meaningful data on exposure, including that of downstream users, are required.

- Monitoring programmes with international participation should be used to study chemical pollution, including that from endocrine disrupters.

- The basis for assessments, including those of endocrine effects, should be developed further.

5.1 General measures (not applying to particular substances)

These principles, as well as the aspects outlined above, point to the following as priorities:

- Validation and further development of test guidelines to identify endocrine effects: the OECD's standardisation of test guidelines is a major indispensable step in being able to test substances systematically for any dangerous characteristics in respect of endocrinal potential. Complementing the currently discussed procedures with methods for studying invertebrates is a priority.

- Including such testing requirements in the licensing procedure for new substances and the authorization procedure for crop protection agents and biocides.

- Examining the numerous substances for which *in vitro* tests have provided evidence of endocrinal activity with valid *in vivo* tests is a priority. Levels of exposure, persistence and toxokinetic information should be considered in setting priorities (N.B. Even today, before the conclusion of the OECD's standardisation efforts, valid *in vivo* tests are available, to confirm or refute suspected endocrine effects).

- Reconsidering and developing the principles for assessing industrial chemicals (TGD) and crop protection agents. Especially important would be an agreement on greater margins of safety for endocrine effects (proposal: an additional factor of 2 to 5). If the

substances are also persistent, the long-term hazards make substitution essential in all open applications.

- Substances whose endocrine potential has been shown in *in vivo* tests, but where the available data is (as yet) insufficient for legal restriction or prohibition, should be named publicly in "blacklists", and made subject to a substitution requirement under § 16 par. 2 GefStoffV (Hazardous Substances Ordinance). Such a list could provide sufficient incentive to substitute, even where there is only a suspicion of danger. It should also be considered whether a hazard label for endocrine disrupters should be introduced.

- Existing analytic chemical monitoring programmes should be developed so as to gather representative data on exposure to endocrine disrupters.

- To identify the total pollution of ecosystems by endocrine disrupters, the analytic chemical monitoring programmes should be complemented by biological monitoring of organisms (e.g. gender ratios, vitellogenin content) and chemical/biological combination methods (effect-specific analytics).

- To assess effects on humans, a perinatal archive (lactate, placenta, umbilical blood) should be built up in the Environmental Specimen Bank, in order to be able to determine later the levels of contamination of substances which are not yet recognised as having an endocrine effect, and in order to interpret data on any effects.

- A national register of malformations should be built up within the Action Programme on the Environment and Health (APUG).

5.2 Substance-specific Measures

5.2.1 Pesticides and Biocides

In general, the environmental impact of *crop protection agents* is assessed most thoroughly. Under § 15 par. 1. 3 PflSchG (Crop Protection Act), endocrine effects must explicitly be included in the tests for unacceptable effects as part of the permissions procedure for crop protection agents, and the likelihood is correspondingly high that a permissions application will reveal any reasonable cause for concern about endocrine effects. The OECD test guidelines targeted at endocrinal activity, which will soon be available, should be incorporated into the test programme. Many of the substances listed in Chapter 4.2 are no longer permitted in Germany. Those which are still permitted are being assessed in the European Active Agent

Programme, which should pay particular attention to endocrine effects, and should study especially those which frequently appear in surface waters at concentrations above the targets.[120] Nonetheless, in most cases, other endpoints are more sensitive than the endocrine activity (even when increased safety factors are considered). Therefore, endocrine activity will generally not be decisive for the permission for certain applications. According to the currently available data, this (still) applies to triphenyltin as a fungicide for potato farming, but further testing is necessary.

The scope of the required tests for *non-agricultural biocides* has not yet been finally determined in the EU Biocidal Products Directive (98/8/EC). In any case, care should be taken to include tests with endpoints covering endocrine effects. The most important substances here are tributyltin compounds, especially in antifouling paints. The goal should be a complete ban, and stringent restrictions on tributyltin in dibutyltin compounds using Best Available Techniques, at first within Germany According to an expert hearing, conducted by UBA and BgVV in March 2000,exposure to tetrabutyltin, an intermediate in the production of tri-, di- and monobutyltin compounds, is not relevant. High concentrations have only been measured in suspended matter and in sediment in the Mulde, immediately downstream from a production site.

5.2.2 Pharmaceuticals

As drugs are extensively tested before being licensed, their endocrine effects (not only of hormone treatments) are known, although the tests are restricted to humans and mammals. Regarding the assessment of the environmental effects of veterinary medicines, in which the UBA participates, generally no data on the endocrine effects are presented. In the absence of European technical guidelines, the environmental risks from human medicines are not assessed, a situation which is clearly to remedied. Also, data on the quantities and forms of administration of human and veterinary medicines is to be collected, and there is also a coordinated federal/Länder programme to study the incidence of medicines in the environment. Hormone medicines are part of this programme, and it is to be hoped that their impact to ecosystems can be better understood in future.

5.2.3 Industrial chemicals

For new substances, no test results permitting conclusions about endocrine effects are presented in the base set, according to the concept of tonnage thresholds. Only for Stage 1 and onwards data is presented which may provide indications of such effects. As soon as the standardisation and validation of the OECD guidelines for testing endocrine effects is

completed, they should be included, so that effects can be recognised and clarified, at least starting from Stage 1.

There is generally a serious lack of data on the effects and behaviour of Existing substances (see part I). If the currently available data points to a substance being suspected of endcrine effects, and if this could influence the final decision, the remaining issues can be clarified with further tests, which must be completed by manufacturers within a certain period. If the results are not presented by then, or if further tests confirm suspicions, the substances should be published in a "blacklist", accompanied by a request to users to voluntarily refrain from using them.

The great majority of the industrial chemicals listed in Chapter 4.2 are mentioned in one of the four priority lists of the European Existing Substances Programme. The existing findings are included in the risk assessments, but they are only decisive if other effects are less sensitive. With a few strictly limited exceptions, substances evaluated on a European level are not subject to national regulation, and Germany's contribution should therefore be to draw attention to endocrine effects in risk assessments and to push for rapid implementation of any necessary risk reduction measures. If unreasonable delays occur, Germany should – if necessary in co-operation with other EU Member States – use the possibility of domestic regulation to accelerate measures at EU level.

4-octylphenol, 4-nitrotoluol and resorcinol are not mentioned in the EU existing substances programme. 4-nitrotoluol and resorcinol should immediately be included in the programme, as a matter of urgency, and undergo a targeted risk assessment under § 12 (2) Existing Substances Regulation 793/93/EC, to clarify the potential for endocrine effects and assess levels of exposure. Manufacturers should be asked to refute the initial suspicion without delay, that there are environmental hazards which have to be reduced, in order to avoid temporary European or – if the European procedure gets bogged down – domestic restrictions. 4-octylphenol should be considered in conjunction with other alkylphenols and alkylphenol ethoxylates (see below).

Already in 1997, the UBA proposed domestic measures under § 17 ChemG (Chemicals Act), to deal with a*lkylphenols* and *alkylphenol ethoxylates* (alkyl = butyl/C4 to nonyl/C9), as a significant environmental risk still exists, despite a voluntary commitment to reduce the use of these substances in washing and cleansing agents, and the conclusion of a risk assessment of only 4–nonylphenol was not then in sight. In August 1999 (BT-Drucksache 14/1471), the German Bundestag asked the government to review the washing and cleansing industry's voluntary commitment on the use of alkylphenol ethoxylates, to search for a complete solution to the issues involving alkylphenols and alkylphenol ethoxylates, and to implement the

necessary bans and restrictions nationally in order to speed up action at EU level. Due to the voluntary commitment, the consumption by the washing and cleansing industry of APEO had fallen by c. 90 % relative to the 1980s, marking a great success. Nevertheless, considerable remaining quantities (over 100 t/a) continue to be traded, especially by foreign companies or those who are not members of the German industrial associations, and further measures are required to guarantee the success of the agreement in the long term. After a hearing by the UBA in June and December 1998, it was also determined that the majority of APEO discharges into surface waters are diffuse discharges caused by product use. However, in the absence of a product register, quantifying the emissions at this level is not possible. The European risk assessment of 4-nonylphenol has now concluded that there are environmental risks in numerous areas of application (although this is based on the high toxicity to daphnia – which can have different reasons – and not on the potential for endocrine effects). The UK is currently developing a risk reduction strategy. In contrast to 1997, nonylphenol ethoxylates and their degradation products (especially NP1EO and NP2EO) are now also being considered, although alkylphenol(ethoxylat)es with short alkyl chains (C5 to C8) are not. It was nevertheless decided that the UK should, while developing the risk reduction strategy, undertake a targeted assessment of 4-octylphenol(ethoxylat)es, raising hopes of speedy action at EU level. If these hopes should prove premature, the decision by the Bundestag requires action to be taken domestically. The significance of alkylphenols with even shorter chains should be examined more closely. One outcome of the June 1998 hearing is that less 4-tert-butyl- and 4-tert-amylphenol is being processed to ethoxylates, but rather being used in plastics production (e.g. for phenol resins and paints). The industry should be asked to present meaningful data on this development (N.B.: the inclusion of decylphenol in the substance list for the water framework directive is currently being discussed).

Alkylphenol(ethoxylat)es illustrate perfectly the limitations of the European chemicals programme, which operates on the basis of single substances, and which thereby tends to underestimate the risks. Alkylphenols and their ethoxylated derivatives appear in and affect the environment in combination with one another, and risk assessments should therefore try to consider whole substance groups. The concentration additive model is suitable for such cases,[121,122] and is to be developed for implementation in the current revision of the TGD.

In the case of alkylphenol(ethoxylat)es, Germany must - as well as actively taking a critical stance on EU activities and pushing for rapid decisions::

- Check the extent to which additional domestic measures are required for short-chained alkylphenols (butyl to heptyl) – possibly even decylphenol –(if necessary, a ban under § 17 ChemG, Chemicals Act).

- Check whether using an assessment based on *substance groups* (concentration additive model) for nonyl- and octylphenol reveals a greater need for action than the current consideration of *single substances*.

In recent years, the scientific community has been (sometimes bitterly) debating whether the low-dose effects of *bisphenol A* found by the vom Saal working group (premature puberty, reduced sperm production, inflation of the prostate, behaviour disturbance in mice), at concentrations of only a few µg/kg kg bw are reliable enough to form the basis of a risk asessment.[20,123,124,125] Ibrahim Chahoud's team at the Institute for Clinical Pharmacology at the FU Berlin[126,127], as well as a research team in the US[128], have now also been able to demonstrate effects on the male and female offspring of rats at low dosages (20 to 100 µg/kg kg bw). Tests conducted on *Marisa cornuarietis* by Oehlmann indicated effects at the surprisingly low concentration of under 1 µg/l.[129] There is also great uncertainty as to levels of exposure. Information from manufacturers produces an unclear picture of where the substance is used or emitted and of the associated risks. The EU draft risk assessment from the UK points to environmental risks and a need for action in a number of areas of application. The UBA has examined patterns of exposure to bisphenol A more closely in interviews with industry members, finding that key areas are use in thermopaper and as antioxidant or oxidation inhibitor in PVC. The voluntary agreement announced by the European PVC industry in March 2000 contains no commitments on bisphenol A. Other unknown applications are to be examined in agriculture, as the substance has been found in manure, although this result must be confirmed by further analytical data. The following is recommended for this substance, a matter of debate for many years:

- Rapid preliminary conclusion of the EU risk assessment, with the goal of taking immediate risk reduction measures in those areas where a PEC/PNEC ratio > 1 already exists, and where clarification of unanswered questions is not in view (see the RAR draft of June 2000).

- Active participation in a research programme aimed at clarifying the open questions on low-dose estrogenic effects (both of invertebrates and vertebrates).

- Reviewing preliminary European risk assessments when comprehensive data on exposure and effects in low-dose levels become available.

6. Literature

1 Degen, G.H., Foth, H., Kahl, R., Kappus, H., Neumann, H.G., Oesch, F., Schulte-Hermann, R. (1999) Hormonell aktive Substanzen in der Umwelt: Xenoöstrogene. Stellungnahme der Beraterkommission der Sektion Toxikologie der DGPT. DGPT-Forum 24, 30-36.

2 Gülden, M., Turan, A. und H. Seibert (1997) Substanzen mit endokriner Wirkung in Oberflächengewässern. UBA- Texte 46/97, Umweltbundesamt Berlin.

3 Beratergremium für Altstoffe (BUA) der Gesellschaft Deutscher Chemiker (1999) Biologische Bedeutung synthetischer und natürlicher endokrin wirkender Stoffe- Auswirkungen auf die menschliche Gesundheit. BUA- Stoffbericht 212, S. Hirzel Wissenschaftliche Verlagsgesellschaft,

4 Carlsen, E. Giwercman,A.; Keiding,N.; Skakkebaek,N.E. (1992).; Evidence for decreasing quality of semen during past 50 years. Brit. Med. J. 305, 609-613

5 Golden,R.J. Noller,K.L.; Titus-Ernstoff,L.; Kaufman,R.H.; Mittendorf,R.; Stillman,R.; Reese,E.A. (1998).Environmental endocrine modulators and human health: an assessment of the biological evidence. Crit Rev Toxicol.;28, 109-227

6 Swan, S.H. Elkin,E.P.; Fenster,L. (1997): Have sperm densities declined? A reanalysis of global trend data.; Environ. Health Perspect. 105, 1228-1232

7 Swan S.H., Elkin E.P., Fenster L. (2000): The Question of Declining Sperm Density Revisited: An Analysis of 101 Studies Published 1934 – 1996, Environ. Health Perspect. 108, 991 - 996

8 Jouannet, P. (2000) Trends in semen quality in Europe and world wide, RH Workshop Hormones and Endocrine Disrupters in Food and Water: Possible Impact on Human Health, Copenhagen, 27-30 May 2000

9 Iwamoto, T. (2000) Semen Quality of fertile Japanese men, RH Workshop Hormones and Endocrine Disrupters in Food and Water: Possible Impact on Human Health, Copenhagen, 27-30 May 2000

10 Licht,M., (1998) Retrospektive Untersuchung der zwischen 1956 und 1995 in der Abteilung für Andrologie des Universitätskrankenhauses Hamburg-Eppendorf erhobenen Spermiogramme. Dissertation, Universität Hamburg

11 Thierfelder,W. Seher,Ch.; Dortschy,R.; Engel,S. (1999): Abnahme der Spermienqualität bei gesunden Männern aus ungewollt kinderlosen Partnerschaften. Bundesgesundheitsbl. 42, 471-478.

12 Glöckner, D, Gaevert, K, Kleinstein, J, ,(1998) Declining sperm quality in men of childless couples. Andrologia; 30, 55

13 De Mouzon, J., Spira, A, Thonneau, P, Multigner, L. (1996): Declining sperm count. BMJ;313:43

14 Andersen, A.G,. Jensen, T.K., Carlsen, E., Jørgensen, N., Andersson, A.M., Krarup, T., Keiding, N., Skakkebæk, N.E. (2000): High frequency of sub-optimal semen quality in an unselected population of young men. Hum Reprod. 15: 366-372

15 World Health Organisation (1992) : WHO laboratory manual for the examination of human semen and sperm - cervical mucos interaction. Cambridge University Press, Cambridge

16 MacLeod,J. (1946) The semen specimen. Laboratory examination. In: Engle, E.T. (ed.) Conference on Diagnosis in Sterility, Charles C. Thomas Springfield, IL, 3-15

17 Bonde JP, Kold Jensen T, Brixen Larsen S, Abell A, Scheike T, Hjollund NH, Kolstad HA, Ernst E, Giwercman A, Skakkabaek NE, Keiding N & Olsen J (1998) Year of birth

and sperm count in 10 Danish occupational studies. Scand. J. Work Environ. Hlth. 24: 407-413.

18 Gill W.B, Schumacher G.F.B., Bibbo M. (1978): Genital and Semen Abnormalities in Adult Males two and one-half decades after in utero exposure to diethylstilbestrol. In: intrauterine Exposure to Diethylstilbestrol in the Human. (Ed. A.L. Herbst) p. 53, American College of Obstericicians and Gynecologists, Chicago

19 BUA-Berichtsentwurf: Biologische Bedeutung von Phytoöstrogenen- Auswirkung auf Umwelt und menschliche Gesundheit am Beispiel von Genistein (Fassung Oktober 1999) Der Bericht ist inzwischen erschienen, bitte einfügen

20 vom Saal, FS, Cooke, PS, Buchanan, DL, Palanza,P, Thayer,K.A., Nagel, SC, Parmigiani, S, Welshons, WV(1998): A physiological based apprroach to the study of bisphenol A and other estrogenic chemicals on the size of the reproductive organs, daily sperm production and behavior. Toxicol. Ind. Health 14, 239-260

21 Mylchreest, E, Sar, M, Cattley, RC, Foster PM:Disruption of androgen-regulated male reproductive development by di(n-butyl) Phthalate during late gestation in rats is different from flutamide. Toxicol. Appl. Pharmacol. 156, 81-95 (1999)

22 Rösch, C., Vetter, E., Götz, D., Steinbicker, V.(1999).: Pilotstudie: Prävalenz genitaler Fehlbildungen - Datenbasis - Auswertung - Ursachenhypothese. UBA- Texte 39/00 , Umweltbundesamt ed.

23 Möller, H. (2000) Trends in incidence of testicular cancer and prostate cancer, RH Workshop Hormones and Endocrine Disrupters in Food and Water: Possible Impact on Human Health, Copenhagen, 27-30 May 2000

24 Toppari,J. Larsen,J.C.; Christiansen,P.; Giwercman,A.; Grandjean,P.; Guillette,L.J.; Jegou,B.; Jensen,T.K.; Jouannet,P.; Keiding,N.; Leffers,H.; McLachlan,J.A.; Meyer,O.; Muller,J.; Rajpert-De Meyts,E.; Scheike,T.; Sharpe,R.; Sumpter,J.; Skakkebaek,N.E. (1995). Male reproductive effects and environmental chemicals with estrogenic effects, Ministry of Environment and Energy, Denmark, Miljöprojekt nr. 290

25 Moller, H., Skakkebaek, N.E., (1999): Risk of testicular cancer in subfertile men: case-control study, BMJ, 318: 559-562

26 Jacobsen R., Bostoffe E., Engholm G. Hansen J., Olsen J.H., Skakkebaek N.E., Moller H. (2000): Risk of testicular cancer in men with abnormal semen characteristics: cohort study, BMJ 30; 321, 789 - 792

27 Möhner, M et al. (eds.) (1994) Atlas der Krebsinzidenz in der DDR 1961-1989, Ullstein Mosby, Berlin

28 Schuz J, Schon D, Batzler W, Baumgardt-Elms C, Eisinger B, Lehnert M, Stegmaier C: (2000)Cancer registration in Germany: current status, perspectives and trends in cancer incidence 1973-93. J Epidemiol Biostat;5: 99-107

29 Hsing A.W., Tsao L., Devesa SS. (2000): International trends and patterns of prostate cancer incidence and mortality. Int J Cancer 85: 60-67

30 Joossens, J.V., Kesteloot, H. (2000): Cancers, mainly male, as population biomarkers for breast cancer mortality. Prev. Med. 30: 167-173

31 Dich, J., Wiklund, K. (1998): Prostate cancer in pesticide applicators in Swedish agriculture: Prostate 34: 100-112

32 Morrison H, Savitz D, Semenciw R, Hulka B, Mao Y, Morison D, Wigle D. (1993): Farming and prostate cancer mortality. Am. J. Epidemiol. 137: 270-280

33 Parker AS, Cerhan JR, Putnam SD, Cantor KP, Lynch CF. (1999): A cohort study of farming and risk of prostate cancer in Iowa. Epidemiology 10: 452-455

34 Fleming LE, Bean JA, Rudolph M, Hamilton K. (1999): Cancer incidence in a cohort of licensed pesticide applicators in Florida. Occup Enviro Med 56, 14-21

35 Keller-Byrne JE, Khuder SA, Schaub EA. (1997) Meta-analyses of prostate cancer and farming. Am J Ind Med 31: 580-586

36 Santti R, Newbold RR, Makela S, Pylkkanen L, McLachlan JA (1994): Developmental estrogenization and prostatic neoplasia. Prostate;24 67-78

37 Garcia-Rodriguez J, Garcia-Martin M, Nogueras-Ocana M, de Dios Luna-del-Castillo J, Espigares Garcia M, Olea N, Lardelli-Claret P(1996): Exposure to pesticides and cryptorchidism: geographical evidence of a possible association. Environ Health Perspect;104:1090-1095

38 Huang CS, Chern HD, Chang KJ, Cheng CW, Hsu SM, Shen CY (1999): Breast cancer risk associated with genotype polymorphism of the estrogen-metabolizing genes CYP17, CYP1A1, and COMT: a multigenic study on cancer susceptibility. Cancer Res 59, 4870-4875.

39 Wolff MS, Toniolo PG, Lee EW, Rivera M, & Dubin N(1993): Blood levels of organochlorine residues and risk of breast cancer. J. Natl. Cancer Inst., 85, 648-652

40 Krieger N, Wolff MS, Hiatt RA, Rivera M, Vogelman J, & Orentreich N(1994): Breast cancer and serum organochlorines: a prospective study among white, black, and Asian women. J. Natl. Cancer Inst., 86, 589-599.

41 Hunter DJ, Hankinson SE, Laden F, Colditz GA, Manson JE, Willet WC, Speizer FE, Wolff M (1997)Plasma organochlorine levels and risk of breast cancer in a prospective study. N Engl. J. Med., 337, 1253-1258.

42 Hoyer AP, Grandjean P, Jorgensen T, Brock JW, & Hartvig HB Organochlorine exposure and risk of breast cancer. The Lancet, 352:1816-1820 (1998).

43 Dorgan JF, Brock JW, Rothman N, Needham LL, Miller R, Stephenson HE JR, Schussler N, & Taylor PR: Serum organochlorine pesticides and PCBs and breast cancer risk: results from a prospective analysis (USA). Cancer Causes and Control, 10:1.11. (1999)

44 López-Carrillo L, Blair A, López-Cervantes M, Cebrián M, Rueda C, Reyes R, Mohar A, Bravo A(1997): Dichlorodiphenyltrichloroethane serum levels and breast cancer risk: A case-control study from Mexico. Cancer Research, 57: 3728-3732.

45 Howdeshell, KL, Hotchkiss, AK, Thayer, KA, Vandenbergh, JG, vom Saal, FS(1999): Exposure to bisphenol A advances puberty:.Nature.;401, 763-764.

46 James, WH(1995): What stabilizes the sex ratio? Ann. Human Genet. 59, 243-249

47 Egeland G.M., Sweeney M.H., Fingerhut M.A. Wille K.K. Schnorr T.M, Halperin W.E. (1994): Total Serum Testosterone and Gonadotropins in Workers Exposed to Dioxin. Am. J. Epidemiol. 139, 272 - 281

48 Mocarelli,P., Brambilla,P., Gerthoux, P.M., Patterson, D.G., Needham, L.L. (1996): Change in sex ratio with exposure to dioxin. Lancet 10, 409

49 Zober A, Hoffmann G, Ott MG, Will W, Germann C, van Ravenzwaay B. (1995) Study of morbidity of personnel with potential exposure to vinclozolin. Occup.Environ.Med.;52:233-241

50 James,W.H. (1995). Offspring sex ratio as an indicator of reproductive hazards associated with pesticides. Occup.Environ.Med. 52, 429-430.

51 Davis, D. L., Gottlieb, M. B. and Stampnitzky, J. R. (1998). Reduced ratio of male to female births in several industrial countries: A sentinel health indicator? Journal of the American Medical Association 279, 1018-1023

52 Vartiainen, T., Kartovaava, L., Tuomisto, J.(1999):Environmental chemicals and changes in sex ratio: Analysis over 250 years in Finland, Environ. Health Perspect. 107, 813 – 815,

53 Winneke, G, Borte, M, Dunemann, L, Herbarth, O., Krämer, U, Steingrüber, H.J. Walkowski, J. (2000): Polychlorierte Biphenyle und geschlechtsgebundene kognitive Funktionen bei Kindern in: Vorträge zum BWPLUS Statusseminar 2000, Karlsruhe

54 Brouwer A., Longnecker, M-P., Birnbaum, L.S., Cogliano J., Kostyniak, P., Moore J., Schantz S., Winneke, G. (1999)Characterization of potential endocrine-related health effects at low-dose levels of exposure to PCBs. Environ.Health Perspect. 107, 639-649,

55 Tilson, H.A., Jacobson, J.L., & Rogan, W. J. (1990): Polychlorinated biphenyls and the developing nervous system: Cross species comparisons. Neurotoxicol. Teratol., 12, 239-248,

56 Jacobson, S.W., Fein, G., Jacobson, J.L. et al. (1998) The effect of intrauterine PCB exposure on visual recognition memory. Child. Develop. 56, 853-860,

57 Jacobson, J.C., Jacobson, S.W., Humphrey, H.E.B.(1990) Effects of in utero exposure to polychlorinated biphenyls and related contaminants on cognitive functioning in young children. J. Pediatr, 116, 38-45,

58 Jacobson, J.L. & Jacobson. S.W. (1996) Intellectual impairment in children exposed to polychlorinated biphenyls in utero. N. Engl. J. Med. 335, 783-9.,

59 Rogan; W.J., Gladen, B.G. et al (1986). Neonatal effects of transplacental exposure to PCBs and DDE.J. Pediatr., 109, 335-341,

60 Gladen, B.C., Rogan, W.J., Hardy, P., Thullen, J., Tingelstad, J., Tully, M. (1988)Development after exposure to polychlorinated biphenyls and dichlorodiphenyl dichloroethene transplacentally and through human milk. J. Pediatr.,113,991-995

61 Chen, Y.C.J., Guo, Y., L., Hsu, C.C., Rogan, (1992) W.J. Cognitive development of Yu-Cheng (Oil Disease) children prenatally exposed to heat-degraded PCBs. JAMA, 268, 32-3218

62 Chen, Y.J., Hsu, C.C, (1994) Effects of prenatal exposure to PCBs on the neurological function of children: a neuropsychological and neurophysiological study. Dev. Med. Child Neurol., 36, 312-320

63 Koopman-Esseboom, C., Morsen, D.C., Weisglas-Kuperus, N., Lutke-Schipolt, I.J., van der Paauw, C.G., Tuinstra, L.G.M.Th., et al. (1994) Effects of dioxins and polychlorinated biphenyls on thyroid hormone status of pregnant women and their infants. Pediatr Res., 36, 468-473,

64 Huisman, M., Koopman-Esseboom, C., Touwen, B.C.L., et al. , (1995) Perinatal exposure to polychlorinated biphenyls and dioxins and its effect on neontal neurological development. Early Hum.Dev., 41, 111-127

65 Schantz, S.J. (1996)Developmental neurotoxicity of PCBs in humans: what do we know and where do we go from here? Neurotoxicol. Teratol., 18, 217-228,

66 Lanting, C.I. (1999) Effects of perinatal PCB and dioxin exposure and early feeding mode on child development. Thesis. University of Groningen. ISBN 90-367-1002-2,

67 Lanting, C.I, Huisman, M., Muskiet, F.A.J., v.d. Paauw, C.G., Essed, C.E, & Boersma, E.R. (1998) Polychlorinated biphenyls in adipose tissue, liver and brain from nine stillborns of varying gestational ages. Pediatric Res. 44, 1-4

68 Patandin, S. (1999)Effects of environmental exposure to polychlorinated diphenyls and dioxins on growth and development in young children. Dissertation. Erasmus Universiteit Rotterdam

69 Winneke, G., Bucholski, A., Heinzow. B., Krämer, U., Schmidt, E. et al. (1998) Developmental neurotoxicity of polychlorinated biphenyls (PCBs): cognitive and psychomotor function in 7-months old children. Tox. Lett. 102/103, 423-428,

70 Brouwer A., Longnecker, M.P., Birnbaum, L.S., Cogliano J., Kostyniak, P., Moore J., Schantz S., Winneke, G. (1999) Characterization of potential endocrine-related health effects at low-dose levels of exposure to PCBs. Environ.Health Perspect. 107, 639-649,

71 Hany J., Lilienthal H., Sarasin A., Roth-Härer A., Fastabend A., Dunemann L., Lichtensteiger W., Winneke G. (1999) Development exposure of rats to a reconstituted

PCB-mixture or Arochlor 1254: Effects of organ weights, aromatase activity, sex hormone levels, and sweet preference behavior. Tox.Appl.Pharmacol., 158, 231-243,

72 Kalbfus, W. et al. (1991): Gewässergefährdung durch organozinnhaltige Antifouling-Anstriche, F+E-Bericht des UBA, FKZ 126 05 10, UBA-Texte 44/91

73 Oehlmann, J. et al. (1996): Tributyl biomonitoring using prosobranches as sentinel organisms. Fresenius J. Anal. Chem.; 354, 540-545

74 Isensee, J et al. (1994): Emissions of antifouling-biocides into the North-Sea - an estimation; Deutsche Hydrographische Zeitschrift, 46 (4) 355-365

75 Bettin C. et al. (1996): TBT-induced imposex in marine neogastropods is mediated by an increasing androgen level. Helgol. Meeresunters., 50, 299-317

76 Matthiessen, P., Gibbs, P.E. (1998): Critical appraisal of the evidence for tributyltin-mediated endocrine disruption in mollusks; Environ. Toxicol. Chem., 17, 37-34

77 Stroben, E. (1996): Imposex und weitere Effekte von chronischer TBT-Intoxikation bei einigen Mesogastropoden und Bucciniden. Thesis, Westfälische Universität Münster

78 Länge, R.: Monitoring of current levels of TBT; - seawater and evaluation of the risk for the environment in the context of recent ecotoxicity data; -The Present Status of TBT-Copolymer Antifouling; Paints-Proceedings-; International Symposium on Antifouling Paints for Ocean-going Vessels, 21.02 1996, The Hague

79 Mesinsk et al. (1996): The development of imposex in relation to organotin contamination in the common whelk, Buccinum undatum; Nederlands Instituut voor Onderzork der Zee, NIOZ-Rapport 1996-3

80 Kussatz C. et al. (1999): Zielvorgaben für Pflanzenschutzmittelwirkstoffe zum Schutz oberirdischer Binnengewässer, Umweltbundesamt, UBA-TEXTE 76/99,

81 Norunn Folsvik et. al. (1999): Quantification of organotin compounds and determination of imposex in populations of dogwhelks (Nucella lapillus) from Norway, Chemosphere, 38, 691-691

82 Fent, K. (1996): Ecotoxicology of organotin compounds; Critical Reviews in Toxicology; 26 (1), 1-117,

83 Sherry J. et al(1999).: Vitellogenin induction in fish as an indicator of exposure to environmental estrogens. In: Roa S.S. Impact Assessment of Hazardous Aquatic Contaminants; Concepts and Approaches; Lewis Publishers

84 Kime, D.E. (1998): Endocrine disruption in Fish. Kluwer Academic Publishers, Boston

85 Länge, R. et al. (1997): Growth and reproduction of fathead minnow (Pimephales promelas) exposed to the synthetic steroid hormone ethinylestradiol in a life cycle test. 7th Setac-Europe Conference, Amsterdam, April 6-10,1997

86 Arukwe, A. and Goksøyr, A.: Xenobiotics, xenoestrogens and reproduction disturbances in fish. Sarsia 83, 225-241, (1998)

87 Reinboth, R. (1988):Physiological problems of teleost ambisexuality. Environ. Biol. Fish. 22, 249-259

88 Herman, R.L. and Kincaid, H.L. (1988): Pathological effects of orally administered estradiol to rainbow trout; Aquaculture 72, 165-172

89 Cyr, D.G. and Eales, J.G. (1996): Interrelationships between thyroidal and reproductive endocrine systems in fish. Rev. Fish Biol. Fish. 6, 165-200,

90 Emmersen, J., Korsgaard, B. and Petersen, I. (1979): Dose response kinetics of serum vitellogenin, liver DNA, RNA, protein and lipid after induction by 17-ß-estradiol- in male flounders (Platichthys flesus L.). Comp. Biochem. Physiol. 63B, 1-6,

91 Johnson, L.L., Stein, J.E., Collier, T.K., Casillas, E., McCain, B. and Varanasi, U. (1992): Bioindicators of contaminant exposure, liver pathology, and reproductive development in prespawning female winter flounder (Pleuronectes americanus) from urban and nonurban estuaries on the northeast Atlantic coast. U.S. Department of Commerce, National

Oceanic and Atmospheric Administration, NOAA Technical Memorandum NMFS-NWFSC-1, 76 pp.,.

92 Harries J E; Sheahan D A; Jobling S; Matthiessen P; Neall P; Routledge E; Rycroft R; Sumpter J P; Tylor T.(1996): A survey of estrogenic activity in United Kingdom inland waters; Environ. Toxicol. Chem. 15, 1993-2002,

93 Hansen, P.-D. und Dizer, H. (1999): Die Fische im Berliner Gewässersystem - Bestand, Entwicklung - Erfolgt eine Begrenzung durch endokrin wirksamen Substanzen? In: Zukunft Wasser. Hrsg. Stadt Umwelt, Dokumentation zum Symposium zur Nachhaltigkeit im Wasserwesen in der Mitte Europas, Berlin 17.-19. Juni 1998, 51-54

94 Hansen P.-D. et al. (1998): Proceedings of the „EU-Workshop on Environmental Technologies“, July 16-19 1998, European Commission (DG XII-D1) and the WAR Institute at the TU Darmstadt,

95 Borkmann, J., Untersuchungen zum Geschlechterverhältnis, zum Wachstum und zur Gonadenstruktur von Plötzen (Rutilus rutilus) und Barschen (Perca fluviatilis) aus Spree- und Havelgewässern. Diplomarbeit Univ. Potsdam, 141 Seiten (1998)

96 Lehmann J. et al. (1999): Ökotoxikologische Untersuchungen am freilebenden Brassen (Abrama brama) mit Schwerpunkt auf den Einfluss von Xenoöstrogenen in NRW – Ein Vergleich der Fischbestände aus dem Trinkwasserresevoir Wahnbachtalsperre und aus dem Niederrhein (Fluß-km-Strecke 798-804); LÖBF-Jahresbericht, NRW;

97 Hecker, M et al. (1999): Erhöhte Vitellogenin- und Steroidkonzentrationenen im Blutplasma von Brassen (Abramis brama) aus der Elbe: „Endocrine Disruption“ oder natürliche Variabilität? – Poster presentation SETAC Europe, Leipzig

98 Schiemenz, P. (1937): Über die Verteilung der Geschlechter bei einigen unserer Süßwasserfische; Fischerei-Zeitung, 40, (27), 317-318,

99 Environment and Climate Research Programme of the European Commission, DGXII; (1997) Report of Proceedings, EUR 17549, European Workshop on the impact of endocrine disrupters on human health and wildlife; 2-4 December 1996; Weybridge, UK

100 Zellner, A.; Kalbfus, W. (1995): Belastung bayerischer Gewässer durch Nonylphenole. In: Bayerisches Landesamt für Wasserwirtschaft: Stoffe mit endokriner Wirkung im Wasser. 50. Fachtagung, 7-8. November 1995, München

101 Kalbfus, W.; Zellner, A.; Frey, S.; Stanner, E. (1991): Gewässergefährdung durch organozinnhaltige Antifouling-Anstriche. UBA-Texte 44/91

102 Rüdel,H, Böhmer,W, Bruckert, H-J, Lepper, P, Sohn, H, Steinhanses, J, Wenzel, A. (1999): Verfolgung von Umweltbelastungen durch Alkylphenole, Bisphenol A und organische Zinnverbindungen in repräsentativen Umweltproben: Methodische Entwicklung und aktuelles sowie retrospektives Monitoring. UBA-Forschungsbericht 297 63 155

103 Umweltbundesamt(1998): Wasserbeschaffenheit in ausgewählten Fließgewässern der Bundesrepublik Deutschland. UBA-Texte 56/98, Berlin, 368 p..

104 Kannan K, Corsolini S, Focardi S, Tanabe S, Tatsukawa R. (1996): Accumulation pattern of butyltin compounds in dolphin, tuna, and shark collected from Italian coastal waters. Arch Environ Contam Toxicol.; 31,19-23.

105 Lepper, P. (1999), Teilbericht A2: Bewertung der Analysen von organischen Zinnverbindungen. In: Rüdel, H. et al.: Verfolgung von Umweltbelastungen durch Alkylphenole, Bisphenol A und organischen Zinnverbindungen in repräsentativen Umweltproben, FKZ 297 63 155

106 Bruhn, T.; Gülden, M.; Ludewig, S.; Seibert, H. (1999): Einstufung von Schadstoffen als endokrin wirksame Substanzen. UBA-Texte 65/99

107 LAWA AK „QHF“ (Qualitative Hydrologie der Fließgewässer) (1998): Wasserbeschaffenheit in ausgewählten Fließgewässern der Bundesrepublik Deutschland - Datensammlung Pestizide. UBA-Texte 56/98

108 IKSR (Internationale Kommission zum Schutze des Rheins) (1994): Aktionsprogramm Rhein - Stoffdatenblätter für die Zielvorgaben.

109 Hock, B., Rothe, S., Seifert, M., (2000)"Hormone in der Umwelt" – die Tests im Überblick". Nachr. Chem. 48, 918 – 924,

110 Cook J.W., Dodds E.C., Hewett C.L., Lawson W. (1994) The estrogenic activity of some condensed-ring compounds in relation to their other biological activities. Proc. Roy., B., 114: 272 - 286

111 Sheehan, D.M., Willingham, E., Gaylor, D. , (1999), Bergeron, J.M., Crews, D.: No Threshold Dose for Estradiol-Induced Sex Reversal of Turtle Embryos: How Little is Too Much?, Environ. Health. Perspect. 107, 155 – 159

112 David. J.M. and Svensgaard, U-shaped dose-response curves: their occurrence and implications for risk assessment, J. Toxicol. Environ. Health 30, 71 – 83, 1990

113 Mc Lachlan, J.A.: Synergistic Effect of Environmental Estrogens: Report Withdrawn, Science 277, 462 – 463, 1997

114 Ternes , T.A. et al.(1999): Nachweis und Screening von Arzneimittelrückständen, Diagnostika und Antiseptika in der aquatischen Umwelt, Abschlussbericht des ESWE Instituts, im Auftrag des BMBF Projekts Nr. 02WU9567/3, März

115 Ternes, T.A., Stumpf, N., Müller, J., Haberer, K., Wilken, R.-D. und Servos, M.: Behaviour and Occurrence of Estrogens in Municipal Sewage Treatment Plants – I. Investigation in Germany, Canada and Brazil, The Science of the Total Environment 225 (1999) 81 – 90

116 Fraunhofer Institut für Umweltchemie und Ökotoxikologie, Annual Report 1999, S. 49 - 52

117 Urich, K.(1990): Vergleichende Biochemie der Tiere, G. Fischer Verl. Stuttgart, , S. 577

118 North K. Golding J. (2000): A maternal vegetarian diet in pregnancy is associated with hypospadias. The ALSPAC Study Team; Avon longitudinal Study of Pregnancy and Childhood, BJU Int. 85 ,107 - 113

119 Rosenberger, G., Dirksen, G., Gründer, H.-W., Stöber, M.(1978).: Pflanzliche Gifte, in: Krankheiten des Rindes, Verlag Paul Parey, Berlin und Hamburg

120 Landesumweltamt Nordrhein-Westfalen(1989): Gewässerschutzbezogene Zielvorgaben für Pflanzenschutzmittel, Materialien 55, Essen

121 Payne, J., Rajapakse, N., Wilkins, M. und Kortenkampf, A.(2000): Prediction and assessment of the effects of mixtures of four xenoestrogens, Environ. Health Perspect. 108, 983 – 987,

122 Altenburger, R., Bödehar, W., Faust, M., Grimme, L.H., (1993) Aquatic toxicology, analyses of combination effects, in Corn., M. (Ed.): Handbook of Hazardous Materials, 15 – 27, Academie Press, San Diego

123 Nagel SC, vom Saal FS. Thayer KA, Dhar MG, Boechler M, Welshons WV. (1997) Relative binding affinity-serum modified access (RBA-SMA) assay predicts the relative in vivo bioactivity of the xenoestrogens bisphenol A and octylphenol., Environ. Health Perspect. 105: 70-76

124 Howdeshell KL, Hotchkiss AK, Thayer KA, Vandenbergh JG, vom Saal FS. (1999) Exposure to bisphenol A advances puberty. Nature; 401 (6755): 763-764

125 Welshons WV, Nagel SC, Thayer KA, Judy BM, Vom Saal FS. (1999) Low-dose bioactivity of xenoestrogens in animals: fetal exposure to low doses of methoxychlor and other xenoestrogens increases adult prostate size in mice. Toxicol Ind Health; 15: 12-25

126 Fialkowski, O., Merker, H-J, Talsness CE, Chahoud, I.(2000): Histopathological findings in the testes of rat male offspring following prenatal exposure to a low and a high dose of bisphenol A. in: Hormones and endocrine disrupters in food and water: Possible impact on human health. Workshop, Copenhagen, 27-30 May 2000, p. 94-95

127 Talsness, CE, Merker, H-J, Chahoud, I.(2000): Histopathological findings in the vagina of rat female offspring following prenatal exposure to a low and a high dose of bisphenol A. in: Hormones and endocrine disrupters in food and water: Possible impact on human health. Workshop, Copenhagen, 27-30 May 2000, p. 95

128 Gupta C (2000): Reproductive malformation of the male offspring following maternal exposure to estrogenic chemicals. Proc Soc Exp Biol Med; 224: 61-68

129 Oehlmann J; Schulte-Oehlmann U; Tillmann M; Markert B (2000): Effects of endocrine disruptors on prosobranch snails (Mollusca: Gastropoda) in the laboratory. Part I: Bisphenol A and octylphenol as xeno-estrogens. Ecotoxicology, 9, 383-397