# HUMAN AND WILDLIFE EXPOSURE TO ENDOCRINE DISRUPTORS WITH EMPHASIS ON PERSISTENT AND BIOACCUMULATIVE CHEMICALS

Bergman A*

Environmental Chemistry Unit, Department of Materials and Environmental Chemistry, Stockholm University, SE-106 91 Stockholm, Sweden

## Introduction

Exposure to anthropogenic endocrine disrupting chemicals (EDCs) has historically almost only been discussed in relation to DDT, and its metabolites DDE and DDD, PCBs and "dioxins", i.e. PCDDs/PCDFs. This was clearly the results presented in several reviews on EDCs in the late 1990'ties, referred to and extended in the United nation Environmental Program and World Health Organization supported review by the International Program on Chemical safety (IPCS), 2002 [1]. Apart from these three persistent organic pollutants (POPs), severe ED effects have been reported in both daughters and sons to women taking diethylstilbestrol, a pharmaceutical prescribed to pregnant women from the 1940's up to the 1980's [2]. However, over the last decade many more chemicals have been brought into the discussion of EDCs, both being POPs and semi-persistent pollutants. In the last few years, with a concentration to 2011 and 2012, several major reports have emerged on EDCs [3-6], and to be launched shortly, as is the case with a UNEP/WHO report on the "State-of-the-Science on Endocrine Disrupting Chemicals – 2012" [7,8].

This presentation is aimed to give an update of the EDC exposure situation in humans and wildlife. Which are the changes in our knowledge that have emerged over the last decade and which are the knowledge gaps we face today? A few needs for the future are also brought forward.

## Materials and methods

This presentation is based on extensive scientific data base on EDCs available to us today. Due to the limited space in this extended abstract, I want to refer the readers to the reviews mentioned above, including the upcoming "State-of-the-Science on Endocrine Disrupting Chemicals – 2012" [7,8] and the references cited therein.

## Results and discussion

First, it is difficult to estimate the total number of chemicals being handled by humans, including both truly anthropogenic chemicals and refined or industrially synthesized natural products, all being manufactured for human use. Only within the European Union more than 143.000 chemicals have be preregistered as part of the REACH legislation, by April 2011. It is however unknown how may chemicals (e.g. pesticides, pharmaceuticals, food contact material and personal care product ingredients (individual compounds)) that are left out due to regulatory exemptions. Muir and Howard indicated 2006 that over 8 million chemicals are commercially available with some 240.000 being kept in inventories or other registers [9]. All chemicals are transformed, abiotically and biologically, which is leading to an un-countable number of transformation products, many of which have short half-lives, but some may be stable and bioaccumulative, i.e. they are fulfilling the P&B criteria of POPs. Assuming 1% of all preregistered chemicals to be P&B chemicals indicate some 1000-1500 to be of potential concern. One of the major problems in this discussion is that we do not know which chemicals really are in use and where they are applied. Hence it is notable that only 22 chemicals/chemical mixtures are regulated within the Stockholm Convention as POPs [10]. Further, the majority of these POPs have been regulated since long in most countries worldwide. On the other hand there are a number of chemicals known to have high persistency and being bioaccumulative that are not yet regulated. Among those we see many brominated and chlorinated flame retardants and polyfluorinated chemicals, compounds related to PFOS and PFOA. However, there are also chemicals with P&B properties manufactured and applied for other purposes, but yet to identify.

Second, a question may be asked regarding which of the POPs and P&B chemicals exert endocrine activities. So far most of the 22 POPs have been shown to act as EDCs. Over 50 hormone systems may be considered for disruption in humans and since endocrine systems are conservative, this may also be the number relevant in

many of the vertebrates in general. We do see over 100 different signaling endogenous compounds active in a health organism. So far the ED field of research has concentrated on EAT (estrogens, androgens and thyroidogenic) chemicals leaving behind the majority of hormone systems in an intact organism. Only lately other endpoints such as diabetes, obesogenicity, cardiovascular diseases, bone effects, cancer effects on the immune system, neurodevelopmental diseases and disorders have been introduced as in part being caused by EDCs. Hence the number of endpoints to look into is much wider than previously expected looking into chemicals with ED properties.

Third, adding to the complexity of hormone disruption is the very large number of species among wildlife, invertebrates and vertebrates. So far only a very limited number of species have been studied. When it comes to wildlife it is common that field observations are among the first reports indicating possible on ED effects. This has been very obvious looking back on population declines among top predators, e.g. seals, otters, sea lions, birds of prey.

Changes in health among humans are more easily recorded, but due to human behavior, preferences for food, drugs, exposure to anthropogenic chemicals, wealth/poverty and social class strongly influences health it is difficult to identify which parameter is the most important to impact health, incl. reproductive health. Humans are exposed to a myriad of anthropogenic chemicals, many more than wildlife, via use of cosmetics, personal care products, prefabricated food, goods for our homes and offices, etcetera. This means that the cocktail of chemicals we are subjected to consists of substances with short, intermediate and long half-lives. Consequently we are also exposed to their metabolites. The chemicals are reaching us via ingestion, inhalation and through dermal uptake from the matrices: food, dust/particulates, air, water and soil, the latter only at young ages. Wildlife is primarily exposed via food and water or air, depending on compartment of living.

Exposure to POPs and other P&B chemicals play a particular role in both wildlife and humans. Hence, these compounds travel long distances and concentrations often increase with trophic level. This is why high concentrations of these chemicals are observed in both humans and wildlife from Arctic regions. The load of accumulated chemicals is also a source for metabolites. Internal transformations of POPs, in humans and wildlife, may lead to formation of chemicals (metabolites) that can interfere with the endocrine systems. Further, all these chemicals can be transferred to the embryo and growing fetus. Chemicals are transferred to the mammalian offspring via the placenta or for egg laying wildlife, via the egg content of anthropogenic chemicals. There is no barrier for fetal exposure to anthropogenic chemicals, POPs and/or EDCs.

Over the last decade it has become very clear that the newborn and the toddlers are exposed to anthropogenic chemicals via their hand-to-mouth activities. Several reports are available describing higher levels of polybrominated diphenyl ethers (PBDEs) in children than in their mothers [11,12]. The situation is similar for indoor cats, animals licking their fur, showing highly elevated concentrations of PBDEs in their blood [13,14]. Cats as well as small children may be similarly unintentionally exposed to any other chemicals present in indoor environments.

Even though there are 22 POPs according to the Stockholm Convention there is still a major lack of information on several of these pollutants if we look in a global perspective. Taking POPs in mothers' milk as an example it is still only PCDDs/PCDFs, PCBs and DDTs that are reasonably well covered geographically. Over the last decade clearly improved data sets have been produced for PBDEs and PFOS. But still there is a lack of data from Africa, South America and large parts of Asia. Temporal trend data are rare for any of the POPs in mothers' milk as well as any other human matrices, independent of geographical area. The situation is similar when looking at wildlife. Exposure analyses are pretty much anecdotal, without coordination. The Swedish environmental pollution monitoring program is together with Canadian program in the forefront of reporting POPs in wildlife. In humans the U.S. National Health and Nutrition Examination Survey (NHANES) is outstanding with no similar programs in e.g. the EU.

***EDCs and exposure: Examples of knowledge gains over a decade***

- The number of emerging and novel EDCs has increased dramatically over the last ten to twelve years, also including many more POPs or compounds with the corresponding properties (e.g. BFRs and PFCs). Over 800 anthropogenic chemicals have been indicated as EDCs, i.e. including also semi-persistent and pseudopersistent chemicals. However, many of these emerging and novel EDCs have not been linked to neither human nor human exposures.

- EDCs are chemically diverse, coming from as many sources as there are chemicals manufacured and used. They can also be formed in the environment through abiotic transformation reactions, and in humans wildlife and plants – the EDCs are everywhere. Occurence data are mainly lacking for these chemicals.

- Humans and wildlife are exposed to complex mixtures of EDCs. The situation is more complex than dealing with exposure to congener mixtures, like for dioxins. Real environmental mixtures are made up of structurally very different compounds including e.g. heavy metals, pesticides and chemicals used in materials and goods, to mention a few sources. Each of the chemicals has its own pharmacokinetics and present at highly different concentrations. Further, depending on organism the levels of different EDCs are highly different. The mixtures of POPs to which humans and wildlife are exposed are, due to their inherent properties, more stable than what is the case for semi-persistent chemicals. This is making it somewhat simpler to assess POP exposures.

- Early life exposures to EDCs always occur in humans and wildlife, i.e. *in utero* or *in ovo* exposures. A fertilized egg, embryo, the developing new organism (offspring) is not protected to almost any anthropogenic chemical or their metabolites, all potential EDCs. Hence, the placenta is not a barrier for EDCs. When it comes to POPs and P&B chemicals the maternal load of these chemicals will play a role for the offspring exposure, both in regard of the original POP but also of their metabolites, formed in the adult organism with the ability to be transferred over e.g. the placenta. Early life exposures to EDCs include nursing, in which POPs play a particularly important role due to their properties.

- Exposure to dust and particulates in indoor environments have turned out to be much more important for small children than previously expected. This means environments where the child is present which mainly is their home but is of course relevant also for day-care environments. The hand-to-mouth activities of a child are of particular importance for this type of exposure. Further, it is well known that dust and particulates play an important role in occupational exposure to chemicals.

***EDCs and exposure: Some data gaps and concerns***

- Poor knowledge on uses of chemicals and consumption volumes. Apart from some specialized uses, e.g. as pharmaceuticals, pesticides, uses in personal care products, cosmetics, there is almost an entire lack of information on where different chemicals are being applied. This is causing serious problems in all work related to exposure assessments, i.e. identification of which analytes to prioritize, selection of compartment, biological matrices or tissue for chemical analysis. The lack of data concerning volumes applied for different purposes (e.g. volumes of BFRs, CFRs and other additives in materials and goods) is a hindrance for proper prioritization of method development for analysis and exposure assessments of environmentally relevant pollutants in general, but for EDCs in particular. Data on consumption of chemicals is required to enable us to prioritize chemicals for EDC testing as well.

- Only a few EDCs are being measured. Among all indicated EDCs only a limited number are being measured analytically. This is a consequence of poor knowledge on uses of chemicals and consumption volumes (previous bullet) but also of reluctance among scientists to break new ground and look into new classes of potential environmental contaminants and also a consequence of financial bodies for environmental research to rather promote more of the same than novelty. So far exposure assessments are concentrated to POPs and P&B chemicals but also here there are major data gaps.

- Lack of global EDC exposure data. Exposure assessment data for EDCs are still lacking for large parts of the world. This is true for both humans and wildlife levels, even though the situation is somewhat better for a few POPs (DDTs, PCBs and dioxins) today, than ten years ago.

- Poor knowledge on chemical reactivity of anthropogenic chemicals and formation of transformation products. Since any anthropogenic chemical, EDC or not, can undergo a large number of abiotic and/or biologically catalysed reactions to form compounds with ED activity, it is relevant to understand both reactivity and to know which the transformation products are. This is to some extent known for the POPs but for chemicals in general this information is still lacking.

- The Sherlock Holms dilemma. It is of major concern that scientist for so long have had to act as detectives for finding "new pollutants", chemicals that are well known to manufacturers and downstream users. The resources are better spent if invested in development of analytical methods for exposure assessments. Still, researchers need the detective skills to identify truly unknowns, i.e. transformation products and unknown by-products.

***EDCs and exposure: Some future research related needs***

- Scientists need to get access to the full lists of chemicals in materials and goods, not only in pesticides, pharmaceuticals and some other products. It is needed to make it possible to evaluate their chemical properties and to prioritize them for chemical analytical method development and exposure analysis.

- Development of well-designed and coordinated environmental monitoring studies of human, wildlife, plants and abiotic matrices. This need to be done both on a national and a global level.

- Interdisciplinary research must be promoted to allow a holistic perspective on risks to EDCs to emerge.

- Exposure to EDCs during early life stages need to be intensified.

- Improved knowledge required for identification and formation routes of transformation products with potential EDC properties. This goes both for abiotically formed products and metabolites.

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