

# The Prague Declaration on Endocrine Disruption

## Summary

- There is serious concern about the high prevalence of reproductive disorders in European boys and young men and about the rise in cancers of reproductive organs, such as breast and testis. Lifestyle, diet and environmental contamination play a role in the observed regional differences of these disorders and their changes with time.
- Hormone action is important in the origin or progression of the aforementioned disorders. Therefore it is plausible that exposure to endocrine disrupters may be involved, but there are inherent difficulties in establishing such causal links in humans.
- There is a serious gap of knowledge regarding the effects of endocrine disruptive compounds on other serious human diseases such as obesity, neuronal disorders, stress etc.
- Causality is well established for detrimental effects in wildlife as a direct consequence of exposure to endocrine disrupters. In some instances the severity of effects is likely to lead to population level impacts. Wildlife provides early warnings of effects produced by endocrine disrupters which may as yet be unobserved in humans.
- Wildlife represents a protection target in its own right. The severity of endocrine disrupting effects observed in the laboratory indicates that these substances may pose a threat for wildlife biodiversity as already shown for organotin compounds and marine snails.
- Europeans are exposed to low levels of a large number of endocrine disrupters which can act in concert. Many of these chemicals, drugs or natural products are found in human tissues and in breast milk. Humans are exposed to these chemicals from very early on in their lives when the developing organism can be particularly sensitive.
- The existing safety assessment framework for chemicals is ill-equipped to deal with endocrine disrupters. Testing does not account for the effects of simultaneous exposure to many chemicals and may lead to serious underestimations of risk.
- The current safety testing guidelines are based on reproductive effects, and thus do not take into account the deleterious effects of endocrine disrupters in other tissues. New test systems need to be developed to solve this shortcoming.
- In view of the magnitude of the potential risks associated with endocrine disrupters, we strongly believe that scientific uncertainty should not delay precautionary action on reducing the exposures to and the risks from endocrine disrupters.
- The challenges posed by endocrine disrupters require a long-term commitment to monitoring and research which is dedicated to characterising human and wildlife exposure and their mechanisms of action and interaction. This will help ensure better protection of the health of European citizens and the environment.

## Introduction

International experts and scientists representing many different disciplines came together in Prague on 10 – 12 May 2005 for a workshop on chemicals that interfere with hormone systems, so-called endocrine disrupters. The workshop was convened to discuss recent European research on the health risks associated with these chemicals. Much of this work emanated from large research projects funded by the European Union, and joined together in the cluster for research on endocrine disrupters, CREDO. The results presented at the Prague workshop have reinforced concerns over the long-term consequences of exposure to endocrine disrupters to humans and wildlife.

Endocrine disrupters are a very diverse group of chemicals, including some pesticides, bulk produced chemicals, flame retardants, agents used as plasticisers, cosmetic ingredients, pharmaceuticals, natural products such as plant-derived estrogens and many more. These substances may alter the function of hormonal systems and cause adverse effects by mimicking the effects of natural hormones, blocking their normal action, or by interfering with the synthesis and/or excretion of hormones.

The following position statement was agreed by the undersigned scientists. This document is intended to update European citizens, policy makers and regulators on research progress, to highlight shortcomings and flaws in current regulation and to make constructive suggestions that might lead to better protection of human and wildlife health in Europe and beyond.

### **Research updates: Human health concerns**

1. We are concerned about the high prevalence of male reproductive disorders in some European countries. There have been rises in genital malformations in baby boys, and recent data indicate that in parts of Europe, sperm quality is approaching crisis levels that may impair fertility.
2. The incidence of cancers, such as breast, testis and prostate cancer, continues to increase in many European countries, although there are notable differences between countries. The descendants of people who have migrated between countries adopt the cancer incidence of their new home country. This shows that these cancers are linked to factors in the environment, including the diet.
3. Genital malformations, testis cancer, and some cases of reduced sperm quality arise early in life, even during development in the womb. These conditions have common causes during reproductive organ development in the fetus, which is controlled by hormones. The concern is that endocrine disrupters may interfere with these processes to disturb male genital development during pregnancy. Similarly, hormonal dysregulation may lead to the formation of breast cancer in women and abnormal pubertal development in girls.
4. The immune system of young children can be affected by exposure to polychlorinated biphenyls (PCBs) and dioxins during development in the womb. As a result, the likelihood of contracting infectious diseases is increased. PCBs and dioxins are hormonally active pollutants found in the diet. These substances degrade very slowly, accumulate in fatty tissue and are able to reach the developing fetus. After birth, they are passed to babies via mother's milk. We are concerned that these contaminants, at levels found in food, induce unwanted health effects in young children. Steroid and thyroid hormones are involved in brain development and brain ageing and many other effects. Environmental contaminants which affect these systems may increase the risk of brain dysfunction.
5. Although at this point there is no clear link between exposure to thyroid hormone disruptors, cancer, mental retardation reduced fertility and neurodegenerescence in humans these issues need urgent evaluation, as such problems can be expected from our basic knowledge of the thyroid hormone physiology.
6. Little or no information is currently available regarding the effects of endocrine disrupters on disease condition outside the reproductive system such as metabolic syndrome, neuronal development, childhood cancers, cognitive development, immune problems, psychological disorders learning and memory development, and other. In many cases

there are casual links between endocrine disrupters and these diseases and more scientific information is required.

7. Use of novel research technologies in understanding the mechanisms of endocrine disruptor action at the molecular level is required. By understanding the molecular mechanisms that are affected by endocrine disruptors it will be easier to extrapolate the information between different exposed tissues.

#### **Research updates: Linking cause and effect**

8. Undoubtedly, European citizens have experienced rises in reproductive disorders and hormone-dependent cancers. What is unclear, however, is whether these diseases are linked to exposure to endocrine disrupters. Establishing a link is difficult as human diseases are the result of many interacting influences, of which chemicals are but one determinant. Only when a chemical exerts a very strong impact, has it been possible to uncover its role in disease processes, as is the case with steroidal estrogens and breast cancer. It is much more difficult, to prove small, albeit existing, influences of chemicals on health. Thus, we are convinced that failure to demonstrate direct links between hormone-related disorders and exposure to chemicals should not be taken to indicate an absence of risks.
9. The identification of causative chemicals is complicated by the possibility that disorders may become manifest long after exposure has taken place. By this time, causative agents may have disappeared from tissues, thus obscuring identification of risk.

#### **Research updates: Wildlife effects**

10. Beyond the fact that wildlife represents a protection target in their own right, they act as sentinels for effects produced by endocrine disrupters which may as yet be unobserved in humans. Seals living in the Baltic Sea and the North Sea have suffered reproductive failure and population declines that can be attributed to the impact of PCBs and dioxins. The same chemicals can also affect the immune system of seals, making them more vulnerable to infection with viruses.
11. Across Europe, male fish exposed to sewage treatment discharges show abnormal levels of female egg yolk protein due to the presence of endocrine disrupters such as steroidal estrogens and surfactant breakdown products in the sewage effluent. Reproductive abnormalities in fish, notably the appearance of eggs in the testes of male fish have also been observed. These fish have been shown to have a reduced reproductive capacity and 'males' produce sperm of poorer quality. Negative impacts on entire fish populations may be the consequence, as has been shown in recent laboratory studies on several fish species. Fish exposed to the contraceptive pill ingredient at concentrations found in European rivers showed disturbed sexual development and impaired reproductive capabilities at the adult stage, including reduced or inhibited egg production and egg fertilisation hindered release of semen and lower survival of their offspring.
12. Invertebrates are also vulnerable to the effects of endocrine disrupters. Tributyl tin, an ingredient in antifouling paints applied to the hulls of ships, resulted in the formation of male sex organs in female molluscs, with consequent reductions in population numbers. More recently, it was shown that bisphenol A, an industrial chemical, and UV-filter substances utilised in sun screens cause increased egg production in aquatic snails. The consequences of such abnormalities for the balance and well-being of entire ecosystems

are not yet predictable, but the severity of effects observed indicates a potential impact on wildlife biodiversity from endocrine disrupters.

### **Research updates: Exposure**

13. Considerable progress has been made in identifying new endocrine active chemicals. These include chemicals used as UV filters and antioxidants in cosmetics and chemicals used as preservatives in food. It is clear that European citizens are simultaneously exposed to large numbers of endocrine disrupters. However, we do not know the full range that we are exposed to through our diets, drinking water, air and consumer products. This lack of knowledge severely hampers efforts to explore a link between exposure and resultant effects in humans.
14. Human tissue levels of PCBs and dioxins have stabilised at approximately one third of the pollution peak in the 1970s. This indicates that internal exposure to these substances will continue, with European populations having to live with a pollution burden that will be present for generations to come.
15. We are concerned that Europe is currently experiencing an increase in pollution with highly persistent brominated chemicals that are used as flame retardants in many consumer items, including furnishings and computers. These substances and their breakdown products are found in mother's milk, food items, wildlife and many environmental media. Current knowledge regarding the exposures as well as the toxicological profile of these chemicals are insufficient for a proper human and ecological risk assessment.

### **Research updates: Safety testing and regulation**

16. A fundamental element of chemical safety assessment is the assumption of a threshold dose below which there are no effects. This may not be tenable when dealing with endocrine disrupters, because certain hormonally active chemicals act in concert with natural hormones already present in exposed organisms. Thus, even small amounts of chemicals may add to the overall effects, irrespective of thresholds that might exist for these chemicals in the absence of natural hormones. Additionally, due to limited sensitivity of established test methods, it is likely that effects are overlooked.
17. A further complication is that hormonal effects are often masked by other toxic responses. Only when testing is carried out at low doses usually not administered during routine testing do these effects become apparent. Furthermore, a feature of endocrine disrupters is the late occurrence of adverse effects long after exposure has ceased. Existing testing methods are not generally designed to deal with this possibility.
18. These difficulties are exacerbated when the effects of simultaneous exposure to many chemicals (mixture effects) are considered. Recent studies have shown that mixture effects can occur even when each component is present at a dose that individually does not produce effects. These observations further undermine the belief that threshold doses can be applied meaningfully during the safety assessment of chemicals. A dose of a single chemical judged to be safe after testing in isolation may give a false sense of security when exposure includes large numbers of other endocrine active chemicals which may interact with each other.

### **Shortcomings of the current regulatory framework**

19. The array of standardised methods that exists for the safety assessment of chemicals is ill-equipped to identify endocrine disruptors or to anticipate their likely effects on humans and wildlife. Many pollutants now recognised as endocrine disruptors, such as the case of tributyl tin, and certain phthalates (used as plasticisers in consumer goods), were only identified through scientific studies, not by routine safety testing. By this time considerable environmental damage had already been caused. Therefore, there is an urgent need to improve existing, and to develop novel, regulatory test methods.
20. Due to the weaknesses of existing regulations in identifying endocrine disruptors, biological and chemical monitoring programmes become increasingly important for the detection of as yet unidentified effects missed during the current risk assessment of chemicals. Existing monitoring programmes lack the ability to deal appropriately with endocrine disruptors, and chemical and biological monitoring must exist in concert.
21. Environmental exposure is to a mixture of chemicals and not a single agent. However, this is not reflected in test protocols and provisions to take mixture effects into account are totally lacking. Recent research indicates that this may lead to a significant underestimation of risks. The issue is beginning to receive attention among regulators, but jointly, regulators and scientists need to cooperate to develop workable approaches to dealing with mixtures.
22. Current test protocols rely on effects on the male and female reproductive tract. Testing protocols need to be developed to assess the effects of endocrine disruptors in other relevant tissues.

### **Proposed measures and actions to be taken**

23. For the foreseeable future, regulation of endocrine disruptors will have to cope with the tension between the biological plausibility of serious, perhaps irreversible damage and delays in generating data suitable for comprehensive risk assessment. In view of the magnitude of the potential risks, we strongly believe that scientific uncertainty should not delay precautionary action for risk reduction.
24. There are various frameworks to guide decision making about the selection of endocrine disruptors for further testing. Prioritisation is usually achieved by using screening assays to select chemicals for extensive testing which delays regulatory action until further data is available. Though screening assays are not adequate as a basis for risk assessment, they should be utilised to trigger precautionary regulatory action on the basis of the rebuttable assumption that positive results may indicate risks. Precautionary action can include labelling, measures to reduce exposure, restrictions in use patterns or even the ban on certain chemicals.
25. The substances already known to have endocrine disrupting properties should be included in the proposed European chemicals regulation REACH, and subject to the authorisation procedure. Initially, the substances should be drawn from existing lists detailed in the EU strategy for endocrine disruptors. By a dynamic process, it is imperative that new substances should enter and exit the list taking account of new information, particularly including academic studies, as it becomes available.
26. Steps should be taken to restrict inherently the use of persistent chemicals, e.g. brominated flame retardants in order to halt their build-up in humans and the

environment. We are concerned that inaction will lead to a dangerous repeat of the events that have led to the accumulation of dioxins and PCB's in humans and wildlife.

27. The release of endocrine disrupters from sewage treatment works should be reduced significantly. A large fraction of the pollution stems from steroid hormones excreted by humans, and the control of these cannot be easily regulated. Therefore, improvements to sewage treatment technology for the removal of these and other endocrine disrupters are required. However, where practicable, for man-made substances, priority should be given to the prevention of the release, rather than end of pipe solutions.
28. It is regrettable that commercial pressures and property rights often stand in the way of making publicly available the data gathered by industrial companies for the purposes of hazard identification. We propose that relevant data from animal testing should be made publicly available whenever possible. This would avoid costly duplication of experiments, and take account of ethical issues ensuring that the best use can be made of animal data for the development of alternative tests.

### **Research priorities**

29. The challenges posed by endocrine disrupters cannot be solved in the short term, and there is an urgent need for further research to underpin better protection of the health of European citizens and the environment. To aid the planning of the forthcoming 7<sup>th</sup> Framework Programme of EU research funding, we propose that research activities in this area should be prioritised, as follows:
30. The lack of a complete picture of the full array of endocrine disrupters is hampering progress with risk assessment. Further extensive research during the next five to ten years is needed to fill gaps. Emphasis should be placed on the development of new chemical analytical methods and the development and validation of bioassay-directed techniques. Biobanks with suitable human and wildlife reference material, covering European countries with marked differences in relevant disorders and/or chemical exposure should be established.
31. Further understanding of the possible modes of action of endocrine disrupters is required in order to recognise organism functions that might be at risk. Only on the basis of such research will it be possible to develop appropriate biomarkers and biotests of effects for human and wildlife disorders. A considerable strengthening of links to fundamental research into disease processes is necessary. The effects of endocrine disrupters on novel target tissues and a wider array of cellular signalling pathways need to be elucidated, in particular those closely linked to disease conditions.
32. The effects of endocrine disrupters on a wider array of cellular signalling pathways needs to be elucidated, in particular those closely linked to disease conditions. Focus should be placed on signalling pathways involved in major disease conditions such as metabolic syndrome, obesity, and heart disease.
33. The development of new assays and screening methods for the identification of endocrine disrupters relevant to humans and wildlife should be pursued with urgency. This should take advantage of modern technologies such as genomics, proteomics, bioinformatics and metabonomics.

34. More mechanistic information regarding how endocrine disruptors are involved in human disease is required. This information need to take into account the complexity of the effect and exposure scenario with multiple targets, exposure to multiple contaminants and the fact that exposure levels are low and exposure time is long
35. Further systematic work on mixture effects will be needed to underpin better risk assessment procedures. Research should be extended to exploring relationships between exposure time and dose, and to investigations of the effects of sequential exposure to several chemicals. Emphasis should be placed on understanding the mechanistic basis of combination effects.
36. The consequences of endocrine disruption in wildlife for the balance and well-being of ecosystems should be pursued with urgency because some case studies have already shown that endocrine disrupters pose a threat for biodiversity. Emphasis should be placed on better linkage of laboratory and field investigations, considering a broad coverage of vertebrate and invertebrate groups.
37. In wildlife research, mechanistic work linking effects seen at the organism level to population-level and ecosystems effects should be encouraged. There is a need to apply the rigorous methodology of human epidemiology to the wildlife arena. Links with ecological systems approaches should be encouraged.
38. Special programmes focusing on the detection of possible effects on the newborn child giving rise to problems in childhood and adulthood should be initiated in order to overcome the challenge of possible long temporary breach between exposure episode and overt adverse outcome.

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