A PRECAUTIONARY APPROACH TO THE REGULATION OF ENDOCRINE DISRUPTING SUBSTANCES

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1. SUMMARY

This paper highlights the need for a precautionary approach to the control of substances with the potential to disrupt the endocrine system. It summarises briefly the characteristics of the endocrine system and some of the consequences of its disruption which make a high levels of precaution necessary. The paper briefly reviews some of the evidence for impacts on wildlife and humans and highlights some of the gaps which remain in our understanding of this phenomenon. In addition, however, it also highlights important information we do have for some substances and stresses the need for precautionary action in relation to these. Existing commitments within the Treaty and International Conventions are reiterated and the shortfalls of current approaches described. Finally the paper outlines some practical measures by which the precautionary principle may be implemented with respect to endocrine disrupting substances.

2. WHAT IS THE PRECAUTIONARY PRINCIPLE?

Perhaps the most commonly used formulation of the precautionary principle is that used within the 1992 Rio Declaration on Environment and Development:-

"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" (Rio 1992).

Several variations on this general theme exist. However, the basic premise is that the threat of serious or irreversible damage should be avoided, even in the face of

considerable scientific uncertainty, i.e. that prevention is better than cure. The aims of the principle were clearer from its earlier formulations, arising within German Federal Law (FRG 1986). The Principle of Precautionary Action required that:-

- harm should be avoided before it occurs
- high quality scientific research should act to provide early warnings of the potential for damage
- action not merely can, but MUST, be taken on the basis of available information as necessary to avoid threats, even when evidence of causality remains limited
- all technical, social and economic developments should tend towards a progressive reduction in overall environmental burden

Implemented on this basis, the principle thereby represents a strong and overarching mandate for protective action, using information from scientific research as a guide to ensure that policies and resulting action are both timely and effective.

3. WHY IS PRECAUTIONARY ACTION ESSENTIAL FOR ENDOCRINE DISRUPTERS?

The endocrine system plays a fundamental role in the development and metabolism of animals. It is instrumental in the control of growth and development of tissues and organs from conception through adulthood. Some of its most profound and irreversible effects occur during the early stages of development of the embryo or young offspring. It also monitors changes in both internal and external environments throughout life and controls the responses of the body. Disruption of this system can, therefore, have severe and wide ranging impacts.

The endocrine system operates through the synthesis, transport, reception and metabolism of chemical messengers which can trigger specific but diverse effects, often at very low concentrations. Each hormone may act on a single tissue or organ, or have wider effects, and may have differing functions at different stages of development or activity. Control of endocrine activity is highly complex, involving numerous positive and negative feedback mechanisms. Concentrations of natural hormones may vary greatly over time, particularly during early development.

Endocrine activity relies on the recognition and binding of hormones by receptors. The endocrine system may, therefore, be susceptible to interference from chemicals which are able to bind to or block hormone receptors, or alter hormone activities in other ways, with a high sensitivity and time-dependence in some instances.

Our understanding of precisely which mechanisms are involved in the disruption of the endocrine system by exogenous chemicals (i.e. not naturally produced hormones) is limited and uncertainties remain high with respect to cause-effect relationships. Nevertheless, the potential for serious or irreversible damage to occur as a result of exposure to endocrine disrupting substances is clear. The Erice Statement, arising from the Wingspread Conference on endocrine disruption held in 1995, recognises

that:-

"...the potential risks [of endocrine disruption] to human health are so widespread and far-reaching that any policy based on continued ignorance of the facts would be unconscionable".

Action to prevent exposure of wildlife and humans to such substances is necessary if this potential is to be avoided. Hence the key role for the precautionary principle with respect to endocrine disrupting chemicals.

4. IS THERE EVIDENCE OF ENDOCRINE DISRUPTION IN HUMANS OR WILDLIFE?

A number of studies have demonstrated effects on reproduction and development in wildlife populations resulting from exposure to specific chemical agents. Mechanistic evidence suggests that such impacts are probably mediated through interference with the endocrine system . The work of Guillette and colleagues (Guillette *et al.* 1994, Vonier *et al.* 1995) on alligator populations in Florida lakes is perhaps the best known, but by no means the only, example. Impacts on reproduction in the Florida panther are also well documented (Facemire *et al.* 1995) and reductions in reproductive success, and changes in sexual behavior, have been reported in bird populations exposed to certain pesticides and industrial chemicals (Fry 1995). Exposure to alkylphenolic compounds, among others, has been demonstrated to cause feminisation in freshwater fish (Jobling *et al.* 1996).

Two more recent studies have described the feminisation of freshwater fish as a widespread phenomenon in UK rivers and identified similar impacts in coastal waters (Jobling *et al.* 1998, Matthiessen *et al.* 1998). Although estradiol (natural or synthetic) may well contribute to the feminsation of trout placed downstream from sewage outfall, Jobling *et al.* (1998) note that the potential contribution from other compounds, including synthetic industrial chemicals, cannot be ruled out. Indeed, Matthiessen at al (1998), reporting estrogenic activity responses in flounder in both estuarine and coastal waters of the UK, noted no clear correlation with input from domestic sewers, which may be expected to introduce natural or synthetic estrogens. A much clearer correlation was found between estrogenic effects on flounder and overall inputs of industrial chemicals. The precise causative agents remain to be determined.

To date, the majority of interest and research has centred on the interactions of exogenous chemicals with steroid hormone systems, particularly the female estrogens, which are involved in the regulation of reproduction and the development of secondary sexual characteristics. These hormones, however, represent only one component of the endocrine system. A recent review by the Swedish Environment Protection Agency draws together research on the impacts of a range of chemicals not only on steriod hormone-mediated processes, but also those regulated by thyroid and retinoid hormones, responsible for growth, development and differentiation of tissues and organs from the very earliest embryonic stages (Olsson *et al.* 1998). For example, lindane, some PCB metabolites and polybrominated diphenyl ether flame

retardants can disrupt thyroid hormones, acting either on the liver or directly on the thyroid (Yadav and Singh 1986, Lans *et al.* 1993, Morse *et al.* 1996, Fowles *et al.* 1994, Darnerud and Sinjari 1996). Similarly, polychloronated dibenzodioxins and furans, lindane and halogenated phenols and benzenes are capable of interfering with the retinoid hormones (den Besten at al. 1993, Sewall *et al.* 1995).

The wealth of evidence from animal studies, both in the field and in the laboratory, coupled with an understanding of the endocrine system and its conservation through evolution, suggests that exposure to endocrine disrupting chemicals could result in widespread impacts on human populations . Trends identified in human health and development, particularly increases in some reproductive disorders and cancers in both men (Santti *et al.* 1994, Toppari *et al.* 1995) and women (Gladen and Rogan 1995, Rier *et al.* 1995) could be mediated through effects on the endocrine system. At the same time, several epidemiological studies undertaken within the general population have revealed correlations between chemical exposure in the womb and subtle effects on cognitive and neurological development in children (Koopman-Esseboom *et al.* 1995, Jacobson and Jacobson 1996). While these studies do not provide direct evidence of cause-effect relationships, they do represent effects for which the underlying mechanisms could well be interference with endocrine function.

The 1996 European Workshop on the Impact of Endocrine Disrupters on Human Health and Wildlife (The Weybridge Meeting) reached a number of conclusions regarding observed or potential impacts and limitations to knowledge (EC 1996):

Human Effects

- sufficient evidence for increase in testicular cancer rates
- apparent decline in sperm counts in some countries could not be accounted for by conventional confounding factors
- evidence was not sufficient to link effects to chemical exposure

Wildlife Effects

- observed cause-effect relationships were more limited within the EU than in US
- requirement for adequate baseline data and sentinel species was recognised
- the development and validation of screening and monitoring techniques were essential but remained very much underway

General Recommendations

- greater weight needed to be placed on *in vivo* studies than *in vitro*
- priority was to identify active chemicals rather than elucidate mechanisms of action
- when deemed necessary, implementation of the precautionary principle (as defined in the Rio Declaration) to reduce exposure

Although the meeting made numerous recommendations for the direction and requirements of future research, it stopped short of elaborating precisely how, and under what circumstances, precautionary action would be taken. Moreover, the first and second of the General Recommendations listed above would appear to contradict, to some degree, the precautionary principle (the substance of the third recommendation). By increasing the focus on the need to demonstrate effects in whole organisms, some important chemical interactions with hormone receptors or metabolic pathways which occur on a fundamental level may be overlooked simply because the consequences to the whole organism have yet to be identified.

5. WHICH COMPOUNDS ARE CURRENTLY LISTED AS KNOWN OR SUSPECTED ENDOCRINE DISRUPTERS?

Numerous lists of known or suspected endocrine disrupters have been published (e.g. Colborn *et al.* 1993, Topparri *et al.* 1995). What most of these reflect is the existing evidence that a diverse array of chemicals may be capable of interacting and interfering with the endocrine system. While this is, perhaps, unsurprising, given the complexity of the endocrine system itself and the numerous possible mechanisms, it does suggest that it may remain very difficult, if not impossible, to predict endocrine disrupting activity on the basis of chemical structure or the possession of particular active groups (e.g. see Harris *et al.* 1997 with respect to phthalate esters).

The following list (Table 1) is the working list of endocrine and potential endocrine disrupters according to the European Endocrine Disrupters Research Inventory, maintained by the German Umweltbundesamt (EEDRI 1998). It represents a typically diverse list of chemical groups, a significant proportion of which are organohalogens. Many of the groups listed are well known for other aspects of their toxicity, although it is possible that some of this conventional toxicity may be mediated through their ability to disrupt the endocrine system. In any case, their known or suspected potential for interference with endocrine systems represents an additional and highly significant aspect of their overall toxicity.

The list includes a number of chemicals or groups which are no longer permitted for manufacture, marketing or use within the EU, but to which exposure in the Community continues as a result of persistence and /or continued use in non-EC countries. Action to address these must, of course, be global in nature, although the EC and Member States should have an important role to play in guiding such legislation.

Nevertheless, by no means all of the chemicals listed are banned in Europe. A substantial proportion are still used widely, including as components of consumer products, or are generated as unintentional by-products of other manufacturing or diposal operations. All of the chemical groups on the OSPAR Priority List (Table 2) have members which are known or suspected endocrine disrupters.

DDT and metabolites
Methoxychlor and derivatives
Phenylhydroxymethylphenyl
Bis(hydroxphenyl)methane and derivatives
Diphenylethane derivatives
Diphenylethylene derivatives
Diphenylpropane derivatives
Triphenylmethane derivatives
Non-chlorinated biphenyls and derivatives
Chlorinated and polychlorinated biphenyls
Chlorinated and polychlorinated terphenyls
Polycyclic aromatic hydrocarbons
Naphthol and derivatives
Alkylphenols and derivatives
Phenylsiloxane
Chlorinated cyclodienes and camphenes
Phthalate esters
Halogenated dibenzodioxins
Alkyl-substituted halogenated dibenzodioxins
Alkyl-substituted chlorinated dibenzofurans
Linuron, diuron and derivatives/metabolites
Vinclozilin and derivatives/metabolites
Isomers of hexachlorocyclohexane
Thiocarbamate
Brominated and polybrominated biphenyls
Triazine and triazole
Halogenated dibenzofurans
Carbamate
Organophosphate esters
Chlorophenol and chlorophenoxyacetic acid
Halogenated aliphatics and halogenated aromatics
Flutamid
Dicofol
Fenarimol
Trifluralin
Nitrofen
Styrene

Table 1: European Endocrine Disrupters Research Inventory's "Working List of Endocrine and Potential Endocrine Disrupters" (EEDRI 1998)

Polychlorinated dibenzodioxins
Polychlorinated dibenzofurans
Polychlorinated biphenyls
Polyaromatic hydrocarbons
Pentachlorophenol
Short-chained chlorinated paraffins
Hexachlorocyclohexane isomers
Mercury and organic mercury compounds
Cadmium
Lead and organic lead compounds
Organic tin compounds
Nonylphenol/ethoxylates and related substances
Musk xylene
Brominated flame retardants
Certain phthalates - DBP and DEHP

Table 2: OSPAR List of Chemicals for Priority Action (OSPAR 1998a)

6. THERE REMAINS MUCH THAT WE DO NOT KNOW

Despite our rapidly improving understanding, our overall knowledge of the impacts and underlying mechanisms of endocrine disruption remains very limited. This is perhaps understandable given the natural complexity of hormone metabolism, action and interaction coupled with the enormous universe of chemicals to which we are exposed and the inherent difficulties in determining that exposure. We still do not yet understand fully what makes any particular chemical an endocrine disruptor, limiting the application of QSAR approaches (Korner *et al.* 1997, Harris *et al.* 1997).

Although evidence is now gathering for effects on other hormones, historically much research has focussed on one restricted aspect of the endocrine system, the steroid hormones, principally targeting chemicals which mimic endogenous estrogens. Information on interactions with other hormones exists but remains much more limited to date. We still know very little about the significance of the timing of exposure to specific endocrine disrupters, and about the consequences of exposure to mixtures of chemicals rather than singly. Moreover, dose-response relationships for disruptive effects frequently depart markedly from conventional sigmoidal relationships. In some instances higher impacts may be observed at lower doses (Laenge *et al.* 1997, Welshons 1997).

Epidemiological studies which can be used to shed light on cause-effect relationships are rare and are likely to remain so given the inherent difficulties and limitations of such studies. These difficulties may be yet more acute as the full magnitude of certain effects may not be apparent until the next generation.

7. LIMITATIONS TO RISK ASSESSMENT

To date, only a very small proportion of Existing and New Substances on the market in the EU, or generated as by-products of manufacture or disposal, have been screened for their potential endocrine disrupting properties. To test each of these exhaustively, even using existing limited protocols, would be an impossible task. The grouping of substances, on the basis of structural similarity, may enable more effective and timely evaluation and control, although this in itself will not be sufficient.

For the various reasons described above, in addition to other limitations inherent to the risk paradigm (Johnston *et al.* 1996, Santillo *et al.* 1998), risk assessment methodologies may never be capable of addressing endocrine disrupters adequately. The need to develop standardised methodologies will undoubtedly result in oversimplification, relying on a limited range of potential end-points measured, and the loss of information which may be critical. The hazards presented by endocrine disrupters may be very complex in nature, or detectable only at population level in whole organisms. Impacts on performance or behaviour of individuals may go undetected; animals may remain fertile despite other sublethal effects (Gray 1992). At the same time, calculations of predicted no effect concentrations (PNECs), employed in risk assessments, may be confounded by unconventional dose-responses, even assuming that exposure can be accurately estimated.

Clearly further scientific research and methods development are essential if we are to elucidate mechanisms and become more effective at identifying and predicting effects. Nevertheless, further research is not sufficient as it does not, *per se*, provide for protective measures in the mean time. Scientific research can only guide policy making; it cannot decide policy in itself. The consequences of policies being wrong, an essential consideration in their development, differ markedly depending on the approach taken:-

1. the danger of waiting for further “proof” before taking action, only to find that retrospective action is necessary and some damage is already done; or

2. the danger of taking action on the basis of existing indications of a potential problem, only to find that measures were overprotective.

The latter approach is clearly more precautionary and, given the potential severity of the impacts of endocrine disruption, would be the more responsible.

8. NEVERTHELESS, THERE ARE SOME THINGS WHICH WE DO KNOW AND ON WHICH WE CAN ACT

Despite the uncertainties, there exists sufficient evidence that many banned chemicals and many which are still being manufactured, marketed and used in the EU are capable of interacting and interfering with endocrine systems on a fundamental level. Many of the latter are widely used in consumer goods or in industrial or agricultural products for open application or discharge. They have also generally been recognised for some time as problematic, hazardous chemicals as a result of other, more

conventional, toxic effects.

8.1 Case Study: Alkylphenols and their Ethoxylates

The estrogenicity of alkylphenols has long been recognised (Dodds and Lawson 1938), but has received much recent interest since the work of White *et al.* (1994) demonstrated the capability of both octyl and nonylphenol to displace estradiol from the estrogen receptor in rainbow trout. Jobling *et al.* (1996) reported the stimulation of vitellogenesis in freshwater fish following exposure to alkylphenols. Similar impacts have since been observed in both estuarine (Lye and Frid 1997) and marine (Hylland *et al*. 1997) species. More recently, Billinghust *et al.* (1998) recorded inhibition of the settlement of barnacle larvae by nonylphenol at concentrations relevant to those in UK coastal waters (i.e. down to 1 ug/l). Although the mechanism for this last effect is not yet known, some form of interaction with a chemical communication system would seem likely.

Under the auspices of the Paris Commission (and now subsumed under OSPAR), PARCOM Recommendation 92/8 (PARCOM 1992) called for phase out of all household uses of nonylphenol ethoxylate-based detergents by 1995, and of all industrial detergent uses by 2000. Some sectors of industry, particularly the wool processing sector in the UK, continue at present to use these detergents, with evident impacts on waters receiving effluents. Moreover, widespread use of these compounds continues in the form of additives in certain pesticides (to enhance spreading). Initiatives by Sweden to extend the provisions of Recommendation 92/8 to all applications of both octyl and nonylphenol and their ethoxylates have received little support from other Contracting Parties, despite the very clear evidence that these substances can have substantial deleterious effects in receiving waters. Nonylphenol and its derivatives is currently undergoing risk assessment within the EU, although no risk reduction measures have yet been proposed.

Alkylphenols also arise as components of high contact children's products. The analysis of PVC teethers and other toys, sourced from a number of countries, conducted by Greenpeace in 1997 (Stringer *et al.* 1997) identified nonylphenol in a number of plasticised PVC toys. This was in addition to the presence of several phthalate esters (principally DEHP, DINP and DIDP), some of which have been demonstrated to exhibit weak estrogen-binding and estrogenic activity in some *in vitro* tests (Jobling *et al.* 1995, Harris *et al.* 1997). Bisphenol-A was also identified in 2 of the 63 PVC toys analysed. It is not known whether these compounds were present as additives or contaminants in these products, but their presence in toys designed for high contact by young children certainly gives cause for concern.

8.2 Case Study: Brominated Flame Retardants

Recently concern has been raised regarding the presence of significant concentrations of brominated flame retardants (polybrominated biphenyls, PBBs; polybrominated diphenyl ethers, PBDEs) in both the tissue of marine mammals (de Boer *et al.* 1998) and human breast milk (Noren and Darnerud 1998). It has been known for some time that PBDEs can cause some foetal abnormalities in rodents following exposure during

early development, at levels below those which cause any observed toxicity in the mothers (EPA). Recently, Eriksson (1998) also reported subtle impacts on brain development in rodents, resulting in permanent changes in behaviour, memory and learning, although the mechanisms have yet to be elucidated. It is known that PBDEs can reduce the levels of circulating thyroid hormones in blood plasma (Darnerud and Sinjari 1996) and impact retinoid levels (EPA).

Similarly, tetrabromobisphenol-A (TBBA), also used as a flame retardant, appears to be able to compete with thyroxine (Brouwer 1998).

In both case studies above there remain, of course, significant uncertainties. Nevertheless, the evidence which is available, quite substantial evidence in some cases, does indicate the potential for widespread and long-term effects resulting from the continued use and release of these chemicals. Some of these effects are likely to be serious or irreversible. In these cases, there would appear to be a very good basis for the development and implementation of precautionary action. Substitution within a limited time frame for substances which do not show potential endocrine effects, and which are less hazardous in other ways, should be the only effective, long-term solution. Such action would be consistent with the objectives of the OSPAR strategy for hazardous substances (OSPAR 1998a), discussed further below.

9. THE PRECAUTIONARY PRINCIPLE IN THE TREATY AND INTERNATIONAL CONVENTIONS

Article 130(2) of the Treaty Establishing the European Community (EC 1993) states that:-

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

The precautionary principle and the premise that preventative action should be taken at source wherever possible are, therefore, enshrined within the Treaty and must be implemented effectively. Implementation must therefore include development of effective action on endocrine disrupters, although this does not, of course, receive specific mention within the Treaty.

The necessity for adoption of a precautionary approach is made more explicit in both the Final Declaration of the Fourth North Sea Ministerial Conference (MINDEC 1995) and the OSPAR Strategy with Regard to Hazardous Substances (OSPAR 1998a) (and accompanying Ministerial Sintra Statement, OSPAR 1998b), both of which also make specific reference to the need to address the issue of endocrine disruption with some urgency.

Already, however, the work of OSPAR has reflected a lack of will to address endocrine disruption as a hazard criterion until such time as standardised screening methodologies are available. Such an approach would fail to take account of the

strong evidence we have for some substances already.

10. CONTRASTING DEFINITIONS

Discussion continues in relation to whether disruption of endocrine function is simply a mechanism or a toxic effect in its own right. The definition of an endocrine disrupter agreed within the Weybridge meeting (EC 1996) has gained wide acceptance and usage across Europe:-

"An endocrine disrupter in an exogenous substance that causes adverse health effects in an intact organism, or its progeny, secondary [consequent] to changes in endocrine function".

This definition introduces two important considerations into the interpretation of research on endocrine disrupters.

1. Firstly, the impact recorded must have been at organismal level, effectively ruling out the classification of a substance as active on the endocrine system based on *in vitro* studies alone, even where these are conclusive and reproducible. In other words, the absence of *in vivo* effects in a test of a substance known to be active *in vitro* may be used to extend the argument that the substance is of no significance in animal systems. This relies on the assumption that the end-points employed *in vivo* are the only possible indicators of adverse effects, despite the known complexity of the problem, the potential for trans-generational effects and for impacts which are detectable only at population level. This assumption is, at best, highly optimistic. The consequences of the assumption being wrong could prove devastating.

2. Secondly, the impacts must be judged to be adverse, a term which is not defined but which implies that adaptive responses to impacts on the endocrine system following exposure would not be considered to be substantive (Ashby *et al.* 1997).

This definition extends from the view that disruption of the endocrine system is a mechanism rather than an effect in itself. Those substances which cause effects which might only be "*expected to lead to endocrine disruption in an intact organism*" are then defined as "*potential endocrine disrupters"*. Again, the criteria for "expectation" are not specified.

The Weybridge definition contrasts with that agreed within the 4th North Sea Minsterial Conference (Esbjerg Declaration, MINDEC 1995), to which the European Commission is signatory, principally as the latter specifies that adverse effects on the function of the endocrine system are a form of toxicity *per se*:-

i.e. Under Annex 2 of the Esbjerg Declaration hazardous substances were defined as:

…substances, or groups of substances, that are toxic, persistent and liable to bioaccumulate. In this definition toxicity should be taken to include chronic effects such as carcinogenicity, mutagenicity and teratogenicity and adverse effects on the function of the endocrine system.

The latter implies a more inclusive and precautionary approach. It is also subject to binding agreement and, as such, should be closely observed.

11. CONCLUSIONS: OUTLINE OF A MORE PRECAUTIONARY APPROACH

The discussion above has highlighted some of what we do and do not know about the complex and diverse phenomenon of endocrine disruption. It has been stressed that, while ongoing and further research will clearly be invaluable in improving our understanding of mechanisms and effects, enough is already known about the endocrine activities of some compounds in order for precautionary action to be taken. Such action should consist of substitution of these hazardous chemicals or groups for less hazardous alternatives or, preferably, alternatives with no identified hazards, consistent with the principle of substitution as set out in the OSPAR Strategy with regard to Hazardous Substances. In general, continued widespread exposure to chemicals with known endocrine activity must be seen as undesirable.

A number of basic elements which may constitute a more precautionary approach to the identification and regulation of endocrine disrupters are set out in general terms below:-

1. Policies to reduce and, ultimately, eliminate exposure to endocrine disrupting chemicals must be developed alongside the advancement of knowledge if harm is to be avoided in advance. In other words, scientific research should improve our understanding of the mechanisms, effects and implications but also act as an early warning system so that precautionary action to avoid harm may be taken on the basis of incomplete information which, nevertheless, indicates significant cause for concern. Such an approach would be more consistent with the precautionary principle.

2. Evidence that a chemical can interact with elements of the endocrine system at a fundamental level, derived either from *in vitro* or *in vivo* studies, must be taken as sufficient evidence of the potential for that chemical or group to cause adverse effects. In turn, such evidence should be seen as sufficient grounds to target that chemical or group for substitution. Using the Weybridge definitions, it must, therefore, be possible to take precautionary action to substitute *potential* endocrine disrupters as well as endocrine disrupters.

3. The substitution of known or suspected endocrine disrupters currently used as components of consumer products should be a priority because of the high likelihood of direct exposure.

4. Effects in intact organisms which may be classified as “adaptive” must also be seen to be adverse and undesirable since they may indicate a temporary loss of, or reduction in, function and may have subtle longer term impacts which are not yet amenable to study

5. Member States and the Commission must work to ensure the development, early

ratification and enforcement of effective global action on persistent organic pollutants (POPs) in order to address ongoing exposure to chemicals banned in Europe.

6. Furthermore, the Commission should rapidly develop and implement measures to control and substitute those chemicals still in use within Europe which have well established endocrine disrupting activities (including, but not limited to, the alkylphenols and derivatives and brominated flame retardants highlighted above).

7. The OSPAR Strategy with Regard to Hazardous Chemicals (OSPAR 1998a) must be fully implemented, such that discharges, emissions and losses of all hazardous substances, including endocrine disrupters, are eliminated. Most of the chemical groups on the OSPAR List of Chemicals for Priority Action (Table 2) have members which are known or suspected endocrine disrupters.

8. In recognition of the existing concerns regarding the hazards of organohalogens, and of the fact that a substantial proportion of the known or suspected endocrine disrupters are also organohalogens (see e.g. Table 1), complete phase out and substitution of this group should be a priority

9. Any measures adopted must be designed to be protective not only of human health but also of wildlife and the wider environment, and must take into consideration the necessities for protection of sensitive populations or sub-populations, such as developing embryos and newborn offspring

10. (Potential) endocrine disrupters should be regulated as far as possible on a group basis, with any non-evaluated members in that grouping assumed to possess the same characteristics as the most hazardous member of that group.

11. All compounds must be considered to have the potential for endocrine activity until there is evidence to the contrary. In this regard, potential interactions with all aspects of the endocrine system (including steroid, thyroid and retinoid components) must be considered.

12. No new chemicals should be permitted for use until they have been screened thoroughly and unless they show no evidence of endocrine disrupting activity. The financial responsibility for the demonstration that a chemical shows no evidence of endocrine disrupting activity must lie with the manufacturers or marketers.

The implementation of this approach will, of course, require fundamental revisions to the current legislative framework. Indeed, the potential for synthetic chemicals to interfere with the endocrine system, with the possibility of widespread and possibly trans-generational impacts, serves to illustrate the urgent need for such a fundamental review of the way in which chemicals are manufactured, marketed and used in the European Community.

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