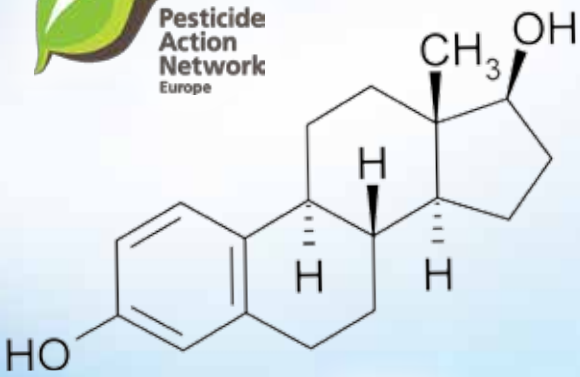
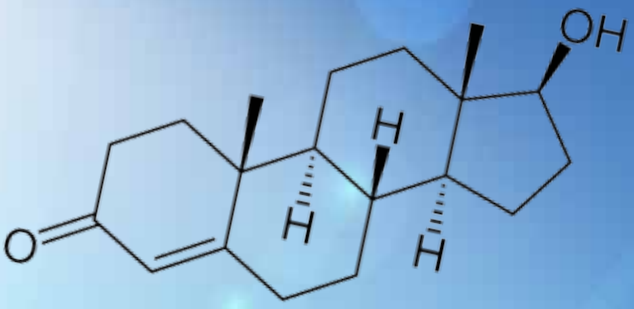
Pesticide Action Network Europe





Endocrine Disrupting Chemicals

and Future Generations: Time for the EU to Take Action

Opinions from the scientific community

Prologue

Following the growing evidence on the hormone-related adverse health effects in human and wildlife due to exposure to endocrine disrupting chemicals (EDCs), the European Union has taken the initiative to regulate and minimise human and environmental exposure to these substances.

The task to develop scientific criteria to identify EDCs was given to the European Commission, who missed its deadline of delivery on 31st of December 2013 as requested by European law. Although initially required by PPPR 1107/2009 and BPR 528/2012, the criteria must be "horizontal"- they will apply across all EU regulations related to chemicals (Industrial Chemicals, Cosmetics, Medical Devices etc).

A final draft of scientific EDC-criteria had been developed by DG Environment -a result of an extensive work among leading scientists in the field of endocrinology and Member States- but the criteria never got published. The Commission's Secretary General broke the agreement in July 2013, stopped the criteria-setting process and requested an impact assessment.

The reasoning behind this action was that Europe was the first to regulate the presence of such chemicals in its products and therefore the impact of such regulation should be assessed. The Commission admitted that several stakeholders had diverging views on the matter and the decision would affect several sectors, particularly the trade and chemical industry sector. The Commission also announced that *"diverging views still exist on many points within the scientific community and amongst regulators worldwide"*. But in reality among the specialists in the field of endocrine disruption there is already a consensus that exposure to EDCs is an issue of concern and we need to act urgently to protect our children and the future generations.

Following the Commission's statement, PAN Europe decided to bring forwards the scientific opinions of experts in the field of endocrinology, by organising a meeting in the European Parliament together with MEP Nicolas Caputo on 30th of June 2015 "Endocrine Disrupting Chemicals and Future Generations: Time for the EU to Take Action".

The criteria requested by European Law have to be scientific. In this report, we have included scientific opinions, and the speeches of the invited scientist from the 2015 Parliamentary meeting but also of the invited European regulators (from EFSA, Commission's Health Directory DG SANTE and Environmental Directory DG ENV).

We hope with this compilation to help the general public and regulators to understand the crucial need to regulate the use of EDCs in Europe in a manner that will protect humans, particularly the most vulnerable babies-in-the-womb, newborns and children as well as the environment and all its ecosystems. The decision of the "correct" scientific criteria will define the health of our future generations.

With kind regards,

Angeliki Lyssimachou, PAN Europe

Opinions from the scientific community

Thyroid Disruption

Prof. Thomas Zoeller (University of Massachusetts Amherst)

Thyroid hormone is essential for normal brain development (1). This fact is so well known that the many countries – and the World Health Organization – have salt iodization programs to ensure that especially pregnant women have sufficient dietary iodine to support thyroid function (2). In addition, newborn babies are nearly universally screened for thyroid function at birth to detect a condition known as congenital hypothyroidism (CH) (3). Children with CH that go undetected will be severely mentally and physically retarded, and this is not reversible (4). Moreover, numerous studies of children with CH designed to optimize treatment with thyroid hormone replacement have demonstrated that the developing human brain is exquisitely sensitive to thyroid hormone insufficiency (5).

Any hazard- or risk-based strategy to control human exposures to endocrine disrupting chemicals must begin with a screening and testing program that adequately evaluates known mechanisms of endocrine disruption. This is currently not the case for the thyroid.

Given the importance of thyroid hormone to human brain development, it is essential to identify industrial chemicals that may interfere with thyroid function or thyroid hormone action and may cause brain damage. A variety of chemical classes are already known to affect circulating levels of thyroid hormone, including pesticides, brominated flame retardants, plasticizers, and others (6). These chemicals were identified by evaluating their ability to cause a reduction in serum thyroid hormone, as well as by changes in thyroid weight and, possibly, histopathology. This is basically the strategy employed by the Endocrine Disruptor Screening Program of the US EPA, and by the OECD assessment of chemicals. Thus, in mammalian (rodent) screens and tests, there are no endpoints captured that reflect thyroid hormone action yet; that is, the effect of thyroid hormone on target tissues including the developing brain.

There are two important kinds of observations demonstrating that this strategy is missing to detect chemicals that can interfere with thyroid hormone action (rather that thyroid hormone circulating levels). First, chemicals such as PCBs and PBDEs can be bioactivated in the body and directly interact with the mechanism by which thyroid hormone exerts its action in tissues. This has been observed in cell cultures in highly controlled experiments (e.g., (7)), in animal studies (e.g., (8,9)), and there is indirect evidence for this in humans (10). Second, we know that thyroid hormone action can be regulated in a tissue-specific manner without concurrent changes in circulating levels of thyroid hormone (e.g., (11,12)). The fact that thyroid hormone is essential for brain development, but that current regulatory systems are not testing for the ability of chemicals to interfere with thyroid hormone action independently of the circulating thyroid hormone levels, represents a gap in logic that can no longer be defended. If not because we should protect the most vulnerable members of our populations – the unborn and newborn – then because the economic consequences are considerable (e.g., (13)). Any hazard- or risk-based strategy to control human exposures to endocrine disrupting chemicals must begin with a screening and testing program that adequately evaluates known mechanisms of endocrine disruption. This is currently not the case for the thyroid.

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Scientific speeches[1]

European Parliament EDC round table 30th June 2015
Pesticides Action Network Europe Hosted by MEP Nicola Caputo, (S&D)

SESSION 1
EDCs: WHAT ARE THEY AND WHY SHOULD WE BE CONCERNED?

Prof. Åke Bergman (Swedish Toxicology Sciences Research Center "Swetox", Sweden)[2]

Semi-persistent chemicals are the ones we are most concerned about at present. We have a large number of chemicals that are stable; they reach out into the environment and only when they get absorbed by organisms they are metabolised leading to a rapid transformation to often numerous metabolites products that may have adverse effects to organisms, but in general it is a detoxification step. Degradation of semi-persistent chemicals may also take place in the environment through abiotic reactions.

In 2013 UNEP/WHO[3] published a report highlighting that exposure to Endocrine Disrupting Chemicals (EDCs) is an issue of concern and poses a risk to human health and the environment. Three points were highlighted that raise concern: 1) there is an increasing trend of endocrine-related disorders in humans, 2) we have several observations of endocrine-related effects in wildlife and a decline in populations (effects that we don't want to see in humans), and 3) studies from laboratory animals show that some chemicals cause endocrine-related diseases.

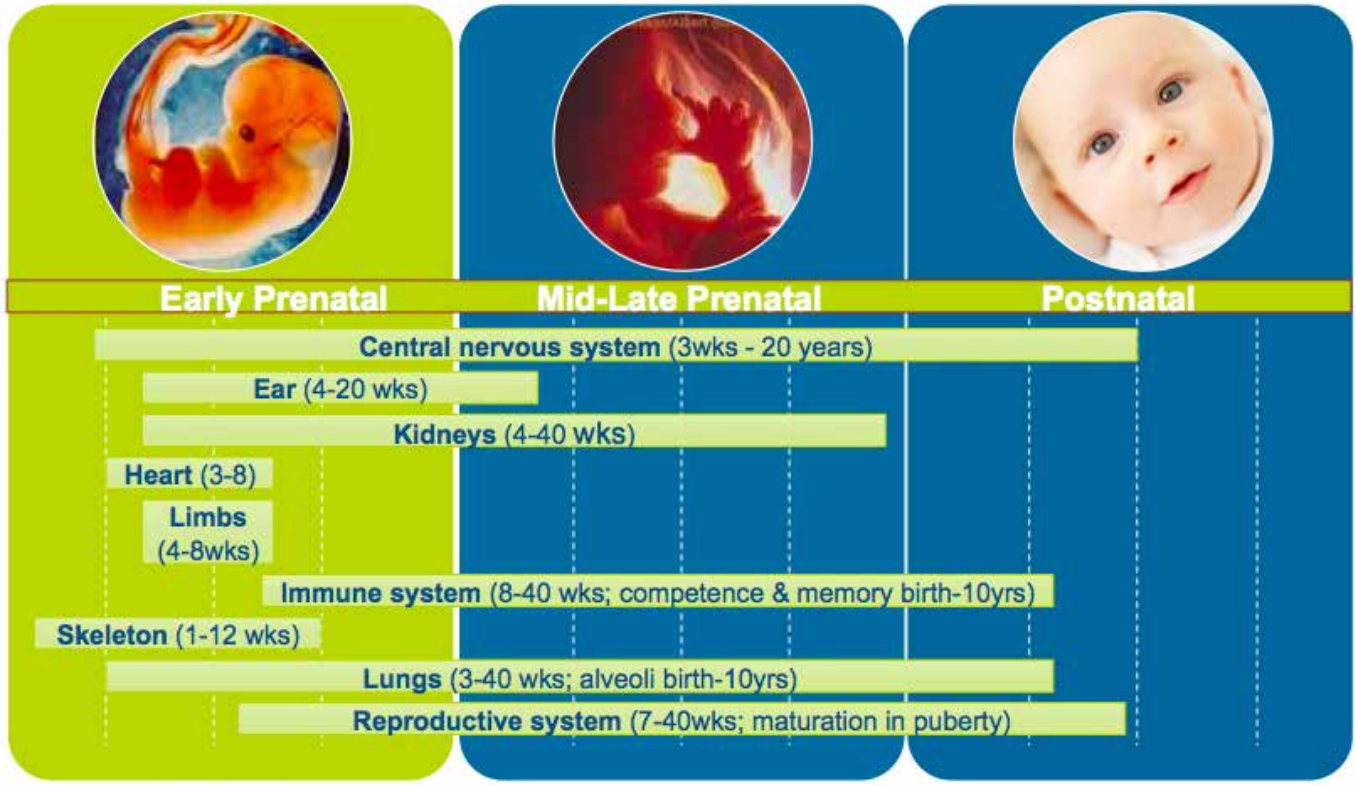
How long will we keep on spending tax money to investigate what is already known by the industry/producers?

[1] Program and introductory speeches given in Annex

[2] Executive Director of Swetox, Head of the Unit of Toxicology Sciences, Södertälje, Karolinska Institutet, Sweden,Professor in Environmental chemistry, Stockholm University, Sweden, High End Foreign Expert and Guest Professor at Tongji University, Shanghai, China, Coordinator of the UNEP/WHO 2013 reports on EDCs from 2013

[3] State of the science of endocrine disrupting chemicals, WHO/UNEP, 2013: www.who.int/ceh/publications/endocrine/en/

Risks related to vulnerable windows of exposure during early-life



One key conclusion from the UNEP/WHO 2013 report is "Disease risk due to EDCs maybe significantly underestimated"

The hormone system is also very complex composed by more than 100 hormones, acting in very low dose concentrations

There is a complex world of anthropogenic chemicals: pharmaceuticals designed to be endocrine active (contraceptives and others for curing certain diseases), semi-persistent pesticides (unstable in vivo, their metabolites may have stronger adverse effects than the parent compound), chemicals in materials and goods (40,000 chemicals), cosmetics and personal care products (25,000 chemicals), additives in food and industrial chemicals, transformation products (biotic/abiotic).

997 potential EDCs were listed in TEDX The Endocrine Disruption Exchange List of Potential Endocrine Disruptors)[4] database in May 2015. These chemicals often have very different chemical structures and uses but many have similar targets in the endocrine system (e.g., testosterone synthesis, oestrogen receptor agonist, thyroid hormone disrupter, androgen receptor antagonist). A fair number of the listed chemicals, 389 according to TEDX belongs to pesticides.

Although we have removed many of the persistent chemicals from the European market, we are still fabricating and using semi-persistent chemicals that remain enough time in the environment to reach biological targets.

Bisphenol A has been discussed extensively. There are 16 very similar structures to substitute BPA but some of them also have ED effects, which is also a problem.

The hormone system is also very complex composed by more than 100 hormones, acting in very low dose concentrations. EDCs that interfere with the hormonal system may also act at very low doses (at picomolar level), equivalent to the levels found in the environment (demonstration with adrenaline).

The hormone systems are governing our lives and active from the very early life-

[4] http://endocrinedisruption.org

stages. EDCs may result in the transmission of the wrong chemical signals during these early stages of development and lead to permanent alterations and disease later in life.

How long will we keep on spending tax money to investigate what is already known by the industry/ producers?

EU has to take into consideration the effects of mixtures that are not currently examined in detail, as well as the low dose effects that are usually not even tested by the industry.

EU has to take into consideration that there are low-dose effects of chemicals at the concentrations that humans and the environment are exposed to.

EU has to be proactive instead of reactive. We don't have to first wait and see chemically induced endocrine-related diseases manifested before society acts. We have enough scientific information to act now.

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EDCs and male reproductive health: Why are we concerned?

Prof. Jorma Toppari (Department of Physiology and Pediatrics, University of Turku, Finland)

There are reasons for concern for human exposure to endocrine disruptors. A report was published by WHO in 2012 on Endocrine disrupters and child health: "Possible developmental early effects of endocrine disrupters on child health". This report focuses on the thyroid and reproductive system where we see a lot endocrine disrupting effects following chemical exposure. This report was followed by the WHO report "State of the Science of Endocrine disrupting chemicals" published in 2013, that was mentioned previously.

Today, this presentation focuses on male reproductive health.

Incidences of testicular cancer are increasing in Europe (1995-2005) at a high rate. Evidence shows that there is something that interferes with the normal function of androgen receptor and testosterone in the foetal life.

There is evidence of endocrine disruption in male reproductive health: cryptorchidism (the failure of one or both testes to descend to the scrotum), hypospadias (urethra not located on the tip of the penis), semen quality/count, testicular cancer etc.

The sperm count is important for positive pregnancy outcome. A study from 20-years ago on pregnancy planners in Denmark [Bonde et al. (1998) Lancet][5] showed that the probability of conception decreased when sperm concentration was below 40 x 10^6 sperms/mL of semen. A trend of lower sperm counts is observed in males in Europe (a median of 40-50 x 10^6 sperms/mL), which means that half of the men have a lower number than this. That means it takes longer time to achieve pregnancy. Sperm concentrations below 15 x 10^6 sperms/mL are in the

[5] Bonde JP, Ernst E, Jensen TK, Hjollund NH, Kolstad H, Henriksen TB, Scheike T, Giwercman A, Olsen J, Skakkebaek NE, 1998. Relation between semen quality and fertility: a population-based study of 430 first-pregnancy planners. Lancet, 352(9135):1172-7.

infertile range.

When do men have testis cancer? When men enter into puberty after 10 years of age, testosterone synthesis increases and testis cancer incidence increases after that. In young men a peak is observed between 20 and 40 years of age. After 50 the risk is rather small. This is because the disease has its origin during foetal life and it needs hormonal stimulation to grow and become apparent. That also means that this disease is always diagnosed as it leads to death if not diagnosed. The good news is that today 95% of men are cured from testicular cancer.

Incidences of testicular cancer are increasing in Europe (1995-2005) at a high rate. Some of the countries register all cases of testicular cancer, others have a poor registration system. Evidence shows that there is something that interferes with the normal function of androgen receptor and testosterone in the foetal life. Example (Nordic countries): Denmark and Norway have the highest incidence. Testicular cancer rate in Finland has quadrupled since 1995. The incidence in Denmark was four times higher than in Finland. Men with poor testosterone production or androgen receptor functioning have ahigh risk for testicular cancer. So high, that there is a recommendation that men that have a poorly functioning androgen receptor (i.e. partial androgen insensitivity) should be castrated in puberty to prevent the disease.

A study measured levels of chemicals in mothers' breast milk and found significant higher levels of known EDCs in Danish mothers than in their Finnish counterparts. The difference was so clear that the Danish and Finnish samples could be distinguished by only looking at the amount of persistent chemicals in breast milk. There was also a weak correlation of cryptorchidism and levels of persistent chlorinated pesticides.

However, at the moment androgen receptors seem to have a normal function in most cases. Therefore the disease should be linked to interference with receptor function or testosterone production. A study in Denmark and Finland followed 5000 families with 2562 boys from pregnancy up to adulthood (18 years). Cryptorchidism incidence was much higher in Denmark than in Finland, and it was in correlation with testis cancer incidence. Cryptorchidism is the best-characterised risk factor for testis cancer. Incidence of hypospadias was also higher in Denmark than in Finland.

From laboratory experiments we have seen that exposure of animals to anti-androgens that block the action of androgens results in: cryptorchidism, hypospadias, nipple retention, shortened anogenital distance, dysgenetic testicular structure and impaired spermatogenesis. If we put several of these chemicals together we see that the effects occur at very low levels, well below the no observed adverse effect level (NOAEL) of an individual chemical. Effects of mixtures are additive. When tested one by one, you get zero percent of hypospadias, but when in combination the percent of hypospadias becomes 100%! E.g. vincozolin, procimydone, prochloraz, linuron and DBP (US Environmental Protection Agency, 2010)

It's difficult to study testis cancer in men because there is a long period between exposure to chemicals and development of testicular cancer. However, there is a shorter period for the development of cryptorchidism.

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Conclusions

- Male reproductive health problems are common, we are in trouble.
- EDCs affect the male reproductive system in experimental animals.
- EDCs act in an additive manner causing problems as mixtures rather than individual compounds.
- Human effects are plausible but epidemiological studies are inadequate to prove causal relationships and take very long- we shouldn't wait for such studies
- We should integrate the data we have from physiology, toxicology and experimental world to protect people in time.

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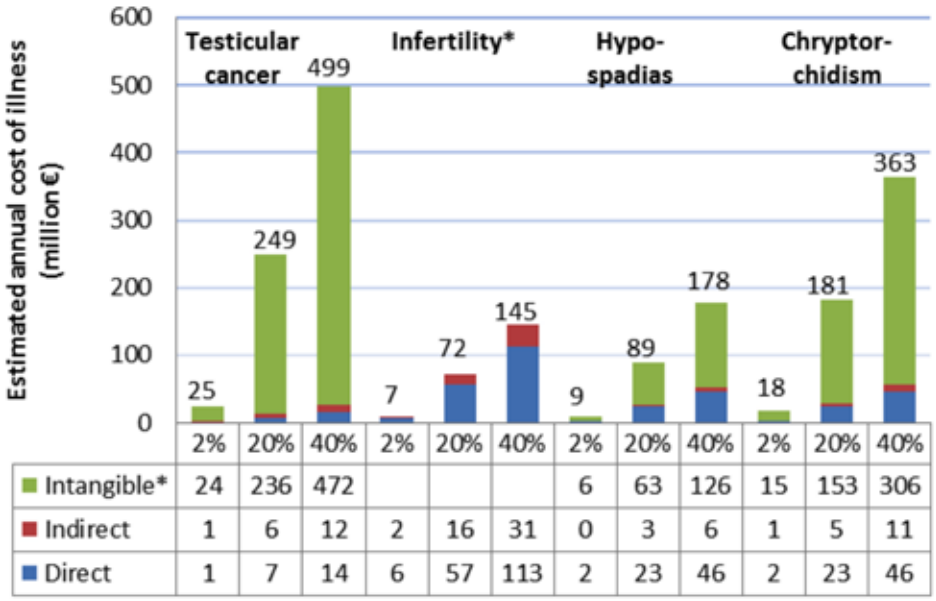
Cost of inaction and endocrine disruptors. What do we know?

Dr. Ing-Marie Olsson Ressner (Swedish Chemical Agency "KEMI", Sweden)

During the last year three different actors have published studies showing costs related to human health and EDCs. These actors are the Nordic co-operation, The Endocrine Society and Health & Environmental Alliance.

I have been involved in a Nordic co-operation where we looked at male reproductive health[6]. Using this report I will compare the data with the other two studies, highlight the



	Testicular cancer			Infertility*			Hypo-spadias			Chryptor-chidism		
	2%	20%	40%	2%	20%	40%	2%	20%	40%	2%	20%	40%
Intangible*	24	236	472				6	63	126	15	153	306
Indirect	1	6	12	2	16	31	0	3	6	1	5	11
Direct	1	7	14	6	57	113	2	23	46	2	23	46

Etiological fractions for male reproductive disorders

[6] The Cost of Inaction: Socioeconomic analysis of costs linked to effects of endocrine disrupting substances on male reproductive health. Technical Report, Nordic co-operation, 2014. http://norden.diva-portal.org/smash/get/diva2:763442/FULLTEXT04.pdf

strengths and weaknesses and conclude with some remarks on what we want to achieve.

In the Nordic study we didn't look at chemicals as such, but at the male reproductive… For each of these diseases we looked at direct cost (cost of hospital treatment), indirect cost (production loss due to disability) and intangible cost (psychological, loss of quality of life).

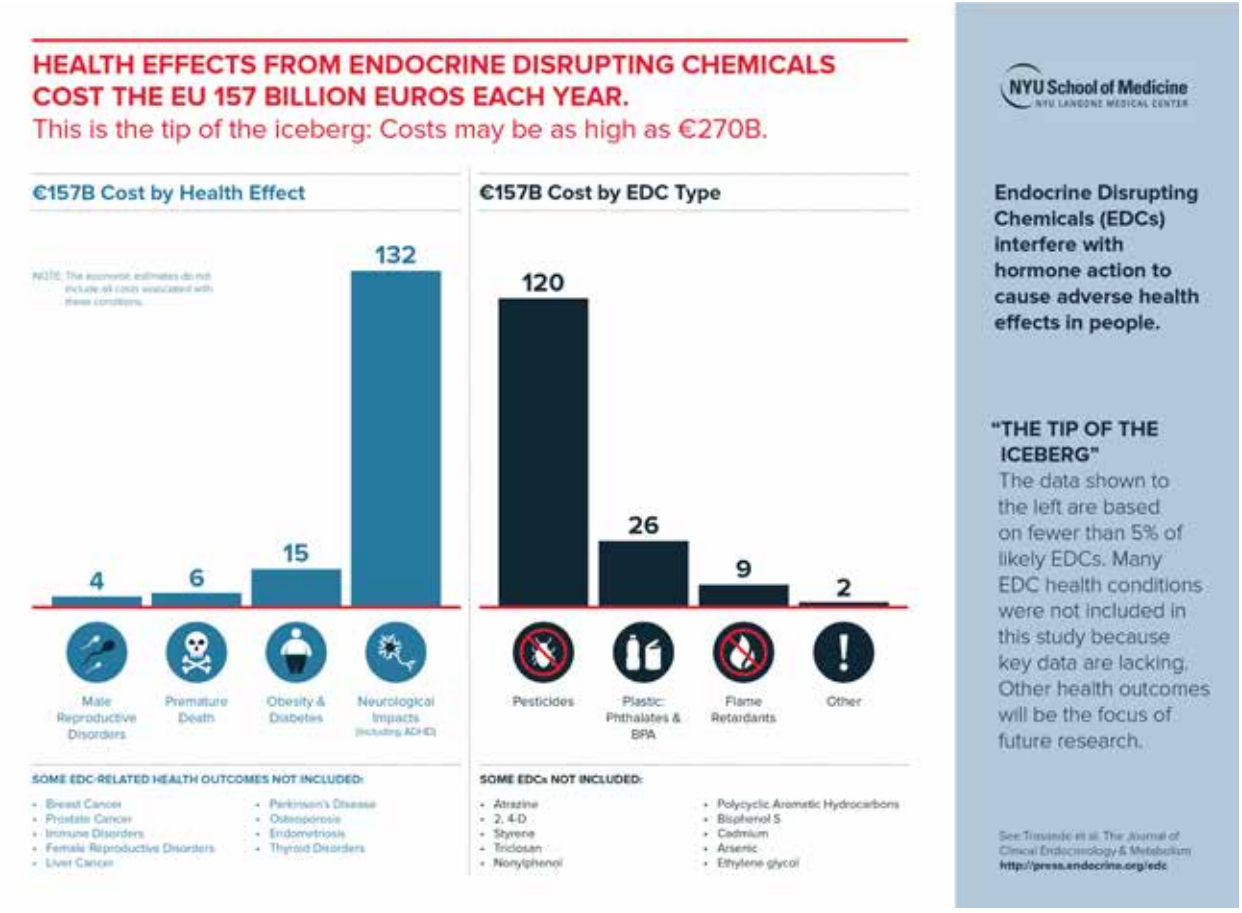
> Health cost due to exposure to EDCs may be up to 1184 million euros/year for male reproductive disorders

It was found that costs were in the order of intangible>indirect>direct. Some costs were left out for example the intangible cost of male infertility, because we couldn't find a method to estimate the psycho-social costs of not having a baby.

In discussion with experts and following what is known about the genetic fraction that influences diseases and the fact that there are other environmental factors that affect the development of these diseases, we estimated how much of the total amount of these diseases could be attributed to exposure to EDCs. The figures we got were between 20-50%. Some scientific papers on other EDCs reported etiological fractions around 2% (for individual substances), so it was decided to use 2, 20 and 40% as etiological fractions resulting in 59, 592 and 1184 million euros/ year for male reproductive disorders, respectively (discounted values).

Comparison with the other two studies:

❖ **HEAL** (Health and Environmental Alliance) 2014: Total EU costs for endocrine related diseases (2-5% etiological fraction) was estimated 13-31 billion Euros per year. They only looked at direct costs, no discounting. If we consider that 0.5-0.7% of these diseases are related to male reproductive dysfunction it results to 66-87 million Euros per year -very close to the Nordic study (59 million Euros).



❖ **Expert panel** (members of the Endocrine Society): A different approach. A group of scientists that present their work in a transparent way, they use methodologies developed by WHO and IPCC. They start from unbanned chemicals (still in use) where there is data available on toxicology, epidemiology and biomonitoring (we can measure that people have been exposed). For male reproductive health their outcome is 5.7 billion Euros per year in the EU. Their overall outcome is 157 billion per year in EU of actual health care expenses and lost earning potential due to endocrine related conditions (infertility and male reproductive dysfunctions, birth defects, obesity, diabetes, cardiovascular disease, and neurobehavioral and learning disorders) that can be attributed in part to exposure to endocrine-disrupting chemicals (EDCs). These values are the mean values (modelling the probability to take account of uncertainties gave values from 2,5 million to 240 billion Euros per year). The biggest cost driver was loss of IQ and intellectual disabilities caused by prenatal exposure to pesticides containing organophosphates.

> It all boils down to if we want to prevent or continue to tidy up?

The strength of this work is that it presents methods that can be used to estimate these health costs and can be used for the Commission's the impact assessment on EDCs. We have information about the costs of producing chemicals and the effects on the market but there is not much information for costs of health or of exposure in the environment. These studies can bring some health related figures in the equation. The weaknesses are that the health costs may be underestimated, for example the Nordic study only looks at male reproductive health, none of the three studies include environmental costs and data are missing (only registered data are taken into account). And as always, you have to make assumptions, which creates uncertainties.

Out of the three studies presented here, the Nordic and HEAL studies have assumed a causal link between these endocrine related diseases and exposure to EDCs and have assumed an etiological fraction. However, in the expert panel they based their work on toxicological and epidemiological studies and related it to exposure levels. But as long as you are open with what you are doing you can still apply these variables as part of the picture when you want to decide of how you will move forward.

> If we want to protect our children and grandchildren we need to start acting now, we shouldn't wait until later.

In this context we have to look at what we want to achieve. The methodology should be developed further.We should use available information and experience (learn from previous experience). We should learn from what has happened and stop having "late lessons from early warnings". We have to consider what level of evidence that is really needed - we need to use methods that can rely on animal studies and also have models to collect data.

It all boils down to if we want to prevent or continue to tidy up?

If we want to protect our children and grandchildren we need to start acting now, we shouldn't wait until later.

Discussion

Question (Prof. Gerard Swaen): In relation to the incidences of the diseases (testicular cancer, hypospadias, cryptorchidism, semen quality etc), there are two factors that are very important. One is the reporting of the incidence, the tools for reporting diseases have evolved we have better registration today that we years ago. Therefore, a higher incidence is due to better reporting and collection of data. The other factor is about the reproductive habits that have dramatically changed. For example, women get their children at a later age, they give birth by cesarean section, we have very small families etc.

An observation is that the risk of testicular cancer in first born boys is 40% higher than the fourth born boys. Since now families have just one or two children we cannot do this comparison. The prevalence of first born boys has increased and therefore its not surprising that testicular cancer has also gone up.

The other matter is cesarean section. Children born from caesarean have 40% increase risk to develop obesity in later life. So its not surprising that these diseases go up because we have changed our reproductive life-style. Have you taken into account these aspects in your evaluation

Answer (Prof. Toppari): Of course one has to take into account all possible risk factors. In relation to testicular cancer, the incidence increases cannot be explained by a better registration system. The men are dying from testicular cancer if they are not diagnosed. The registries in the northern countries have been studied closely to confirm they are correct. Registries show that the numbers have gone up in the northern countries- since all cases of testicular cancer must be recorded.

For the cryptorchidism there are good criteria for scoring from 1960s that if we apply them we see that the incidence has gone up, in 1950., 1980s and 2000. The incidence has gone up from 2.5, to 5, to 7%. Of course there might be differences in reporting but one shouldn't rely on the possibility of an error but rather lean that the findings are true.

In relation to the first boy that has a higher risk for testicular cancer, one should ask why is that? We should take into account that the first born boy always absorbs most lipophilic toxicants from the mother and the other children receive less. Breast feeding is "downloading" toxic chemicals from the mother and with each baby, breast milk contains less persistent/lipophilic chemicals. That's why the mothers that have many children have a lower risk for many cancers. And the first born receives the most toxic chemicals from its mother.

Low fertility and testis cancer risk go together. There is also the susceptibility, the genetic component, different populations have different risks, its not just the environment, of course we take into account all possibilities.

Question (Prof. Alberto Mantovani): If I ask to physicians they tell me that the main endocrine disease is diabetes. But there is a considerable lack of knowledge on mechanisms through which chemicals can produce diabetes, there is a lack of testing methods and a lack of epidemiological knowledge on the link of diabetes/metabolic syndrome and exposure to chemicals

Answer (Prof. Toppari): Very important questions, diabetes is the big killer. There are very few data. We don't know the cause of the disease. It has a strong genetic component but it cannot explain the prevalence of diabetes. There are now big co-hort studies looking for environmental determinants i.e. viruses, bacteria, diet but there is nothing yet on chemical exposure.

Answer (Prof. Bergman): There is an enormous complexity of what is out there. Its impossible to find causality since the mixture of chemicals is so complex. We need more experimental work to be done in the future. There are even more to diseases such as diabetic that we still don't know the underlying cause (partly its genetic).

Answer (Dr. Olsson): Obesity surrenders 50 billion Euros per year in the European Union.

Endocrine disruptors: a panoply of health effects. When is enough, enough?

Prof. Ana Soto (Tufts University School of Medicine, Boston, USA)

Bisphenol A (BPA) as a case study.

Foetal exposure of mice to very low levels of BPA (at nanograms/kg body weight -range) leads to the foetal estrogen exposure syndrome, which was first described following exposure to diethylstilbestrol (DES, synthetic oestrogen). Perinatal exposure to BPA, advanced puberty, altered oestrous cycles and induced cessation of cyclic activity, decreased fertility, increased propensity to obesity, metabolic syndrome, diabetes, autism-like behaviour and cancer. Additionally, BPA exposure resulted in effects that manifested transgenerationally.

Lessons we must learn from human foetal exposure to diethylstilbestrol (DES):

This pharmaceutical compound was used in the late 1940s (1948) to prevent miscarriage. It took 20 years (1971) to discover that girls exposed in utero to DES developed clear cell carcinoma of the vagina. Additional adverse effects were identified, such as malformations of oviduct and uterus and decreased reproductive success. Decades later, in 2006, it was found that foetal exposure to DES increased the incidence of breast cancer at the age of prevalence. This information –that exposure to DES leads to mammary cancer- was known from experimental animals since the 1980s. It is worth noting that 40 years elapsed since the first reports of clear cell carcinoma of the vagina to the discovery of the mechanism underlying this outcome. This is an example of how long it takes to understand the specific mechanisms that underlie endocrine disruption.

Very low doses of BPA, a "supposedly" weak oestrogen can produce the same effects as DES, which is considered a potent estrogen. Bisphenol A is a hormonally active substance and to examine its effects, it must be studied following the principles of endocrinology rather than those used in classical toxicology: EDCs work in non-monotonic dose-response curves, low doses produce different effects than high doses and sometimes low-dose effects are more harmful than high dose effects. Foetuses are more sensitive to EDCs than adults, because foetal exposure hampers organogenesis (the formation and development of the body organs) resulting in irreversible damage, whereas in adults exposure interferes with activation processes, which are reversible for the most part.

EDCs work in non-monotonic dose-response curves, low doses produce different effects than high doses and sometimes low-dose effects are more harmful than high dose effects. Foetuses are more sensitive to EDCs than adults, because foetal exposure hampers organogenesis (the formation and development of the body organs) resulting in irreversible damage, whereas in adults exposure interferes with activation processes, which are reversible for the most part.

Regarding the effects of BPA in rodents, we shouldn't wait to verify that the same effects are revealed in humans. Unlike DES, which was used therapeutically, we are all exposed to BPA - It is not feasible to have a control group of non-exposed people. Moreover, the latency period between exposure to DES and the diagnosis of breast cancer was more than 40 years, making it very difficult to correlate breast cancer incidence with foetal BPA exposure. Instead, we should consider the strong argument based on the similarities between DES effects in humans and rodents, and between DES and BPA effects in rodents.

In 2009 the Endocrine Society published a scientific statement addressing concerns in relation to exposure to EDCs and giving recommendations "to increase the understanding of effects of EDCs, including enhancing increased basic and clinical research, invoking the precautionary principle and advocating involvement of individual and scientific society stakeholders in communicating and implementing changes in public policy and awareness" (Endocrine reviews 30: 293-342, 2009)

We should use the precautionary principle while we are learning more about endocrine disruption in general and BPA effects in particular.

Criteria for evaluating scientific evidence

Science for its own sake: Practitioners of basic science are used to living with uncertainty: there is always a new experiment to be done, a "t" to cross, an "I" to dot… About 100 years elapsed from the time Copernicus stated that the the sun is at the center of the planetary system until Newton proposed a gravitational force and the motion laws that made the heliocentric system universally accepted. There was no real urgency there, because regardless of the validity of the explanation given by scientists, it was beyond their powers to change the planets' orbits. Basic science is in perpetual motion.

Use of science in Medical Practice: In contrast with basic science, time is of the essence, physicians have to reach conclusions and act without delay to prevent, cure, or save a life. A physician cannot afford to wait to first understand every single detail, in order to act.

Science and Medical Epidemiology: When testing a pharmacological agent it is very important to choose a priori which type of error should be avoided. The null hypothesis (no effect expected) is chosen because it is better to error on the side of a false-negative than of a false positive.

We should use the precautionary principle while we are learning more about endocrine disruption in general.

Science and Public Health Epidemiology: When studying exposures to potentially harmful agents choosing the alternative hypothesis (a deleterious effect expected) is a sound practice as it is better to error on the side of a false-positive than of a false negative.

In summary, we must understand that not every mechanism needs to be known and verified in order to act to protect life, because there is no need to know the underlying mechanisms in order to accept the existence of a given phenomenon. For example, our ancestors knew that castration made animals sterile; they found castration useful and performed it while being ignorant about why these animals became sterile. Mechanistic explanations were generated thousands of years after this practice became common.

Risk assessment must be transparent and performed by independent scientists authoring high quality papers in the field of endocrine disruption

Recommendations:

❖ Risk assessment must be transparent and performed by independent scientists authoring high quality papers in the field.

❖ Stakeholder conferences may serve as a forum making transparent the interests and influence of industry and other NGOs.

We must understand that not every mechanism needs to be known and verified in order to act to protect life, because there is no need to know the underlying mechanisms in order to accept the existence of a given phenomenon

❖ The industry may pay for studies once a truly secure firewall is put between them and those that perform the tests.

❖ Academic and independent scientists should be at the core of the regulatory panels. They should be paid well, and released from full-time duties by their employers (universities, government labs).

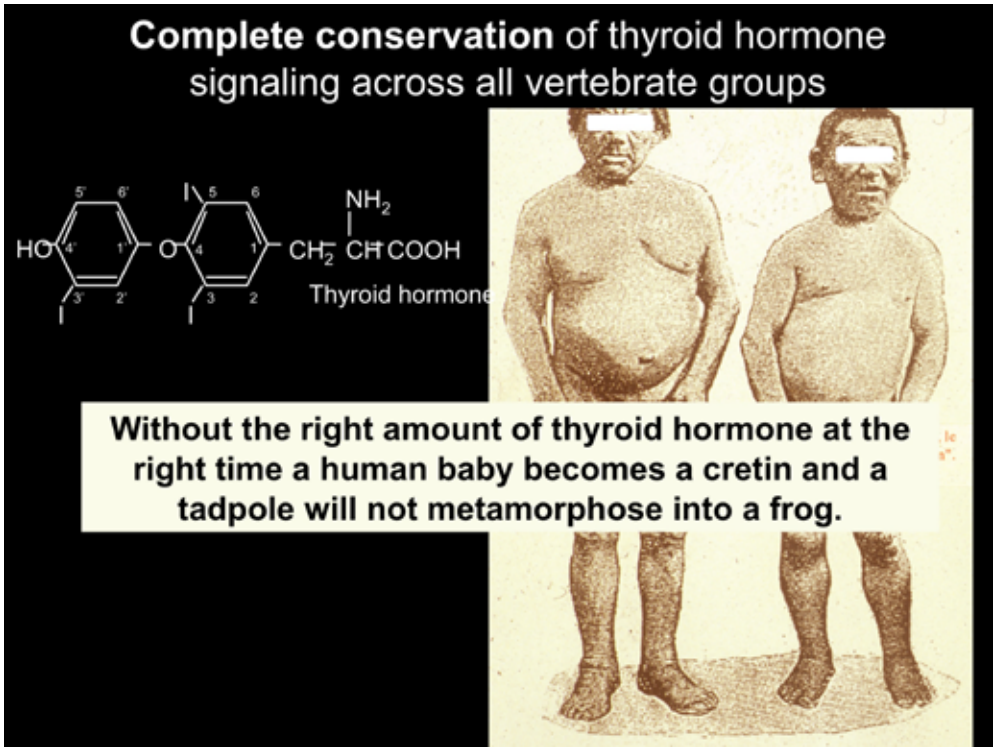
❖ Until final decisions are made, precautionary measures should be taken to lower human exposure well below the doses causing adverse effects in rodents and in humans. It should be noticed that regarding BPA, a rapidly excreted chemical, practically all humans are exposed, hence it is not sound to wait for epidemiological data when there is a long latency period between exposure and effect. Finally, economic arguments usually do not take into account ethical and human rights concerns and ignore the public health burden of disease. Similar economic arguments were made to keep slavery in the south of US. As we now know, slavery was abolished and the US economy didn't fall apart. Likewise, arguments claiming that it was economically unfeasible to provide clean and safe environment for workers were demonstrated to be spurious. History shows that once and again these arguments hindered progress in human rights, public health and environmental justice. As W. Churchill said, "Those that fail to learn from history, are doomed to repeat it." Let's hope that this time, we do learn from history.

Thyroid hormone disruption, brain development and IQ loss

Prof. Barbara Demeneix (Muséum national d'Histoire naturelle/CNRS, Paris)[7]

As an expert in thyroid hormones, I was asked by the French government to participate in the OECD panels to look at testing methods for thyroid effects. Back in 2001, the OECD was not taking into account the current knowledge on thyroid signalling, whereas in my research group we had developed alternative methods and provided

[7] Professor, Head of Department, Evolution des régulations endocriniennes, CNRS
Co-founder of WatchFrog, France, Expert participant in OECD panels



test methods to detect effects of chemicals on thyroid signalling (Watchfrog).

The structure and mode of action of thyroid hormone is the same in all vertebrates, it is conserved across evolution. We all need thyroid hormone for optimal brain development. We don't see cretinism anymore (severe intellectual deficiency due most often to lack of iodine and, as a consequence, impaired thyroid hormone synthesis) but we do see IQ loss in relation to exposure to high levels of certain chemicals, including pesticides that can interfere with thyroid hormone action. What we don't know is the potential subtle effects that are difficult to detect in individuals, but require population-wide studies to be picked up. Similarly we no nothing of the effects of mixtures and yet we are all exposed to mixtures.

> We do see IQ loss in relation to exposure to high levels of certain chemicals, including pesticides that can interfere with thyroid hormone action

> We are also witnessing an increase in autism incidence as well as IQ loss. Clearly, current testing of chemicals is not picking up on windows of vulnerability, notably exposure during early pregnancy.

We are also witnessing an increase in autism incidence as well as IQ loss. Clearly, current testing of chemicals is not picking up on windows of vulnerability, notably exposure during early pregnancy. E.g. 15 years ago we didn't know anything about the need for thyroid hormone in the 1st trimester of pregnancy. We are also not picking up on changes in brain architecture, the relative proportion of certain cell types. The costs of inaction in terms of neurodevelopment is a major fraction of the 157 billion Euros calculated by Trasande and colleagues[8].

[8] Trasande L, Zoeller RT, Hass U, Kortenkamp A, Grandjean P, Myers JP, DiGangi J, Bellanger M, Hauser R, Legler J, Skakkebaek NE, Heindel JJ, 2015. Estimating burden and disease costs of exposure to endocrine-disrupting chemicals in the European union. J Clin Endocrinol Metab, 100(4):1245-55.

Without the right amount of thyroid hormone at the right time a human baby becomes a cretin and a tadpole is not metamorphosed into a frog. These distinct physiological effectsshare the same underlying molecular mechanism. It's this conservation of structure and action that we levered to create the test that is now being validated by the OCDE and is licensed to Watchfrog. Watchfrog uses fish embryos and tadpoles to assess endocrine disruption. These tests are considered non-animal testing due to the very early life stages of the larvae. As non-feeding larvae they are classed at the in vitro, in vivo interface.

The European Parliament called for better protection for pregnant women and babies and its time to take this into account.

T3 (the active form of the thyroid hormone) has a structure like a pair of glasses. Some EDCs may have a very similar structure to T3, e.g. PCBs, TBBPA but others e.g. PFOS (surfactant) have a totally different structure and will not be picked up by structure similarities screens (*in silico*).

Thyroid hormone disruptors are present in amniotic fluid of foetuses, which means that babies are not just exposed to these chemicals once they are born but they are conceived into this chemical mixture. Pesticide metabolites, BPA, flame retardants, DEHPs, PCBs etc they all inhibit iodine uptake by the foetus. We now know that during the first three months of pregnancy the mother's thyroid hormone levels can have a critical effect in the neurodevelopment of the foetus.

Low maternal free thyroxine concentrations during **early pregnancy** are associated with impaired psychomotor development in infancy.

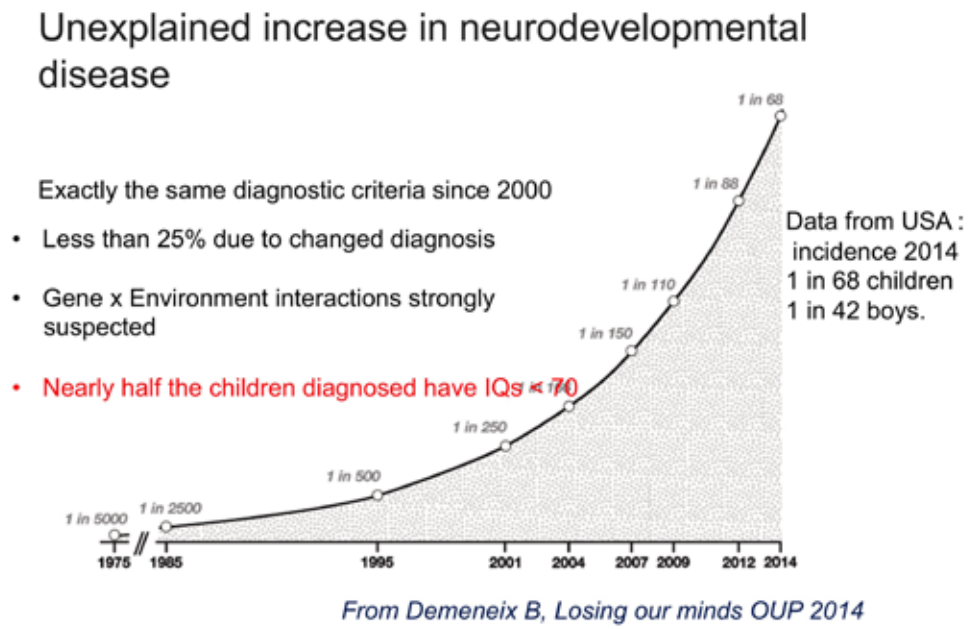
Pop VJ, Kuijpens JL et al. Clin Endocrinol (Oxf). 1999 Feb;50(2):149-55.

Maternal hypothyroxinemia in **early pregnancy** predicts reduced reaction time tests in 5- 6 year offspring. Finken ME et al JCEM 2013

The epidemiological evidence suggests that exposure to certain EDCs is linked to the increase in neurodevelopmental disease, e.g. autism 1 in 42 boys. 1 in 68 children in 2014 compared to 1 in 500 children 1995 or 1 in 250 children in 2001. The diagnostic tools since

2000 are the same. Nearly half of the children diagnosed with autism have IQ<70 (average is between 90-109, 70-79 is the borderline). A recent paper compared current IQs with that of people from Victorian times (end of 19th century). These comparisons were based on tests of reaction time. The authors report a 14 points of IQ loss over a little more than a century. Whats the significance of this? A loss of 5 IQ points results in 60% less gifted individuals in a population. More than or a 5 point IQ loss has been seen in iodine deficiency, in maternal hypothyroidism, exposure to PCBs, lead/ mercury, organophosphates and flame retardants. And of course we have no idea what happens with mixtures. In a population of 100 million that has 6 million gifted people 6 million intellectually challenges, a shift in 5 points of IQ will result in 2.4 million of gifted people- 60% decrease and a corresponding increase, to 9.4 million intellectually deficient children (and adults).

Neurodevelopmental disorder tests can represent reasonable markers of effects of exposure to chemicals as one can monitor the pregnant mother and then her baby until the age of 5-7. Obviously this is faster than waiting for the development of adult diseases, that can also be linked to prenatal EDC exposure, such as breast, testicular or other cancers in a later age or other diseases that are linked to chemicals exposure.



From Demeneix B, Losing our minds OUP 2014

IQ is well monitored. In a study consigned with Leo Trasande from New York University they looked the health effects from exposure to endocrine disrupting chemicals and their costs and found that the costs for EU sum up to 157 billion Euros per year of which 132 billion result from neurological effects of chemicals, including IQ loss. The larger fraction of that was attributable to pesticides exposure. They only had reliable data for 3 groups of chemicals, so this figure is probably the tip of the iceberg

The European Parliament called for better protection for pregnant women and babies and its time to take this into account.

For instance, EFSA has looked into the effect of pesticides on thyroid. In their analysis of 287 pesticides they found that 101 were identified as affecting the thyroid or thyroid hormone systems.

In October 2014, OECD put out a special call stating that we need specific tests to evaluate effects on the thyroid system because the current tests are not effective. Tests with embryo fish and frogs are indeed valid tests.

The European Parliament called for better protection for pregnant women and babies and its time to take this into account.

EFSA's work on the assessment of endocrine active substances

Hubert Deluyker and **Jose Tarazona** (European Food Safety Authority "EFSA")

Hubert Deluyker (Executive Directorate)

EFSA was invited by the European Commission to give a scientific opinion on: identification of EDCs, adverse effects and testing methods, in collaboration with other agencies (EMA, ECHA, EEA and EC scientific committees).

EFSA is making the distinction between chemicals that have endocrine activity and those that are endocrine disrupters, the difference being the adversity as defined by WHO/IPCS EHC 240, 2009.

Thus endocrine activity plus adverse effect if there is a plausible link leads to definition of endocrine disruption.

> Whole life-cycle analysis is missing for mammals, which is important in order not to miss critical windows of exposure.

There is a reference point that concerns test methods, OECD. These methods are mainly focused on modalities related to oestrogen, androgen, thyroid and steroidogenesis, mostly for mammals and fish. Whole life-cycle analysis is missing for mammals, which is important in order not to miss critical windows of exposure. Limitation of some animal models in relation to certain endocrine disorders that EDs may have a role.

There is no single test to identify EDs, tests for EDs are not designed to describe an adverse response by the organism as a whole. Guidance is needed to interpret the outcome of these tests and a testing strategy to produce the appropriate data for regulatory risk assessment.

Areas that EFSA is working on and are relevant to EDs are: non-monotonic dose-response for human risk assessment, chemicals mixtures, biological relevance, systematic literature review, uncertainty, weight of evidence, expert knowledge elicitation. The first three are key points for EDs and EFSA is doing a preparatory work to come up with a scientific opinion.

Jose Tarazona (Head of Pesticides Unit)

Methodological developments in relation to pesticides: mixture toxicity (cumulative risk assessment) to detect similar modes of action of chemicals also in relevance to endocrine disruption (reproductive effects). EFSA is working on the use of epidemiological data in risk assessment, how information from these studies can be used better, for example they are using Adverse Outcome Pathways to establish the link between pesticide exposure and Parkinson's disease or childhood leukaemia. EFSA is trying to produce recommendations to improve the lack of quantifying data for the exposure to pesticides in epidemiological studies.

EFSA has the responsibility of assessing individual active substances of pesticides. EFSA is producing the peer-review to support the position of the Commission. During the risk assessment of pesticides one is trying to identify all information together, all the properties of the active substances, for example the persistence of the chemical in the environment and in the human body is important to consider the hazard and the possibility of a risk. Based on all the properties then they have the toxicological and ecotoxicological profile of the monitoring. This information should be coherent and it's compared with the different criteria of the legislations. If the pesticide is classified as carcinogenic, mutagenic, toxic to reproduction, endocrine disruptor, if its PBT (persistent, bioaccumulative and toxic) or POP (persistent organic pollutant) then they proceed to hazard characterization, potency and then move to exposure

assessment and risk characteristics. EU has a strict regulation for pesticides with huge amount of data requirements and with the new regulation other all scientific studies should be taken into account, as well as the Member States' consultation and also the public consultation. They are happy to increase the participation of the stakeholders to this public consultation.

The output of EFSA's scientific review always includes the following: the identity of the chemical with its physicochemical properties, mammalian toxicology and workers/bystanders/residents risks, environmental fate and behaviour, ecotoxicology and environmental risks.

EFSA is quiet transparent in the assessment of pesticides, in their webpage you can find the summary dossier of every single active ingredient, the DAR prepared by the Rapportuer MS, together with the conclusion of the EFSA but also the assessment of the MS as well as the replies to the public consultation.

In the conclusions EFSA identifies data gaps, issues of concern (when there is an adverse effect that they cannot fully identify OR when a risk/hazard has been identified) and specific endpoints that can be used for the decision-making as well as for the RA of products in the market that is performed by MS.

In relation to EDs, the current information is sufficient to identify several such chemicals. They are assessing real adverse effects in animal studies and when they observe effects related to the endocrine system they have specific provisions that require additional information: to elucidate the mode of action and to provide sufficient evidence for relevant adverse effects. In case there is not enough information, they design studies on an individual basis to investigate further these parameters.

In summary: EFSA's conclusions represent a detailed case-by-case expert assessment for each substance based on current scientific knowledge, all available information is assessed for reliability and relevance, EFSA has identified potential concerns for some substances, leading to recommendations for generating additional data and for clarifying endocrine related mechanisms AND relevant effects have been included and considered in the risk assessments even when not triggered by the interim criteria.

Discussion

Comment (Porf. Walter Lichtensteiger, Zurich University): Indeed there are few problems with reproductive endpoints because of the delay of the detection of the adverse effects. But the brain is different, you can look (children) one year or 2-3 years after exposure and see effects, for example behavioural disturbances have been seen in humans following exposure to identified EDCs in epidemiological studies. We should investigate further how exposure to chemicals affects social, cognitive, emotional behaviour in children. It is quiet clear from neurobiology. Not just the thyroid but also the hippocampus, cerebral cortex, oestrogen and androgen receptor etc. We have very good correlation between exposure to a number of EDCs and disturbances in brain function. The experimental disturbances that have been observed in experimental animals reflect on what we see in humans. This is a very good argument to study the effects of endocrine disrupters.

Answer (Prof. Demeneix): In the 10 minutes she had she decided to focus only on thyroid since many chemicals are known to interfere with the normal function of the thyroid system leading to adverse effects. Thyroid hormone is modulator, modulates oestrogen responses and can be taken as indication of many other forms of endocrine disruption (e.g. behavioural). Its time to act. As a grandmother she gets very disquiet.

Question (Tony Tweedale, consultant): Its good to hear that OECD is coming up with some thyroid methods. But in REACH and other laws you have a legal requirement to use the TG methods. But TG are being developed very slowly.

Answer (Prof. Demeneix): Indeed, it took 10 years to make one test validated in OECD. Innovation is not done correctly in Europe, we are destroying our cognitive capacities.

Question (Toxicology Consultant): 50% of pesticides may have an effect on the thyroid of rats that leads to cancer but this may not be human relevant. It might be a rat specific effect.

Answer (Prof. Demeneix): You are right, looking at the pesticide data, effects are seen in rats, compound goes to the liver, gets metabolised, there is an increased clearance, stimulation of thyroid and thyroid cancer. We thought that this was rat-specific. In the past when we were doing these experiments we didn't know the sensitive windows of exposure, neuron populations, dehydrogenases, and transporters. And a lot of that not relevant to humans because it was seen in rats is unfortunately erroneous.

Question (Hans Muilerman, PAN Europe): According to EFSA EDCs can be treated as every other chemical, with RA. This contrasts what scientists say. How do you explain this difference?

Answer (Hubert Deluyker, EFSA): This is clearly the position of EFSA, risk characterisation is a reliable way forward. Of course if it's a hazard characterization, or hazard based principles are applied then the legal procedures will take place. But indeed that is EFSA's opinion.

SESSION 3
REGULATION OF ENDOCRINE DISRUPTING PESTICIDES/BIOCIDES- UPDATE, ROADMAP AND IMPACT ASSESSMENT

Endocrine disrupters – impact assessment

Prof. Andreas Kortenkamp (Brunel University, London)

We know a few chemicals that have ED properties, DES, flame retardants, certain pesticides, painkillers (e.g. paracetamol) but despite this knowledge there are still major gaps in relation to the spectrum of EDCs that we come in contact in our lives.

What is necessary to regulate chemicals?

When you regulate a new group of chemicals you need a definition to define what you want to regulate, in this case that indicates what is an endocrine disrupting chemical, which is not very controversial.

You need tests: Having defined what to regulate then you need tests to detect the chemicals you have just defined.

Finally, you need criteria to translate the test outcomes to regulatory actions.

> Despite our knowledge on chemicals that have ED properties there are still major gaps in relation to the spectrum of EDCs that we come in contact in our lives

There is a confusion in some people's mind between criteria and definition. What is controversial at the moment, is the criteria; the translation of test results into criteria for regulatory action for EDCs.

The overlooked big gap also concerns tests:

We know about anti-androgens, thyroid-disrupting chemicals, hormonal carcinogens, they all act during specific windows of exposure in foetal life. For adults, effects are expected to be very different- exposure to anti-androgens will have little effect than if exposure takes place in the womb, when the foetus is under development.

This is why EDCs are such a challenge; this window of vulnerability has long been

overlooked in tests. This was the case of phthalates that for years they were tested at the wrong time, with too few animals. Only when specific more appropriate tests were used is when the ED properties of phthalates came to light.

OECD validates ED-Test Guidelines (TGs), if we want tests to be used in the regulatory arena they need to be validated. But currently not a single OECD TG is fully implemented in EU and US laws. Most OECD TGs for EDCs are not implemented at all.

> For adults, effects of EDCs are expected to be very different: exposure to anti-androgens during adulthood will have little effect than if exposure takes place in the womb, when the foetus is under development.

If we consider the EDCs as an iceberg, the tip of the iceberg is the current OECD conceptual framework for EDs, which we are not even dealing with this. If we go beyond the line of the iceberg, we get the endpoints and assays that are not yet validated and a guidance has not been drafted, and further down we have other receptors and pathways that may be affected by EDCs that have not been discovered yet. They could be developed to certain assays.

If one looks at the pesticide draft assessment reports they have very few data from relevant ED tests in there. The current guidelines for data requirements do not ask for ED tests. So the dilemma is, if there are few data from relevant tests how can we assess the impact of future endocrine disrupter regulation properly?

> Not a single OECD endocrine disrupter guideline is implemented in EU or US law

Current lists of pesticides that could be affected by ED cut-offs (developed by NGOs or competent authorities from Member States) vary and are based on indirect indication of endocrine disruption, they are not based on the OECD validation tests, because the data are not there or not publicly available.

These projections from indirect data are largely unreliable. In relation to the current Impact Assessment (IA) exercise, the question that rises is "how the EU will deal with this?" Proper data are not yet available, but the COM has been asked to assess the impact of different regulatory options. How will COM square this circle?

> The dilemma: If there are few data from relevant tests, how do we assess impact?

IA will delay the regulation of EDCs 3-4 years. The irony of this is that during this process the interim criteria apply. Are the interim criteria actually implemented?

We hear a lot about the chemical industry, and the pesticide industry perhaps feels with their backs against the wall, in relation to ED regulation. But overlooked is the fact that other industries also see interest in this in a different way: reinsurance industry- they pay litigation costs. This industry sees EDCs as of one of the big coming issues. Industry is not a monolith, even industry has different interests.

Regulation of EDs under the Plant Protection Product (PPP) and Biocide Product (BP) Regulations and the ongoing impact assessment

Michael Flueh (DG SANTE)

Provisions for regulation of EDCs are included in various EU legislations: PPPR, BPR, REACH, WFD, Cosmetics. The Strategy on EDs started in 1999.

They also have the requirement of using peer-reviewed open literature. Data requirements in pesticides were only recently "modernised" and updated. They have included a number of OECD tests specific for ED.

Adverse effects caused by EDs are already covered by standard risk assessment.

They have already regulated a number of substances that was demonstrated that they have ED effects. We have regulatory measures taken (with BPA and phthalates for example).

There are no international criteria to identify EDs. EU is entering as regulators a new "era". PPPR & BPR: Define regulatory consequences for EDCs, establish Interim Criteria (industry is unhappy with IC), new criteria deadline was missed.

Regulatory consequences:

Plant Protection Products (PPP): ED is an approval criterion but there is not a immediate ban. Exceptions if exposure is negligible or if there is a serious danger to plant health (4.7) exist.

Biocide Products (BP): For professional use the approval decision is based on a risk component and has a derogation in case of disproportionate negative impact on society. For consumers, there is a strict hazard-based non-approval (and no derogation).

The European Commission (COM) is working on the development of criteria since 2009. We have the Kortenkamp report (2001), the EFSA opinion (2013) and the JRC expert advisory group report (2013). Preparatory activities, an AD-hoc working group, lead by DG ENV, ED expert group (lead by JRC), a Commission conference in 2012, and a first draft of the criteria. The draft was discussed in the AD-hoc WG, consensus was not reached in this group and formal European Commission (COM) inter-service consultation did not start on the draft.

It's difficult to find an agreement because the topic is complex, science divergences exist, criteria will affect other sectors (horizontal criteria), regulatory consequences vary across sectors (decision making based on hazard/risk/risk-benefit), impacts vary and depend on criteria and sectors. There are also different legal procedures on how to implement the criteria.

Since there was no consensus in the various groups mentioned, the European Commission (COM) asked the services to start working on an Impact Assessment (IA) (2013). IA is an analytical process to prepare relevant evidence for political decision-making based on available information. It's a standard procedure that COM is asked to do for regulatory purposes. IA is an essential component of "better regulation". IA does not replace the decision-making, attention is given to credible and transparent evidence, helps to distinguish between evidence and opinion.

The roadmap is not a "DG SANTE roadmap", it was approved by the commissions services. The roadmap takes two approaches: aspect 1: EU criteria to identify ED. Four options in total, options 2-4 based on WHO decision-making, all options are hazard-based. Aspect II: regulatory decision-making, 3 options, adding further elements of risk assessment and further socioeconomic considerations.

We, in DG SANTE, did a public consultation, all elements are available on the website. We are doing in parallel a number of studies. JRC is developing a methodology to do a screening on chemicals and apply the 4 options. Once the study is completed the task will be given to a contractor. Once the chemicals are defined in each category they can carry out the socioeconomic impact. We will not just look at the economic impact alone, also other aspects, health & environment are part of this assessment.

Final remarks: EU is entering a new territory, we are getting prepared for taking regulatory actions and we're taking them, the impact assessment is well on track (no more delays).

The Regulation of Endocrine Disruptors within REACH

Bjorn Hansen (Head of Chemicals Unit, DG ENV)

How the EU regulation on EDCs has been developed within REACH.

The work on EDCs was developed in parallel with the work on REACH. REACH negotiations started in 1996 and adoption of REACH was achieved in 20017. In relation to EDCs, first discussion took place in 1996, with our "stolen future" book, which kicked off the debate, and the first discussion on the definition of EDCs took place in Waybridge, UK, in 1996 and the workshop was supported by European Commission, WHO, OECD, European Environment Agency, national authorities and agencies. In 1998 there was a parliamentary resolution. In 1999 the COM came out with a strategy on EDCs. There was an evolution. Back in 1999 they identified a number of steps which needed to be undertaken to address endocrine disruptors, and these steps were implemented in REACH.

Weybridge definition, 1996 (following consensus of the board, scientists from different groups, the Commission, Industry and Member States): *"An ED is an exogenous substance that causes adverse health effects in an intact organism, or its progeny, consequent to changes in endocrine function."*

WHO IPCS Definition (2002): *"An endocrine disrupter is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations."*

The definition applied by the COM is the WHO IPCS definition (2002), while they are waiting for the criteria implementing the definition.

In REACH they apply the three steps previously introduces by Prof. Kortenkamp, we have definition, we have test methods and then we try to apply those and regulate the use of such chemicals. REACH houses the OECD test methods available, and includes new validated tests in the test methods regulation of REACH. Although inclusion is not a legal obligation, but it means that validated TG are available in EU and makes part of MAD (Mutual Acceptance of Data), which is a recognised system world-wide. They have now included OECD screening test methods for EDs, for example they recently included the extended 1-gen test that looks specific ED endpoints as standard information requirement. They are just starting to implement it for substances above 100 tonnes. Through a process called substance evaluation in REACH a number of substances are being identified for ED potential and specific testing requirements are set. They implement the test methods of OECD and generate information that should enable them to apply the definition and the criteria when they come out.

WHO IPCS Definition (2002): "An endocrine disrupter is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations."

Also done in a REACH context, a task carried out by ECHA, 5 substances have already been identified as EDCs for the environment, following the WHO definition and one substance for humans (DEHP). However, due a disagreement within the committee of ECHA, in relation to the interpretation of a specific article, this issue is still under discussion. They have developed "a roadmap" for identifying SVHCs, (Substances of very high concern), the goal is to identify them all by 2020. ECHA has established an expert group (already met 4 times) who are screening all registered substances in order to identify potential EDC, and either feeding them to the authorisation process or recommend further testing.

Risk management: after identification of endocrine disruptors, its decided whether or not they will enter the authorization system; this is a dynamic process which is ongoing. ECHA has to prioritise these substances then the COM has to confirm if these substances are subject to authorisation. Then the Restriction route is always open for Member States to develop restriction proposals, should there be a risk which needs EU control.

Discussion

Question: To Prof. Kortenkamp, in relation to the controversy in science. Is there a divergence among the scientists on the definition of endocrine disrupters?

Answer: We had a meeting in the offices of Ann Glover, with scientists from different fields (pharmacology, toxicology, endocrinology) and it was possible to reach a consensus on specific characteristics of EDCs. Therefore, there is no scientific controversy.

Question: EFSA says that potency is a characteristic for EDCs. Is this justified to use potency as a cut-off for the definition of EDCs?

Answer: (Prof. Kortenkamp) To use potency as a decisive criteria is scientifically not justified, is arbitrary and will not sit well with the regulatory philosophy normally applied to carcinogens, mutagens and toxic to reproduction.

ANNEX

Agenda

Chairing: **MEP Nicola Caputo** (S&D), **Henrik Sundberg** (KEMI, Sweden)

15:00-15:15
General introduction: **MEP Nicola Caputo**
Bringing EDCs back in the European Parliament: **Angeliki Lysimachou** (PAN Europe)

15:15-16:10
EDCs: What are they and why should we be concerned?

Human exposure to potential EDCs, semi-persistent chemicals and current-use pesticides in particular.
Prof. Åke Bergman ((The Academic Center Swetox, Sweden)

EDCs and male reproductive health – why are we concerned?
Prof. Jorma Toppari (University of Turku, Finland)

Cost of inaction and endocrine disruptors what do we know?
Ing-Marie Olsson (KEMI, Sweden)

Discussion

16:10-17:00
EDCs and risk assessment

Endocrine disruptors: a panoply of health effects. When is enough enough?
Prof. Ana Soto (Tufts University, Boston)

Thyroid hormone disruption, brain development and IQ loss.
Prof. Barbara Demeneix (Muséum Nationale d'histoire Naturelle/CNRS, expert OECD, Paris)

EFSA's work on the assessment of endocrine active substances
Hubert Deluyker (EFSA)

Discussion: Why are EDCs different than other toxic chemicals? Are current EU "safe" limits really that "safe"?

17:00-18:00
Regulation of endocrine disrupting pesticides/biocides- update, roadmap and impact assessment.

The debate about regulating endocrine disrupters
Prof. Andreas Kortenkamp (Brunel University, London)

The impact assessment for defining criteria on endocrine disruptors in the context of the plant protection products and biocidal products regulations
Michael Flueh (DG SANTE)

The regulation of endocrine disruptors within REACH
Bjorn Hansen (DG ENV)

Panel (including speakers): **Georg Streck** (DG Growth), **Benjamin Musall** (DG Trade), **Jorge Costa-David** (DG EMPL)

Discussion: Why the COM decided to miss the EDC criteria deadline? Will the impact assessment protect human health and wildlife from the effects of EDCs? Is it based on scientific evidence?

Concluding remarks

Introductory Speeches

MEP NICOLA CAPUTO (S&D)

after identification of endocrine disruptors, its decided whether or not they will enter “Good afternoon.

First of all I would like to thank PAN Europe for its incredible job.

It is good to have so many participants and so much interest at this event on the risks related to exposure to Endocrine Disrupting Chemicals (EDCs). I see policy makers and experts from Member States, representatives from the Commission and EFSA, and I also see scientist, academics, industry groups and NGOs.

Today we have all the classic ingredients of an intensive debate:

signals from science, increasing public and political concern, and maybe doubts from some stakeholders.

Exposure to EDCs is a global issue-of-concern due to the negative effects on humans and on the environment. Exposure to these chemicals, especially during pre-natal and post-natal stages, has been linked to the development of endocrine diseases and disorders.

I have closely followed this issue since my arrival at the European Parliament. On 13 February 2015 I presented an oral question on the criteria for identifying endocrine disrupting chemicals. This oral question was debated in plenary in March in Strasbourg with Commissioner Andriukaitis who guaranteed that and I quote:

"I would do my job very seriously, in full transparency and without compromise on health".

Today we will have the opportunity to discuss about EDCs directly with scientific experts and with the Commission.

This will allow us to know more about the state of science of EDCs and the criteria needed to identify these substances. We will also discuss about the necessary next steps for their correct regulation.

We all know that EDCs can be found amongst others in sprayed fruits and vegetables, plastics, bottles, cosmetics, toys, clothing and cleaning products.

The World Health Organisation has highlighted many times the risk they pose to human health, as well as the European Environment Agency which highlighted the risk to the environment.

EDCs have become a key challenge for European health and environment policies. However, the time plan for action is being continuously delayed. We cannot wait any longer. The time for political action has come. The European Union should act to reduce exposure to EDCs. Even if we don't have all the answers, we do know enough to regulate these substances in accordance with the precautionary principle.

Regarding the Commission's on-going impact assessment on criteria to identify EDCs, I would like to share three concerns with you:

1) my first concern refers to the cost of inaction. I think that DG SANTÉ should consider not only the cost to industry due to action, but also the cost to society due to inaction;

2) my second concern refers to the four criteria-options for determination of EDCs. The current impact assessment includes criteria options that will fail to detect all EDCs, and therefore the use of some of these chemicals will continue threatening public health and the environment.

I think that option One, which calls for no policy change, is totally absurd because the current interim criteria overlook chemicals that contribute to endocrine associated diseases;

3) my third concern refers to the approach chosen by DG SANTÉ that doesn't include the "cocktail effect", which can be much larger than the effect of each of the single substances.

If DG SANTÉ undertakes a strict reductionist-approach which doesn't take into consideration the "cocktail effect", this will contradict essential points in the report of the WHO on EDCs. In that report, the nature of EDCs and the blind spots in epidemiological and toxicological evidence led the World Health Organisation to conclude and I quote:

"a focus on linking one EDC to one disease severely underestimates the disease risk from mixtures of EDCs".

Let me remind you that mixtures of EDCs include not only mixtures among pesticides, but also mixtures between for example pesticides, industrial chemicals, cosmetics and food packaging chemicals.

Now the ball is in the court of the European Commission, and in particular DG SANTÉ, which has a moral obligation to select the right criteria for identifying EDCs in order to properly protect the consumers and the environment.

I am glad to have the opportunity to co-chair this event with Henrik Sundberg who will guide the more scientific aspects given the complexity of this issue.

Henrik is one of the best EDCs experts and he is currently working as scientific officer at the Swedish Chemicals Agency (KEMI).

Let me remind you that Sweden sued the European Commission over delays to rules on EDCs. We should thank Sweden which succeeded with its court case to put more pressure on the European Commission in order to make it act on EDCs.

I feel therefore lucky today to co-chair this meeting with a Swedish expert.

Before giving the floor to Angeliki Lysimachou, an environmental toxicologist working for PAN Europe, who coordinates the campaigns on EDCs and co-organized this meeting here at the European Parliament, let me conclude my speech by quoting once again Commissioner Andriukaitis.

He said during our last EDCs' debate in Strasbourg that "there will be no compromise on health".

There cannot be any compromise on health, this must be our governing principle and this is the reason why we are all here this afternoon.

And now I will give the floor to Angeliki that I would like to thank once again for her efforts."

Dr. Angeliki Lyssimachou
Environmental Scientist/Toxicologist
PAN Europe
"Bringing Science at the forefront of the EDCs discussion"

On the behalf of Pesticides Action Network Europe I would like to thank you all for being here today to discuss the issue of EDCs and their regulation in the EU. I particularly would like to thank MEP Nicola Caputo for hosting this event and sharing our concern about exposure to EDCs. And of course all the speakers and the members of the panel for accepting our invitation to present their work and participate in the discussion.

First, let me introduce you to our organisation. Pesticides Action Network Europe is the regional centre of a global network organisation of more than 600 NGOs worldwide. We are the voice of the European people that are concerned about the use of toxic pesticides in agriculture and want to replace them with ecologically friendly alternatives.

Once pesticide use was an option but today we have progressively developed an agricultural production system that is totally dependent on pesticides. This becomes evident if we look at the statistics: in 2003 approximately 2.5% of the agricultural land in the EU was organic. This number today has increased to 5%, but still this means that the remaining 95% is treated with pesticides.

Following these numbers it shouldn't surprise us that pesticides today are found everywhere, in industrial countries but also in the most pristine environments like the north pole. They are detected in our food, our rivers, lakes, soil, tissues and blood of animal species and humans, even in newborn babies that haven't been in contact with the exterior environment and food yet.

Pesticides are fabricated to be toxic to pests and unfortunately are toxic to other living organisms. Historically, some of the most toxic chemicals released in nature have been pesticides. DDT, dieldrin and agent orange are some dreadful examples. The continuous documentation of toxic effects in wildlife, humans and laboratory animals resulted to gradually ban these pesticides from agriculture. We had to develop new test methods and regulations to guarantee that such toxic chemicals will never be released again in the environment. After all, the assessment of chemicals is not perfect and must always be updated according to the developments in science.

Now scientists are warning us that some chemicals, previously thought to be harmless are not that innocent after all. Evidence of endocrine disruption following chemical exposure is observed in wildlife, laboratory animals and even in humans. The more we learn about the endocrine system, the more adverse effects we detect and the health costs are multiplying. It is now our responsibility to update the current assessment of chemicals, follow the new findings from endocrine principles and incorporate new tests and new regulatory measures to protect human and the environment from EDCs.

This concern was addressed in the Pesticide Regulation that came into force in 2011, followed by the biocide regulation that by applying the precautionary principal they require banning of EDCs from agriculture and households. But first the regulations call to set the correct criteria to identify these chemicals. These criteria must be based on science. All European Regulations must be based on science.

This task was first developed by DG Environment, which in collaboration with experts on endocrinology and toxicology produced a set of draft criteria to identify EDCs. But these criteria never got published and the European Commission missed its deadline in December 2013. Now we have an impact assessment running, lead by DG SANTE, on four potential criteria options, but three out of which are not up to date with the current scientific knowledge on EDCs. Not only we now have a 2-3 years delay in the regulation of EDCs but we may end up selecting criteria that will fail to protect us from exposure to EDCs.

With the aim to avoid any further delays, PAN Europe calls once more regulators to

make use of the important amount of scientific evidence behind these chemicals and take action. Inevitably some pesticides and biocides will be banned. Good, this is a positive outcome. Our aim is to protect our environment, ourselves and our future generations from these chemicals.

This will push us to develop further the alternative practices in agriculture that don't incorporate the use of toxic substances. For example the main focus of Integrated Pest Management -that since 2014 all Member States must adopt - is to use pesticides as a last resource in agriculture and it proposes alternative practices that can be used instead. Unfortunately, this directive which aims to reduce pesticide use is very poorly implemented in MS.

We hope with this meeting to resolve some questions and uncertainties behind EDCs. We want to help regulators accelerate the process of defining the correct EDC criteria and proceed in the regulation of these substances.

And now I pass the floor to Henrik Sundberg from the Swedish Chemical Agency who kindly accepted our invitation to chair this meeting today. Thank you."