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# Workshop 6.3

# Government view of endocrine disruption in wildlife*

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*Abstract*: Like hardly any other issue in ecotoxicology, endocrine disruption has given rise to public concern. Reproductive, behavioral, and immunological effects in wildlife were publicly not only understood as possible threats to wildlife populations, but also as early warning signals that human health could be at risk. Above all, the public has been concerned about negative outcomes in reproductive health, and effects like feminization in fish were regarded as evidence for the biological plausibility of the hypothesis that environmental levels of hormonally active chemicals are high enough to affect human reproductive health.

Public concern has been mirrored by several parliamentary and governmental decisions emphasizing the need for extensive research and rapid measures to reduce the risk associated with endocrine-disrupting substances.

Endocrine disruption in wildlife is clearly a priority issue. At least in densely populated areas like Europe, symptoms of endocrine disruption in wildlife cannot only be detected in areas with abnormally high levels of pollution, but have also occurred in main river systems, estuaries, and even in the open sea. Imposex in mollusks and feminization in fish that were clearly related to disturbances in the hormonal system of these organisms by exogenous substances have been used as markers in monitoring programs. Though symptoms of endocrine disruption can be clearly identified, it is much more difficult to link these outcomes to causative chemicals or mixtures of substances. Natural and pharmaceutical hormones, phytoestrogens, pesticides, and industrial chemicals may all play a role to a different degree depending on the site under study. This means that several different risk-reduction strategies have to be applied, including bans of substances, use restrictions, and installation and optimization of sewage treatment works embedded in a strategy for the overall reduction of chemical input into the environment.

It should be noted that, in addition to national and international regulatory actions taken by state authorities, a considerable reduction of the environmental input could be achieved in several countries by voluntary actions taken by industry.

Regulatory bodies are still facing major problems in the field of risk assessment and risk reduction. Association between effects and causative agents or mixtures are in many cases weak. Important tools for risk assessment such as dose–response relationships or the existence of thresholds are not yet agreed on. These uncertainties are the reason that many national governments and the European Commission have identified precaution as the main element in chemicals policy for the management of endocrine disruptors.

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This paper is based on documents of the German Federal Environmental Agency, but solely represents the view of the author from a regulatory perspective and emphasizes the wildlife aspects of endocrine disruption.

## INTRODUCTION

For more than 60 years, scientists have known that a large number of environmental chemicals can have hormonal activity though their structure does not resemble those of known hormones [1]. As early as 1936, Dodds and Lawson described the estrogenic activity of bisphenol A [2] and as early as the 1950s and 1960s the hormonal activities of phytoestrogens like genistein [3] and common pesticides such as methoxychlor [4] and DDT [5] were already known. Nonetheless, it was not until the early 1990s that the issue of disruption of the endocrine system from chemical exposure became the subject of public and political interest [6].

Publications of various conference documents and scientific articles in the early 1990s totally changed the character of the debate on endocrine disruptors. With these articles a widespread public interest was induced on possible effects of hormonally active environmental chemicals.

In 1991, a group of scientists met in Wingspread, Wisconsin. At the end of their meeting they worded a declaration [6] pointing to developmental impairments in wildlife and laboratory animals that were obviously caused by chemicals interfering with the hormonal system. The effects observed became visible in different species such as birds, fish, and shellfish, and were different in nature, probably affecting different hormonal systems such as the system of sexual hormones and thyroid hormones. Despite all the differences observed in the character of the effects they had several common characteristics:

- The chemicals may have effects in embryos, fetuses, and newborns that differ from those in adult organisms.
- In many cases, the effects may not (or not only) be seen in the parent generation exposed to them, but rather in its progeny.
- There are particular times when organisms are sensitive to these chemicals. Outside these windows of sensitivity, the chemicals may have no effect on the developing organisms.
- The effects may be delayed. Though the organism is exposed in very early life stages, negative effects may not become visible until adulthood.

The participants of the Wingspread meeting saw these effects in wildlife not only as indicators that wildlife populations were possibly at risk, but also warned that the developing human fetus may be negatively influenced by environmental chemicals disturbing the hormonal system.

The debate on the possibility of human health being harmed by substances with effects on the endocrine system was further sparked by a supposed reduction in men's sperm quality in industrialized countries. A meta-analysis published in 1992 (and since then frequently reanalyzed and controversially discussed) originally concluded that the sperm count in ejaculates from test subjects had fallen by approximately 50 % between 1938 and 1990 [7]. It was hypothesized that exogenous chemicals with estrogenic activity may have caused these changes [8,9] (for review see Topic 3.4 [10]).

Not only toxicologists and ecotoxicologists had to critically review their paradigms in the ensuing discussion on endocrine disruption. People working in the government or in governmental agencies were also challenged by this debate that quickly had political dimensions. Those responsible for the safe use of chemicals in society were confronted with several problems and open questions.

First, there were two different groups of experts in the agencies: those responsible for human toxicology and those for ecotoxicology. In most countries, both groups are differently educated, have a different professional history, and work in different ministries or agencies. The lack of communication between these two subgroups of regulators may be one reason for the rather slow reaction of regulatory bodies on the new challenges posed by endocrine disruptors.

Second, no one working in the field of chemical safety was prepared to debate how far effects in wildlife could serve as indicators for human health risks. No one really knew whether, for example, feminization of fish populations in surface waters by estrogenic substances could be interpreted as an early warning signal that similar processes may be induced in humans.

In addition, the regulatory agencies did not know how many out of the approximately 50 000 chemicals that are marketed today are interfering with the hormonal control of life processes.

It was also unclear to what extent wildlife populations were endangered by these types of substances, whether phenomena like morphological and physiological feminization in fish, masculinization in snails, or alteration of behavioral patterns in birds were common throughout the environment and would subsequently need rapid and radical regulatory measures or whether they were restricted to some hot spots, heavily polluted parts of the landscape, and could be easily tackled with measures at a local scale.

Last, several questions arose concerning how to test and assess chemicals in the routine processes of chemical notification. Those questions were associated with the unique features of endocrine disruptors. Do standard tests sufficiently cover transgenerational effects? Were safety factors used for normal chemicals also sufficient for endocrine disruptors? Are there concentration thresholds below which a risk for wildlife is unlikely?

Ten years after these questions were posed to officials, it is time to review whether we have succeeded in answering them and what degree of uncertainty we still face.

## IS ENDOCRINE DISRUPTION WIDESPREAD IN THE ENVIRONMENT?

To analyze the size of the problem posed by endocrine disruption, it is useful to view this problem in relation to the overall endangerment of natural biological systems. Ever since industrialized societies changed the world dramatically, biological diversity on earth has been at risk. Many species have vanished or are endangered. In an industrialized country like Germany, 3 % of 15 850 animal species for which data are available have died out and a further 35 % are endangered [11]. In most cases, it is impossible to understand the reasons why these organisms are in danger, but in many cases drastic changes in the structure of the landscapes and surface waters created unfavorable conditions for the survival of vulnerable species.

Additionally, toxic contamination may play its part in endangering species and populations, though its part in total hazards can hardly be quantified. For macroinvertebrate communities in rivers, for example, toxic contamination is likely to be of the same importance as unfavorable ecological conditions [12]. But even if general toxic effects can be observed in wildlife, in most cases the mechanism of toxicity is not known. Adverse toxic effects like imposex that can be correlated directly to endocrine disruption have been described only rarely. To answer the question whether endocrine disruption is a widespread phenomenon or only restricted to special places with extremely high contamination, one is dependent on data from the aquatic environment. The majority of information as to chemical disruption of the endocrine systems of free-living organisms has been derived 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.

Two phenomena related to endocrine disruption have been intensively investigated during recent years: masculinization of mollusks and feminization of fish. Therefore, these two examples are suitable to look at regional patterns and the worldwide severity of changes due to the disturbance of the hormonal system by exogenous substances.

### Organotins and invertebrates

The incidence of certain disruptions in the fertility and development of marine and limnetic mollusks, such as imposex (female snails are expressing male sex organs additionally to female organs), prosobranch gastropods, or shell malformation and disruption of larval development in oysters, are considered to be direct effects of aquatic pollution by organic tin compounds, especially tributyltin and triphenyltin (TBT and TPhT) [13]. TBT is a nonsteroidal compound, which, for example, is used in antifouling paint for ships. Direct correlations between the occurrence of imposex and TBT pollution were found above all in the vicinity of harbors [14,15], and the degree of imposex in prosobranch snails is related to the degree of TBT exposure [16]. This effect can be shown at TBT concentrations as low as 5 ng/l (as Sn) [17]. More than 150 species of prosobranch snails have been found to be affected by organotin compounds [18].

Occurrence of imposex has been described in many parts of the world: Japan [19], Spain [20], Northern Europe [21], Malta [22], Taiwan [23], Korea [24], Portugal [25], Ireland [26], Argentina [27], Thailand [28], and Australia [29].

In the case of imposex induction by TBT and TPhT, the threat for biodiversity is clearly worldwide due to the global nature of the shipping industry. Population decreases and local extinction have been observed in many places around the world at concentrations that are extremely low and frequently found in the environment. This is clearly one example for the necessity to develop global strategies for chemical control.

In the case of imposex, environmental monitoring revealed that a class of animals was seriously threatened that is not represented in the battery of test methods used routinely to assess chemicals. The threat that TBT and TPhT pose to prosobranch snails was unpredictable by our current assessment methods. This should not be surprising as for decades specific toxicity for some animal classes is one of the selection criteria applied in the development of pesticides. Some invertebrate classes in particular have unique hormonal systems [30]. Effects on these endocrine systems may hardly become evident if a chemical passes routine testing procedures.

## Feminization of fish

Male and immature fish in contaminated inland, coastal, and marine waters have been found to show incidence of high concentrations of vitellogenin in their blood. This precursor of yolk proteins is usually not found in male and juvenile fish as only females produce yolk protein. The production of vitellogenin is under the control of the estrogen receptor. Vitellogenin is an indicator for contamination by estrogens and substances with estrogenic effects [31–33].

Organisms that are induced to synthesize vitellogenin by external estrogenic stimuli may also exhibit other more or less pronounced negative effects, including changes in steroid metabolism, liver atrophy, delayed testicle growth, and occurrence of eggs in male testicles (ovotestis) in juvenile and adult males, as well as disruption of gamete production associated with reduced reproductive success [34,35]. Induction of vitellogenin production in male fish and feminization to different degrees are common in many parts of the world. These phenomena have been reported in Japan [36], Europe including Finland [37], Italy [38], Switzerland [39], Germany [40,41], the United Kingdom 42–45], and the United States [46,47].

The environmental inputs associated with feminization phenomena in fish are highly variable, including: paper-mill effluents [37], effluents of sewage treatment works [39,43], chemical spills and deliberate chemical applications [48], or complex pollution from human activities [36,41]. Even in places without visible input of polluted waters, like the Wahnbach drinking-water reservoir in Germany, slight elevation of the estrogenic biomarkers have been observed [40], giving room to speculations that natural phytoestrogens or deposition of airborne pollution may be the cause. In large rivers like the Elbe, vitellogenin in male fish is elevated at different sites. Wild bream show different patterns of biomarker response in different stretches of this river with different profiles of chemical pollution [41], suggesting that there was no single chemical that alone could explain the observed inhibitory effects on sexual development.

Both examples—masculinization in mollusks and feminization in fish—may illustrate that endocrine disruption in wildlife is a problem warranting worldwide attention and is not restricted to hot spots with uniquely high levels of environmental contamination. In the first case, the syndrome is clearly associated with a small group of chemicals with TBT as the most prominent member. In the latter case, different polluting chemicals and mixtures have been identified as putative causative substances, including industrial chemicals, natural hormones, and pharmaceutical estrogen analogs. Though these two examples indicate that endocrine disruption is not limited to only a few hot spots, very little is known about the geographic patterns of the occurrence of endocrine disruption. This is particularly true for those areas outside the industrialized agglomerations of Europe and North America.

## REDUCING RISKS

The example of fish feminization in surface water clearly shows that the problem of endocrine disruption in wildlife is much more complex than commonly assumed. Several different chemicals are probably involved, and consequently different measures will be needed to reduce the adverse effect of endocrine disrupters in the environment depending on the chemical characteristics of the substance, its use patterns, and its mobility and degradability within the environment. These measures will include the ban of persistent endocrine-disrupting substances. This will be necessary if the substances are widely used in products, and their input into the environment is diffuse so that they hardly can be controlled at the source. TBT and polychlorinated biphenyls (PCBs) are examples for such chemicals where worldwide bans are under way. In other cases, bans are no feasible solution for the problems posed by the substances, and technical solutions have to be sought. The modification of sewage treatment works may be the strategy of choice to remove natural and synthetic hormones more efficiently from sewage and to protect aquatic species. Additionally, several different measures may be useful to reduce the free use of these substances, ranging from voluntary commitments by industry to cease or reduce use of certain chemicals or legally binding use restrictions, to eco-labeling products that do not contain endocrine disruptors (EDs). In the last few years, both for persistent and nonpersistent EDs, substantial progress has been made to minimize their impact on the environment.

### Difficulties assessing the risk of endocrine disruptors

For tracing the chemical contamination of wildlife species, the maintenance of an environmental specimen bank in Germany has proven useful. For this specimen bank, funded by the Ministry for the Environment, tissue samples of free-living animals are taken and stored at ultra-low temperature. Tissue concentrations of environmental contaminants can be analyzed retrospectively. Several persistent and nonpersistent EDs have been analyzed in samples, which were taken in 1985 and later [49]. The results revealed time trends and consecutively reviewed the success of regulatory actions that were taken [49].

Nevertheless, it should be remembered that we are still not able to quantify the risk these substances pose to wildlife. Monitoring wildlife populations is only conducted at a very limited number of sites worldwide, and monitoring programs hardly ever include observations of endpoints that may be related to the disturbance of the hormonal system of free-living animals. This lack of coordinated monitoring programs is a factor obstructing targeted environmental policy in the field of endocrine disruption. Our picture of ongoing processes in wildlife is far from being complete. Incidental reports of observations made in the environment, like hermaphrodite polar bears [50] or feminized fish, are worrying the public and causing the impression that public services are not able to characterize the real situation in the environment.

As for many invertebrates (but also some vertebrates), only little is known about the hormonal regulation of life processes, making it virtually impossible to detect any disturbances of these processes [30]. It has only recently been discovered that mollusks are sensitive to estrogenic chemicals like nonylphenol and bisphenol A [51], leading to the characterization of an estrogen receptor in this class of animals in which estrogenic regulation had not been suspected.

## SUSPECT CHEMICALS

Besides the question of how widespread endocrine disruption may be in the environment, the most urgent question is how many chemicals possess endocrine-disrupting properties. As only a small minority of all chemicals has been tested for endocrine-disrupting properties, no answer to this question will be comprehensive. According to the definition of EDs agreed upon at the Weybridge workshop, in vivo testing is necessary in all cases to decide whether a chemical is an endocrine disruptor or not, as an endocrine disruptor has to show adverse effects in an intact organism or its progeny. Gülden et al. have published a list of substances in surface waters suspected of being EDs [52]. This list of more than 200 chemicals contains many substances for which a definitive judgement is impossible, due to a lack of valid in vivo studies. A candidate list of 564 substances suspected of being EDs was compiled in 2000 by BKH Consulting Engineers for the EU Commission (DG ENV). Subsequently, this list has been condensed to less than 300 substances, which have given rise to concern.

It should be emphasized that even substances definitively classed as EDs are more or less a random selection, as systematic, large-scale testing programs have not yet been conducted (also a consequence of there being no standardized methods). Furthermore, the EDs do not possess a limited set of clearly describable structural characteristics, making a prognosis as to the total number of disruptors impossible at this time. Nevertheless, comprehensive screening of available literature has shown that we have to face the likelihood that some 100 chemicals with endocrine-disrupting properties are relevant to this problem. Considering that in the European Union (independent of the problem of endocrine disruption), less than 100 chemicals were finally assessed during the last 10 years, it seems unlikely that the traditional forms of chemical risk assessment and risk reduction are able to manage the problem of endocrine disruption in an acceptable time frame. 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. The aim of the EU Commission is presently to achieve agreement on a list of substances that should be subject to such a targeted risk assessment.

## TESTING FOR ENDOCRINE DISRUPTORS

The aim of every strategy in the field of chemicals policy is to identify risks associated with chemicals before human health or ecosystems are harmed. In this attempt, biological testing of chemicals plays a key role to identify the characteristic risks a chemical may pose. Many of these tests using laboratory animals as a surrogate for wildlife individuals are internationally harmonized today. Particularly in the case of chemicals interfering with the hormonal system of wildlife species, little is known about their natural hormone system. This makes it difficult to develop internationally harmonized tests for endocrine disruption in animal classes, other than those commonly used in chemical and pesticide testing. Hormonal regulation differs so widely among different taxa that the strategy to test only few animal species as representatives for the whole animal kingdom may be obsolete in this case.

Internationally harmonized test procedures for EDs have been developed under the framework of the OECD in the Endocrine Disruptor Testing and Screening Workgroup (see Topic 4.11 for information on the development of fish-based tests [53]). For three years, this group has focused on developing and validating a short-term test for young and adult fish, a test with fish early life-stages (based on the OECD 210 test), a fish reproduction test, a fish full life-cycle test, and two short-term tests for identifying estrogenic and androgenic effects in rats (Uterotrophic and Hershberger assay), as well as an extended 28-day test on oral toxicity to rats exposed to repeated doses (enhanced TG 407). Although the group conducted very intensive work, and even if their present work is continued, it will only cover a small part of the hormonal systems present in the animal kingdom and the possible mechanisms involved in endocrine disruption.

Today we have to face the situation that comprehensive testing of chemicals for their hormone system disturbing properties is a goal that cannot be achieved in the near future. Comprehensive testing is desirable to exclude delayed transgenerational effects and low-dose effects due to unusual dose–response curves that have been observed for some of these chemicals. Nevertheless, due to the multitude of hormone systems existing in wildlife organisms and the even greater multitude of possible adverse effects, a comprehensive test strategy seems not to be practicable. This makes a precautionary approach for the regulation of EDs even more important than in other fields of chemicals policy.

## ASSESSING THE RISK OF ENDOCRINE DISRUPTORS

Even if the hazard assessment of a chemical concludes that a chemical is an endocrine disruptor, regulatory bodies have to face the problem of how to conduct a quantitative risk assessment [54]. Many elements of a quantitative risk assessment both for humans and wildlife are still debated controversially.

In traditional risk assessment, a threshold for effects of a chemical agent is assumed. Below that threshold, the body is able to compensate for the exposure, above it, effects become visible. There are some types of effects that do not show thresholds, like mutagenic and carcinogenic effects where theoretically one single molecule may lead to an adverse effect like cancer induction. It has been doubted that such a threshold exists for EDs [55,56]. The absence of a threshold would make it impossible to define a safe concentration.

Risk assessment for wildlife species aims to protect the population rather than the individual. In many cases, adverse effects on the individual level can be detected (e.g., lower sperm production) but the consequences for wildlife populations remain unclear [57].

The largest problem for environmental risk assessment of EDs is the extrapolation of high concentrations to low ones. Some studies suggest that effects of low concentrations of EDs may be more pronounced than of high concentrations [58]. Though this issue is currently subject to heated discussions and intense research, it seems not to be justified to apply linear extrapolation models to data derived from studies with EDs. As a consequence, regulatory bodies do not have a valid model to undertake quantitative risk assessment to date. The German Federal Environmental Agency has recently proposed to perform risk assessment according to procedures agreed for other substance classes, but to apply additionally an extra safety factor of 3 to 5 in human health and environmental risk assessments until the major problems of the methodology of risk assessment for endocrine-disrupting substances are solved.

## REGULATION OF ENDOCRINE DISRUPTORS—WHAT HAS HAPPENED DURING THE LAST 10 YEARS?

Some of the most prominent persistent EDs like dioxins, PCB, DDT, toxaphene, aldrine, and dieldrine will be banned worldwide by the Stockholm convention on persistent organic pollutants (POPs), which has been signed in 2001 and will probably enter into force in 2004. This worldwide ban provides that environmental concentrations of these substances will continue to fall, as is observed in most industrialized countries. Humans and other organisms on the end of the food chain will profit most from the further worldwide reduction of the POPs. These substances are probably responsible for some wildlife effects, like reproductive disorders in polar bears [50] and immune suppression in seals [59] (that may be one of the causes of the seal die-offs in the 1980s and very recently in the Baltic and the North Seas). The hypothesis that disturbances of the hormonal systems of these vertebrate species may be part of the mechanisms causing these adverse effects has been discussed.

Because POPs are subject to long-range transport, the highest concentrations in animals were observed in northern and arctic regions to which these substances are transported. Though the POP treaty is open for the incorporation of further substances, work with the aim of internationally prohibiting other persistent pollutants is only progressing slowly, so that the hope to phase out other persistent EDs (such as pentachlorophenol) globally under the framework of this treaty will probably be disappointed at least for the next few years.

The use of TBT is already heavily restricted in many industrialized countries. The application in antifouling paints on vessels less than 25 m in length is prohibited in Canada, Australia, and Europe, while Japan totally banned the use of TBT. The major problem internationally, and for the protection of the sea, is the use of TBT as an antifouling agent on the hulls of ocean-going ships. In October 2001, the International Maritime Organization (IMO) adopted a convention on the control of harmful antifouling systems on ships (AFS-Convention) agreeing that the application of all antifoulings containing TBT should be globally terminated by 2003 and that a complete ban on the presence of TBT antifoulings on ship's hulls should be in place by 2008. The agreed timetable of this treaty will probably be delayed, as the process of ratification in the signing countries is slower than anticipated. Nevertheless, with this agreement in the framework of the IMO, the main source for the input of TBT into the environment will be stopped.

Due to consequent reduction of TBT (and in some countries TPhT) in the environment, invertebrate populations are recovering in many parts of the world [50,60,62] though in others the imposex is still widespread despite a 10-year partial ban of TBT [61]. This may be due to continuous use in large ship paintings or to high contents of TBT in the sediments that may be subject to remobilization. It was reported from the United Kingdom that not only prosobranch snails, but also many taxa of the macrobenthic fauna recovered after TBT was banned for use as hull paint on small boats, and TBT concentrations dropped in an estuary [62,63].

The remaining source of TBT in the environment is its use in many products as a biocide. TBT is still quite frequently found in textiles and other consumer products, though in Europe the TBT industry does not support any other use than in antifoulings. TBT has been found in effluents of Bavarian sewage treatment works in concentrations up to 180 ng/l, which is well above the concentration of 1 ng/l, causing adverse effects in invertebrates [51].

In the European Union, risk assessments for some EDs of major concern have been finalized recently or are close to finalization. These substances include nonylphenol, bisphenol A, and some phthalate plasticisers. For some uses, risk-reduction measures are necessary and risk-reduction strategies are currently being drafted.

It should be noted that, in addition to national and international regulatory actions taken by state authorities, a considerable reduction of environmental inputs could be achieved by voluntary actions taken by industry. The German washing and cleansing industry voluntarily committed to phase out the use of alkylphenolethoxylates (APEs) in household detergents by 1992 and in industrial detergents by 1999. Due to this commitment, the consumption of APEO by the washing and cleansing industry has fallen in Germany by approximately 90 % relative to the 1980s, marking a great success. Nevertheless, considerable remaining quantities (more than 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.

In the case of bisphenol A, European industry has agreed to terminate use of this substance as a stabilizer for polyvinylchloride (PVC), thus closing down one of the two major sources of bisphenol A for the environment. The environmental input caused by recycling thermal paper, the other major source, needs further regulatory action. It should be noted that relatively high concentrations of bisphenol A found in the environment could not be attributed to any identified source and is likely due to diffuse input from bisphenol A-containing products or from degradation products of plastics manufactured using bisphenol A. However, in the absence of a product register, quantifying the emissions at this level is not possible.

## POLITICAL IMPLICATIONS

Even more than most other issues in the field of environmental protection, the debate on endocrine disruption was never only a scientific one. Maybe due to the fact that impairments in wildlife species were understood as early warning signals for possible threats to human health, this issue has always been important in political discussions throughout Europe, Asia, and America.

In Europe, the European Parliament, European Commission, and many national governments in the European Union have come to recognize the importance of the issue of EDs and have been asking for more activity with a greater integration into the chemicals safety program. Key documents are the commission's communication on a community strategy for EDs [64] and the document on its implementation [65], which set out the necessity of further research, informing the public, and taking political action. Short-term proposals are prioritizing 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), and deciding on monitoring programs, international coordination, and information for the general public. In the medium term, xenobiotic EDs should be determined and assessed, and impetus given to research and development of an 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 adjustments.

In two decisions in 1999 and 2000, the European Parliament encouraged the commission in its aim to compile a list of EDs and advised the commission to supply sufficient resources for endocrine disruptor research in its research framework programs. The EU parliament called upon the commission in the strongest terms to take rapid action to reduce the risks from EDs, rather than waiting for further tests.

In Germany in August 1999, a decision of the German Bundestag called for a staged but drastic reduction in discharges of proven EDs, drawing on the similar decision by the European parliament on January 26, 1999. Furthermore, it asked that those chemicals that can also reach groundwater and drinking supplies, and that can regularly be shown to have done so should be banned, and that 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 EDs. Domestically, special measures should be taken for alkylphenol (ethoxylate)s, phthalates, and TBT compounds.

Similarly, as early as 1996 the U.S. Congress directed the U.S. Environmental Protection Agency to develop a screening program to determine whether certain substances may have hormonal effects in humans. This led to the development of an Endocrine Disruptor Screening Program, aiming to test all chemicals being marketed in the United States systematically for their endocrine-disrupting properties.

These interventions from political bodies helped to speed up hazard and risk assessment for endocrine-disrupting chemicals, and to allocate research funds in this field. The parliament and government decisions picked up public concern and emphasized application of the precautionary principle to achieve risk reduction quickly. Nevertheless, in many cases the time frames set for risk assessment and risk reduction were exceeded by the regulatory bodies due to complexity of the legal framework underlying chemicals policy.

## WHAT HAS TO BE DONE?

From a governmental view, the following are main priorities for further work:

- Set up a program for coordinated monitoring combining chemical analysis and effect monitoring. This program should include not only fish and mammals, but also invertebrate species, birds, reptiles, and amphibians.
- Promote research on problems associated with quantitative risk assessment, such as extrapolation of high doses to low doses and existence of thresholds.

- Promote research on integrated risk assessment, particularly whether and how wildlife species can serve as models for endocrine disruption in humans and vice versa.
- Continue the work on a list of potential EDs and seek international cooperation in this field.

## REFERENCES


1. H. Seibert (Ed.). In *Endocrinically Active Chemicals in the Environment. Umweltbundesamt,* pp. 10–14, UBA-Texte 3/96, Berlin (1996).
2. E. C. Dodds and W. Lawson. *Nature* **137**, 996 (1936).
3. R. B. Bradbury and D. E. White. *Vit. Horm.* **12**, 207–233 (1954).
4. W. W. Tullner. *Science* **133**, 647–648 (1961).
5. J. Bitman, H. C. Cecil, S. J. Harris, G. F. Fries. *Science* **162**, 371–372 (1968).
6. A. E. Fischli, T. Godfrain, I. F. H. Purchase. *Pure Appl. Chem.* **70**, 1863–1865 (1998).
7. H. Bern et al. In *Chemically-Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection*, T. Colborn and C. Clement (Eds.), pp. 1–8, Princeton Scientific Publishing, Princeton, NJ (1992).
8. E. Carlsen, A. Giwercman, N. Keiding, N. E. Skakkebaek. *Brit. Med. J.* **305**, 609–613 (1992).
9. R. M. Sharpe and N. E. Skakkebaek. *Lancet* **341**, 1392–1395 (1993).
10. N. E. Skakkebaek and R. M. Sharpe. *Pure Appl. Chem.* **75** (11/12), 2023–2038 (2003).
11. M. Binot, R. Bless, P. Boye, H. Gruttke, P. Pretscher. *Rote Liste gefährdeter Tiere Deutschlands. Schr. R. f. Landschaftspfl. u. Natursch.* **55** (1998).
12. E. T. Peeters, A. Dewitte, A. A. Koelmans, J. A. van der Velden, P. J. den Besten. *Environ. Toxicol. Chem.* **20**, 2883–2891 (2001).
13. J. Oehlmann and U. Schulte Oehlmann. *Pure Appl. Chem.* **75** (11/12), 2207–2218 (2003).
14. J. Oehlmann, E. Stroben, U. Schulte-Oehlmann, B. Bauer, P. Fioroni, B. Markert. *Fresenius J. Anal. Chem.* **354**, 540–545 (1996).
15. S. Takahashi, S. Tanabe, I. I. Takeutchi, N. Miyazaki. *Arch. Environ. Contam. Toxicol.* **37**, 50–61 (1999).
16. G. W. Bryan, P. E. Gibbs, L. G. Hummerstone, G. R. Burt. *J. Marine Biol. Assoc. UK* **68**, 611–640 (1986).
17. C. Bettin, J. Oehlmann, E. Stroben. *Helgol. Meeresunters*. **50**, 299–317 (1996).
18. P. Matthiessen, T. Reynoldson, Z. Billinghurst, D. Brassard, P. Cameron, G. Chandler, I. Davies, T. Horiguchi, D. Mount, J. Oehlmann, T. Pottinger, P. Sibley, H. Thompson, A. Vethaak. In *Endocrine Disruption in Invertebrates: Endocrinology, Testing, and Assessment*, P. deFur, C. Crane, C. Ingersoll, C. L. Tattersfield (Eds.), pp. 199–270, SETAC Press, Pensacola, FL (1999).
19. T. Horiguchi, C. Hyeon-Seo, H. Shirashi, Y. Shibata, M. Soma, M. Morita, M. Shimizu. *Sci. Total Environ.* **214**, 65–70 (1998).
20. Y. Morcillo and C. Porte. *Environ. Res.* **81**, 349–354 (1999).
21. J. G. Vos, E. Dybing, H. A. Greim, O. Lagefoged, C. Lambre, J. V. Tarazona, I. Brandt, A. D. Vethaak. *Crit. Rev. Toxicol.* **30**, 71–133 (2000).
22. V. Axiak, A. J. Vella, D. Agius, P. Bonnici, G. Cassar, R. Casson, P. Chircop, D. Micallef, B. Mintoff, M. Sammut. *Sci. Total Environ.* **258**, 89–97 (2000).
23. T. C. Hung, W. K. Hsu, P. J. Mang, A. Chuang. *Environ. Pollut.* **112**, 145–152 (2001).
24. W. J. Shim, S. H. Kahng, S. H. Hong, N. S. Kim, S. K. Kim, J. H. Shim. *Mar. Environ. Res.* **49**, 435–451 (2000).
25. M. F. Pessoa, A. Fernando, J. S. Oliveira. *Environ. Toxicol.* **16**, 234–241 (2001).
26. A. J. Power and B. F. Keegan. *Mar. Pollut. Bull.* **42**, 761–772 (2001).
27. P. E. Penchaszadeh, A. Averbuj, M. Cledon. *Mar. Pollut. Bull.* **42**, 790–791 (2001).
28. M. Bech. *Environ. Pollut.* **117**, 421–429 (2002).

29. T. J. Reitsema, J. A. Thompson, P. Scholtens, J. T. Spickett. *Mar. Pollut. Bull.* **44**, 257–261 (2002).
30. P. L. deFur, M. Crane, C. G. Ingersoll, L. Tattersfield. *Endocrine Disruption in Invertebrates: Endocrinology, Testing and Assessment*, SETAC-Publications, Pensacola, FL (1999).
31. J. Sherry, A. Gamble, P. Hodson, K. Solomon, B. Hock, A. Marx, P. Hansen. In *Impact Assessment of Hazardous Aquatic Contaminants; Concepts and Approaches*, S. S. Roa (Ed.), Lewis Publishers, Boca Raton, FL (1999).
32. P. Matthiessen. *Pure Appl. Chem.* **75** (11/12), 2249–2261 (2003).
33. S. Jobling and C. R. Tyler. *Pure Appl. Chem.* **75** (11/12), 2219–2234 (2003).
34. D. E. Kime. *Endocrine Disruption in Fish*, Kluwer Academic, Boston (1998).
35. A. Arukwe and A. Goksøyr. *Sarsia* **83**, 225–241 (1998).
36. S. Hashimoto, H. Bessho, A. Hara, N. Nakamura, T. Iguchi, K. Fujita. *Mar. Environ. Res.* **49**, 37–53 (2000).
37. A. Karels, E. Markkula, A. Oikari. *Environ. Toxicol. Chem.* **20**, 1517–1527 (2001).
38. M. C. Fossi, S. Casini, S. Ancora, A. Moscatelli, A. Ausili, G. Notarbartolo-di-Sciara. *Mar. Environ. Res.* **52**, 477–483 (2001).
39. T. Wahli, W. Meier, H. Segner, P. Burkhardt-Holm. *Histochem. J.* **30**, 753–758 (1998).
40. J. Lehmann, F. Paris, F.-J. Stürenberg, V. Blüm. In: LÖBF Jahresbericht 1999, Recklinghausen; Germany (2000).
41. M. Hecker, C. R. Tyler, M. Hoffmann, S. Maddix, L. Karbe. *Environ. Sci. Technol.* **36**, 2311–2321 (2002).
42. Y. Allen, P. Matthiessen, A. P. Scott, S. Haworth, S. Feist, J. E. Thain. *Sci. Total Environ*. **233**, 5–20 (1999).
43. S. Jobling, N. Beresford, M. Nolan, T. Rodgers-Gray, G. C. Brighty, J. P. Sumpter, C. R. Tyler. *Biol. Reprod.* **66**, 272–281 (2002).
44. R. van Aerle, T. M. Nolan, S. Jobling, L. B. Christiansen, J. P. Sumpter, C. R. Tyler. *Environ. Toxicol. Chem.* **20**, 2841–2847 (2001).
45. M. G. Simpson, M. Parry, A. Kleinkauf, D. Swarbreck, P. Walker, R. T. Leah. *Mar. Environ. Res.* **50**, 283–287 (2000).
46. M. S. Sepulveda, W. E. Johnson, J. C. Higman, N. D. Denslow, T. R. Schoeb, T. S. Gross. *Sci. Total Environ.* **289**, 133–144 (2002).
47. L. C. Folmar, N. D. Denslow, K. Kroll, E. F. Orlando, J. Enblom, J. Marcino, C. Metcalfe, L. J. Guilette. *Arch. Environ. Contam. Toxicol.* **40**, 392–398 (2001).
48. P. Matthiessen and J. P. Sumpter. *EXS* **86**, 319–335 (1998).
49. A. Gies, C. Gottschalk, P. Greiner, W. Heger, M. Kolossa, B. Rechenberg, E. Rosskamp, C. Schroeter-Kermani, K. Steinhaeuser, C. Throl. In *Sustainable and Precautionary Risk Assessment and Risk Management of Chemicals*. UBA-Texte 30/01, pp. 1–54, Berlin (2001).
50. J. U. Skaare, A. Bernhoft, A. Derocher, G. W. Gabrielsen, A. Goksoyr, E. Henriksen, H. J. Larsen, E. Lie, O. Wiig. *Toxicol. Lett. Mar.* **15**, 103–109 (2000).
51. J. Oehlmann, U. Schulte-Oehlmann, M. Tillmann, B. Markert. *Ecotoxicology* **9**, 383–397 (2000).
52. M. Gülden, A. Turan, H. Seibert. *Substanzen mit endokriner Wirkung in Oberflächengewässern*. UBA-Texte 46/97, p. 362, Berlin (1997).
53. T. Hutchinson. *Pure Appl. Chem.* **75** (11/12), 2343–2353 (2003).
54. S. M. Barlow. *Chemosphere* **39**, 1287–1292 (1999).
55. J. J. Amaral Mendes and E. Pluygers. In: VI Cogliano, *Perspectives on Biologically Based Cancer Risk Assessment*, NATO series on Challenges of Modern Society, E. G. Luebeck and G. A. Zapponi (Eds.), Vol. 25, pp. 81–182, Kluwer Academic/Plenum, New York (1999).
56. D. M. Sheehan, E. Willingham, D. Gaylor, J. M. Bergeron, D. Crews. *Environ. Health. Perspect.* **107**, 155–159 (1999).
57. J. P. Sumpter. *Toxicol Lett.* **102–103**, 337–342 (1998).
58. E. J. Calabrese and L. A. Baldwin. *Toxicol. Sci.* **71**, 246–250 (2003).

59. H. Van Loveren, P. S. Ross, A. D. Osterhaus, J. G. Vos. *Toxicol. Lett.* **15**, 319–324 (2000).
60. P. Matthiessen and P. E. Gibbs. *Environ. Toxicol. Chem.* **17**, 37–34 (1998).
61. C. P. Gibson and S. P. Wilson. *Mar. Environ. Res.* **55**, 101–112 (2003).
62. H. L. Rees, R. Waldock, P. Matthiessen, M. A. Pendle. *Mar. Pollut. Bull.* **42**, 137–144 (2001).
63. P. Matthiessen, R. Waldock, J. E. Thain, M. E. Waite, S. Scrope-Howe. *Ecotoxicol. Environ. Saf.* **30**, 180–194 (1995).
64. European Commission. Communication from the Commission to the Council and the European Parliament. Community Strategy for Endocrine Disrupters. COM (99)706 (1999).
65. European Commission. Communication from the Commission to the Council and the European Parliament on the implementation of the Community Strategy for Endocrine Disrupters—a range of substances suspected of interfering with the hormone systems of humans and wildlife. COM (2001) 262 (2001).